**Study protocol**

# "Prostate Cancer Outcomes - Compare & Reduce Variation in DKG-Certified Prostate Cancer Centres"

Short title: PCO-D

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## 1. Abstract and registration number

### 1.1. Abstract

Background: The assessment of health outcomes quality beyond survival rates is of particular importance with regard to prostate cancer, as the four most commonly applied treatment strategies (radical prostatectomy, percutaneous radiotherapy, LDR or HDR brachytherapy, active surveillance) each have specific side-effect patterns, which significantly co-vary with provider and patient/disease characteristics. In the past, numerous observational studies have investigated the advantages and disadvantages of different strategies in terms of survival and major physical side-effects such as incontinence, erectile dysfunction and bowel problems, as well as differences between clinicians. Possible psychological and social effects, such as fear of progression/recurrence of the disease or reduced participation in public life, in addition to the physical consequences of treatments are contributing to the complexity of health outcome assessments.

Objectives of the study: The primary objective of the study is to compare the quality of health outcomes (patient-reported and clinical) in participating prostate cancer centres that have been certified according to the requirements of the German Cancer Society with each other and - in the second step - with international centres. The secondary objective of the study is the analysis of selected (and, in this form, new) methods for identifying potential pitfalls in patient inclusion and representation, in the user-friendliness of the survey tool as well as in data linking (formative evaluation of methods).

Methods: In this multicentric observational study with consecutive full survey of the study population, patients with localised prostate cancer are interviewed at baseline and then periodically following therapy (follow-up to 10 years) using standardised tools. The survey data will be linked to clinical features gathered by the centres. Additionally characteristics of the centres are recorded. Statistical analysis is performed using the common descriptive and (multilevel) regression analysis methods. Health outcomes are compared case-mix-adjusted.

Anticipated results: Statements about the quality of care in prostate cancer centres taking into account the patient's perspective and where applicable regional/hospital-related differences. Measures to improve quality in certified centres will be taken based on the results of the study. It is anticipated that the differences in the quality of health outcomes will decrease over time as measures are introduced in less high-quality centres. Possibilities for the identification of individual measures to improve poor quality of life shall additionally be highlighted.

### 1.2. Registration number

German Clinical Trials Register (DRKS): DRKS00010774, recorded on 28 June 2016

## 2. Responsibilities

2.1. Study management

The primary responsibility for implementing the project lies with Dr. med. Simone Wesselmann and Dr. rer. medic. Christoph Kowalski (Deutsche Krebsgesellschaft e. V., Kuno-Fischer-Str. 8, 14057 Berlin, +49 (0)30 322 93 29-47). Responsibility for the coordination of data collection lies with the German Data Coordination Centre (2.2.1.), while every participating clinic (2.2.3) is responsible for the collection and anonymised forwarding of data. Patients are represented by the patient support organisation Bundesverband Prostatakrebs Selbsthilfe e. V. (BPS) (2.2.2.).

2.2. Participating institutions with responsible investigator / contact person

*2.2.1. German Data Coordination Centre*

OnkoZert GmbH, Gartenstraße 24, D-89231 Neu-Ulm, +49 (0)1 51 / 40 21 20 25: Sebastian Dieng, Leitung XML-OncoBox, Head of Data Management, System Manager for Prostate Cancer Centres.

*2.2.2. Representatives for patient support organisation*

German Federal Association for Prostate Cancer Self-Help, Thomas-Mann-Str. 40, D-53111 Bonn, 0228 33889 – 500, Günter Feick, Ernst-Günther Carl

*2.2.3. Participating clinics (DKG-certified prostate cancer centres) with contact persons (as of: 08 September 2016)*

1. Prostate Cancer Centre Straubing, St. Elisabethstr. 23, 94315 Straubing, Dr. med. Christian Gilfrich
2. Prostate Cancer Centre Sindelfingen, Arthur-Gruber-Str. 70, 71065 Sindelfingen, Prof. Dr. med. Thomas Knoll
3. Prostate Cancer Centre Oberhausen/Niederrhein, Steinbrinkstraße 96a, 46156 Oberhausen, Dr. med. Franz Kaiser
4. Interdisciplinary Prostate Cancer Centre AMEOS Clinic Haldensleben, Kiefholzstraße 27, 39340 Haldensleben, Prof. Dr. med. Frank Heron

5. Martini-Klinik, Prostate Cancer Center Hamburg, Martinistraße 52, 20246 Hamburg, Dr. med. Burkhard Beyer
6. Prostate Centre Wolfsburg, Sauerbruchstraße 7, 38440 Wolfsburg, Reinhard Hofmann, Doctor
7. Prostate Cancer Centre Ludwigsburg, Posilipostraße 4, 71640 Ludwigsburg, Dr. med. Bastian Müller
8. Prostate Cancer Centre Trier, Barmherzigen Brüder Hospital, Nordallee 1, 54292 Trier, Dr. med. Claus Luxemburger
9. Prostate Cancer Centre Vinzenz Hospital Hannover, Lange Feld Straße 31, 30559 Hannover, Dr. med. Martin Burmester
10. Prostate Cancer Centre University Clinic Cologne, Kerpener Straße 62, 50937 Cologne, Prof. Dr. med. Axel Heidenreich
11. HELIOS Prostate Cancer Center Erfurt, Nordhäuser Str. 74, 99089 Erfurt, Prof. Dr. med. Thomas Steiner
12. University Prostate Cancer Centre Bern, Inselspital, Freiburgstraße 4, 3010 Bern, Switzerland, Prof. Dr. med. Martin Spahn
13. Prostate Cancer Centre Rostock, Ernst-Heidemann-Straße 6, 18057 Rostock, Prof. Dr. med. Oliver Hakenberg
14. Prostate Cancer Centre Hegau-Bodensee Singen, Virchowstraße 10, 78224 Singen, Dr. med. Jens Tonhauser
15. Tübingen Prostate Cancer Centre Eberhard-Karls-University, Hoppe-Seyler-Straße 3, 72076 Tübingen, Prof. Dr. med. Arnulf Stenzl
16. University Prostate Cancer Centre Erlangen, Rathsbergerstr. 57, 91054 Erlangen, PD Dr. med. Bastian Keck
17. Prostate Cancer Centre Ulm, University Clinic Ulm, Prittwitzstraße 43, 89075 Ulm, Dipl.-Dok. Saha Dedic
18. Prostate Cancer Centre University Clinic Münster, Niels-Stensen-Str. 12, 48149 Münster, Prof. Dr. med. Axel Semjonow
19. Prostate Cancer Centre Brüderkrankenhaus St. Josef Paderborn, Husener Straße 46, Dr. med. Andreas Kutta
20. Prostate Cancer Centre Gütersloh Clinic, Reckenberger Straße 19, 33332 Gütersloh, PD Dr. med. Rüdiger Kläm
21. Prostate Cancer Centre Dortmund-Ost, Klinikum Westfalen GmbH, Urologie Clinic, Am Knappschaftskrankenhaus 1, 44309 Dortmund, Dr. med. Stefan Orth

22. Prostate Cancer Centre St. Antonius-Hospital Gronau, Möllenweg 22, 48599 Gronau, Dr. med. Gabriele Poppenburg
23. Prostate Cancer Centre Bielefeld, Schildescher Straße 6, 33611 Bielefeld, Prof. Dr. med. Jesco Pfitzenmaier

## 2.3. Project sponsors

Movember Foundation, Melbourne, AUS, partial financing; Deutsche Krebsgesellschaft e. V., OnkoZert, participating centres (own resources); Förderverein Hilfe bei Prostatakrebs (FHbP) for the administration of funds from Germany provided by the Movember Foundation.

## 2.4. Scientific Advisory Board

Günter Carl, Förderverein Hilfe bei Prostatakrebs (FHbP), Bonn

Prof. Dr. Jan Fichtner, Evangelisches Klinikum Niederrhein, Oberhausen

Prof. Dr. Michael Fröhner, Universitätsklinikum Dresden

Prof. Dr. Hartwig Huland, Martini-Klinik Universitätsklinikum Hamburg-Eppendorf

Prof. Dr. Thomas Wiegel, Universitätsklinikum Ulm

## 3. Rationale

3.1. Background and current state of research

With an estimated 65,830 patients initially diagnosed in 2010, prostate cancer is the most common cancer among men in Germany [1]. 12,676 people die from prostate cancer annually in Germany. With the, until recently, significantly increasing and ultimately stagnant incidence, whose development is probably due, to a large extent, to the use of the PSA test, the age-standardised mortality rate is declining, with a current relative five-year survival rate of 93 % [1]. The highest new diagnosis rate in Germany is in the 70-74 age range. The lifetime risk of disease is 13.2 %, and the lifetime risk of death 3.3% [1].

The health outcomes quality beyond survival rates is of particular importance with regard to prostate cancer, as the four most commonly applied treatment strategies (radical prostatectomy, percutaneous radiotherapy, LDR or HDR brachytherapy, active surveillance) each have specific side-effect patterns, which significantly co-vary with provider and patient/disease characteristics [2,3]. In the past, numerous observational studies have investigated the advantages and disadvantages of different strategies in terms of survival, as well as major physical side-effects such as incontinence, bowel problems and erectile dysfunction (e.g. [4-7]). Possible psychological and social effects, such as fear of progression/recurrence of the disease or reduced participation in public life, in addition to the physical consequences of treatments are contributing to the complexity of health outcome assessments [8].

As the fundamental superiority of any one treatment strategy over the others has not yet been proven, various efforts have been made to test this in randomised trials. This includes, for example, the PREFERE trial, which is currently recruiting [9].

In view of patient centeredness, the assessment of health-related quality of life (QOL) in general, and of erectile function, intestinal problems or urinary incontinence in particular, is of considerable importance. Not only can measures derived from QOL analyses be used to improve structures and processes for care [10,11]. They can also be used to identify individual patient-relevant measures or to compare providers and help identify causes for differences in quality through the combination of structural and process data [12,13]. For this however, standardized QOL recording implemented in the routine therapy is a necessary prerequisite.

3.2. DKG certification system: collection of quality indicator data and patient-reported outcomes (PROs)

Since the introduction of the German Cancer Society (DKG) certification system for prostate cancer centres in 2008, the number of patients being treated at these centres has risen [14,15]. In 2013, this amounted to 20,682 initially diagnosed patients from 94 prostate cancer centres, which treated a median 155 primary patients [14]. In order to be (re-)certified by the German Cancer Society, centres must meet the requirements formulated in the survey sheet [16]. The documented data are tested for completeness and plausibility and processed for benchmark purposes [14]. As part of tumour documentation for the cancer registry, pre- and post-therapy clinical and treatment parameters are also gathered. These are documented in various tumour documentation systems, and can be harmonised with the OncoBox developed by the OnkoZert certification institute so that, looking ahead, overall and/or disease-free survival, stratified according to treatment type or treating centre, can be determined. Unlike the documentation of clinical structures, processes and operational results (revision surgery, wound infections), the systematic, longitudinal assessment of patient-reported outcomes (PROs), as well as QOL, currently only takes place in the individual centres [17].

### 3.3. "Prostate Cancer Outcomes Study - Compare and Reduce Variation" - an international comparison of treatment and quality of health outcomes

Ideally, PROs are collected regularly in order to map the development of quality of life over time and in conjunction with clinical indicators and other patient characteristics, such as the socio-demographic data. This is used primarily for case-mix adjustment for a fairer comparison of providers [18,19], and secondarily, the identification of patient groups that have been affected in a particular way [20]. Recently, a set was developed from the ICHOM (International Consortium for Health Outcomes Measurement) initiative for mapping patient-relevant outcomes for patients with localised prostate cancer, for which regular repeat measurements over a period of up to ten years after diagnosis or primary therapy were also suggested [21] (cf. Appendix 4). As part of the "Prostate Cancer Outcomes Study - Compare and Reduce Variation", initiated and funded by the Movember Foundation, this data set is to be gathered and compared on a standard basis in prostate centres in a variety of countries (currently Australia, Austria, Canada, Germany, Switzerland, Ireland, Italy, Spain, UK, USA, Netherlands and New Zealand). The project described here is the German substudy of the Prostate Cancer Outcomes Study, for which the data collection and much of the evaluation are performed independently. The forwarding of anonymised data in the next step allows the subsequent comparison with results from other countries (cf. Chapt. 7.1. and Appendix 5).

The linking of different prospective data sources for the comparison of providers requires a considerable effort with regard to coordination and data protection. Individual initiatives have found partially functioning solutions, for example, the merging of the American SEER with CAHPS data [22]. The

linking of different personal data sources therefore regularly poses challenges in coordination and data protection for health services research in Germany, as well as numerous other countries. This applies, for example, to the linking of register, billing and patient survey data [23]. As Germany lacks the required legal basis for data linking, the informed consent of patients must always be sought. Depending on the purpose of data linking and type of evaluation, the sensitive interests of third parties, for example the centres involved, must also be taken into consideration. If the merging of survey and clinical respectively treatment data within a research project occurs prospectively, it is, in principle, quite possible to obtain consent with an appropriate study protocol [24-26]. Often, however, at the time of data collection or reporting, for example of registry data, it is not yet clear how and with which other data sources it will be evaluated, which, firstly, would require a comparatively time-consuming retrospective obtaining of consent. Secondly, the pseudonymisation of registry data essentially complicates linking with other data sources. In this study, a method is used in which personal data is stored locally in a uniform collection infrastructure in participating centres and data is merged and assessed anonymously.

### 3.4. Rationale for the study

To date, there has been a lack of uniform, patient reported and patient relevant metrics for comparing the quality of health outcomes of various providers in the treatment of localised PCa [27].[1] The project described here allows this comparison and at the same time examines how the standardised assessment of clinical and patient-reported results can be transferred into routine practice. The participating centres will thus be given an instrument for tracking their patients' health outcomes over time and comparing them with those of patients from other centres in Germany and abroad. In addition, they will have the opportunity to identify individual measures to improve poor quality of life [11].

### 3.5. Benefit/risk assessment

This is a non-interventional study in which clinical data that has already been collected during treatment shall be linked to patient-reported observation data, to be collected additionally, and subsequently evaluated. No study-specific risk is anticipated. The benefit for centres and future patients (group benefit) consists of the timely comparison of outcomes and identification of measures for improvement. The immediate benefits for the individual patient (personal benefit) consists of individual, indicator based monitoring - provided that the centres make use of this opportunity - and any

[1] This study refers to localised PCa; the statement is valid, for (almost) all oncological diseases, not accounting for possible exceptions.

interventions based on this in the event of poor quality of life. No study-specific insurance is provided.

3.6. Compensation for expenses

Participating patients shall receive no compensation for expenses.

## 4. Objectives of the study

The primary objective of the project described here is to compare the quality of outcomes (PROs and clinical outcomes) in the participating DKG-certified prostate cancer centres, with simultaneous adjustment for the patient mix [19]. In the second step, the quality of results in the DKG-certified prostate cancer centers is to be compared with those of the international project partners (cf. Chapter 7.1. and Appendix 5). Should any differences between the centres become apparent, these are to be clarified through centre (structures, processes) and treatment characteristics. To this end, PROs are collected both before and after treatment, and then annually, and linked to data from tumour documentation, additionally collected (ICHOM standard set-based) data and the certification system through the OncoBox tumour documentation harmonisation tool (and, if required, structured quality reports). The linking of PROs and clinical data is performed in the hospitals. As described in Chapter 7, data is forwarded anonymously from the clinics to OnkoZert/DKG. Pursuant to the superior (international) project objective of "Compare and Reduce Variation", measures to improve care are to be identified based on the results. The following is thus formulated as a research question for the primary objective of the study: "Are there differences in the quality of results following localised prostate cancer between DKG-certified centres, between these centres and international institutions and, if so, can structural and procedural characteristics be identified to explain these differences?"

The secondary objective of the study is the analysis of selected (and, in this form, new) data collection methods for identifying potential pitfalls with patient inclusion and representation, in the user-friendliness of the survey tool and data linking. Based on the evaluation of this methodological data (e.g. variation and determinants of response rate), any necessary measures are identified to optimise data collection in order to transfer the procedure to routine clinical practice. The contents of the study is therefore important and can also be used for formative evaluation. Comparison with international partners gives us reference values for data quality. In addition, patient and provider comments and queries are documented and evaluated in terms of a user experience analysis. The following is thus formulated as a research question for the secondary objective of the study: "How well suited is

the proposed method for the routine, concomitant measurement of the quality of outcomes after localised prostate cancer and can elements with a need for subsequent improvement be identified?"

## 5. Patients and methods

### 5.1. Study design

This is a prospective, multicentric observational study consecutively incorporating all patients of participating certified centres who, as of 1 July 2016 (until 30 June 2018, continuation intended), meet the inclusion criteria, and continues to survey them for a period of ten years. The study is restricted to DKG-certified centres, as these already keep the necessary routine documentation of much of the necessary component of the study data (primarily clinical indicators) and allow the linking of the tumour documentation system to the OncoBox. In exceptional cases, centres that intend to apply for certification may participate. A statement on the possibility of the transferability of results to non-certified clinics and certified centres not participating in the study can be made following comparison of the metrics results or freely accessible structural parameters (e.g. due to the structured quality reports). Within the participating centres, statements can be made on potential selection bias (participants vs. non-participants in the PRO survey) with regard to certain characteristics by means of the data collected for all patients for certification purposes in the course of routine practice (e.g. disease severity, age).

### 5.2. Patients

Included in the study are all primary cases with localised prostate cancer who have given their informed consent to participating in the study. Primary case patients are regarded as patients with initial contracting of a disease as a subset of all centre cases (centre cases as defined in Section 1.2.1 of the prostate cancer centre survey: "all patients with a diagnosis of prostate cancer, localised and/or metastasised, primary diagnosis or recurrence or metastasis, who have been admitted to the centre or the tumor conference and received significant portions of their treatment there (surgery, radiotherapy, systemic therapy, watchful waiting, active surveillance or similar.); a patient can be counted as a centre case for one centre only; second opinion patients are not counted; interdisciplinary treatment plans must exist; time of counting is their (initial) presentation in the centre; coverage in the tumour documentation system must be complete") [28]. Exclusion criterion: inadequate language skills to answer a German or, if available, a foreign-language survey (to be expected over the course of the project, validation is pending). The patient's regular doctor shall make the decision

on suitability. In the event of patient unsuitability, the corresponding field of "study exclusion/participation refused" must be marked in the tumour documentation system.

### 5.3. Number of cases

All patients who are receiving treatment in the participating centres and meet the inclusion criteria should be included consecutively. For a meaningful comparison of the centres, high and as representative as possible participation is required, and to achieve this, multiple reminders are intended (cf. Chapt. 5.9.). As this is an observational study with exploratory characteristics, with the consecutive inclusion of patients who meet all relevant criteria, the statistical calculation of the number of cases is not necessary based on expected effect sizes.

### 5.4. Informing patients about the study and consent

Patients are informed about the possibility of participation in the study by the study coordinator of the study centre or a designated representative. After a detailed explanation of the study and receipt of a patient information document (cf. Appendix 1), the patient is asked to give his written consent. The consent form (cf. Appendix 1) includes explicit consent to the recording of patient data, for the linking of survey data with clinical data and its anonymous forwarding to the study centre and subsequent evaluation. Consent may be revoked at any time and without giving reasons. In this case, notification can be made through the corresponding field in the OncoBox/tumour documentation system. The patient gives their consent in writing. Should the patient not give their consent of fail to meet the defined inclusion criteria, the corresponding field in the OncoBox must be marked.

### 5.5. Timing of measurements

In accordance with the ICHOM Reference Guide (cf. Appendix 4), the times of measurement are: at baseline (T0, pre-therapeutic), relevant socio-demographic data, clinical features and the PROs are collected. Follow-up surveys are carried out six months after primary therapy or inclusion in AS and WW (T1), twelve months after primary therapy or inclusion in AS and WW (T2) and then every year up to 10 years after primary therapy (T3-T11, cf. Fig. 1: Patient Flowchart); in case of index events next measurements are at six and twelve months after the event and then annually.

### 5.6. End points

Firstly, the end points are the six quality of life dimensions of "incontinence", " irritative/obstructive", "gastrointestinal", "sexuality", "hormonal" (all EPIC-26) and "libido" (supplementary question according to ICHOM data set), each of which is assessed after six and twelve months, and then annually, by

survey. The evaluation of the five EPIC-26 quality of life dimensions is performed according to the Scoring Manual (Appendix 6), as a mean value for items belonging to a dimension for subjects with at least 80% answered items. "Libido" is a single item. Other end points are overall survival and progression-free survival, which is assessed continuously through the centres as part of the clinical cancer registry.

5.7. Statistical analysis

The national statistical evaluations are performed jointly by OnkoZert (Alisa Lüll, MSc Mathematical Biometrics) and the German Cancer Society (Dr. rer. medic. Christoph Kowalski, MA Sociology), and the international analyses by the International Data Coordination Center (responsible: Prof. Sue Evans) of Monash University and UCLA, as described in Chapt. 6 Appendix 5.

*5.7.1. Quality of life*

Quality of life dimensions are reported and compared separately for the DKG centres per post-therapeutic time of survey for regular treatment centres: on the one hand as a crude average, and on the other as a risk (i.e. case-mix-)adjusted value as described by Iezzoni et al. and implemented for patient-reported information, for example as with Kowalski et al. [18,19]. As there is no established standard for risk-adjusted comparison of quality of life with localised PCa to EPIC-26 data, a three-step exploratory process is performed for five EPIC 26 and the libido dimension. The first step is the identification of relevant influencing variables. For this purpose, in the first step the potential influencing variables at $p \leq 0.05$ are determined in a linear regression mode based on the baseline variables (the following, as collected in the survey and documentation: nationality, insurance status, education, age, pre-therapeutic quality of life, comorbidity, T, N, M (each at baseline in non-operated patients and pathological in operated patients), Gleason score, relevant pretherapeutic PSA level). In the second step a check is performed per quality of life dimension to determine whether these potentially influencing variables are distributed differently over the treatment centres, and thus whether the "risk of complex patients" varies. Here, with $ICC \geq 0.01$, a lower value is used in order to take into account risks that are unevenly spread only sporadically. By analogy to Iezzoni et al., in the third step the risk-adjusted values are calculated and reported per quality of life dimension and centre, as well as for treatment type.

Should there be any differences between centres, the structural and process characteristics of participating centres are identified by means of multilevel models that are associated with the differences [29-31]. In order to determine relationships between the centre features (number of beds, number of primary cases, ownership, teaching status, expertise treatment units) and the selected

treatment and quality of life, hierarchical linear models are calculated with the influencing variables identified above and the treatment type as independent level-1 variables and the centre features as independent level-2 variables. In order to depict changes in the quality of life dimensions over time, multilevel models are calculated (again per dimension) as before, supplemented by the "time of measurement" level (then Level 1) *in* Patients (Level 2) *in* Centres (Level 3).

*5.7.2. Survival*

In order to determine the risk of "recurrence", "remote metastasis" and "death" occuring, the cumulative incidence functions are estimated using the Aalen-Johansen estimator, taking right censoring into account. A joint model is additionally calculated in order to determine the effect of baseline influencing variables and longitudinal variables (quality of life dimensions and PSA value) on progression-free survival.

The same models based on the participating centres are suggested for the international comparison of quality of life and survival. As the ultimate implementation and data collection can vary in the participating countries, a deviating analysis plan cannot be ruled out, cf. international study protocol (Appendix 5), in which as yet only the following statement is made: "Conduct internal analysis of outcomes in order to identify organisations with better and worse outcomes and to identify contributing structure and process factors"(p. 14).

*5.7.3. Management of missing values*

The aforementioned analyses must initially be performed without the replacement of missing values. Missing values are then replaced, on the one hand, through multiple imputation and on the other, (if necessary) by pseudo-observations, analogously to Andersen & Perme [32]. Once the missing values have been replaced, the aforementioned analyses are repeated.

5.8. Formative evaluation

In order to pursue the secondary study objective, the formative evaluation of the chosen method, exploratory evaluations are made of the response rate, missing value and representation diagnostics on both a centre-wide basis, and comparatively between centres. For this purpose, the response rates are compared in the centres and correlated with the aforementioned centre features (response diagnostics). The response rates are delivered to the centres on a quarterly basis. The missing value diagnostic is used to identify variations between centres and the interrelationship with the patient

characteristics used for case-mix adjustment. These results are used in any required development of the survey instrument, for example, for the re-wording in the event of differences between survey answers to individual items that are dependent on social status. To determine whether the respondents represent the population of patients in Germany and Switzerland suffering from localised PCa, representation diagnoses are performed in order to identify underrepresented groups of patients. If the determination of this type of patient group varies in quality between centres, better achieving centres are requested to give the others tips on how to achieve this ("learn from the best").

### 5.9. Individual order of study

When introduced at certified centres, patients are informed of the study and asked for their consent by clinic staff. Assuming that informed consent is granted, the patient is included in the study population. Shortly after their inclusion, and in any event prior to therapy (in the case of active surveillance, as soon as possible following agreement), they are first presented with an online or paper survey using the standard text (EPIC-26 [33] and additional items, cf. Appendix 2) in the clinic. The survey is repeated after six and twelve months, and subsequently every year until up to ten years after the primary survey (if no index event occurs). In the event of an index event, a follow-up survey is performed six and twelve months, and then annually, after this occurs. When every survey is due, the patient is sent a link and password for opening and responding to the online questionnaire. Upon request (at baseline or at any time thereafter by notification), the patient can receive the questionnaire with an addressed return envelope at their place of residence. For every post therapeutic (in the case of AS: performed after inclusion) survey, up to three reminders/thank you letters based on the Dill Mans Total Design Method [34] are sent: ten days after initial notification - a reminder e-mail with renewed notification of the link and password or, for paper-based surveys, a postal reminder; 21 days after initial notification - postal reminder with paper-based questionnaire and return envelope; 42 days after initial notification - reminder e-mail with renewed notification of link and password or, for paper-based questionnaires, a postal reminder.

The granting of consent is also accompanied by the documentation of clinical data as per the ICHOM standard sets as laid out in Appendix 4. As described in Chapter 8, the data transmitted to the relevant tumour documentation system is transferred to the OncoBox and linked to the survey data from the web application. If the patient has opted for the paper questionnaire, the questionnaire is transmitted by the responsible documentation officer to the OncoBox. Assignment in the centre is performed via a pseudonymising number generated using the OncoBox. This means that assignment is possible only in the centre by an authorised employee. In the follow-up, the questionnaire is re-

turned by postage-paid envelope. Optionally, in the follow-up clinical indicators are recorded either directly through the tumour documentation system and/or additionally by the patient based on their diagnostic data.

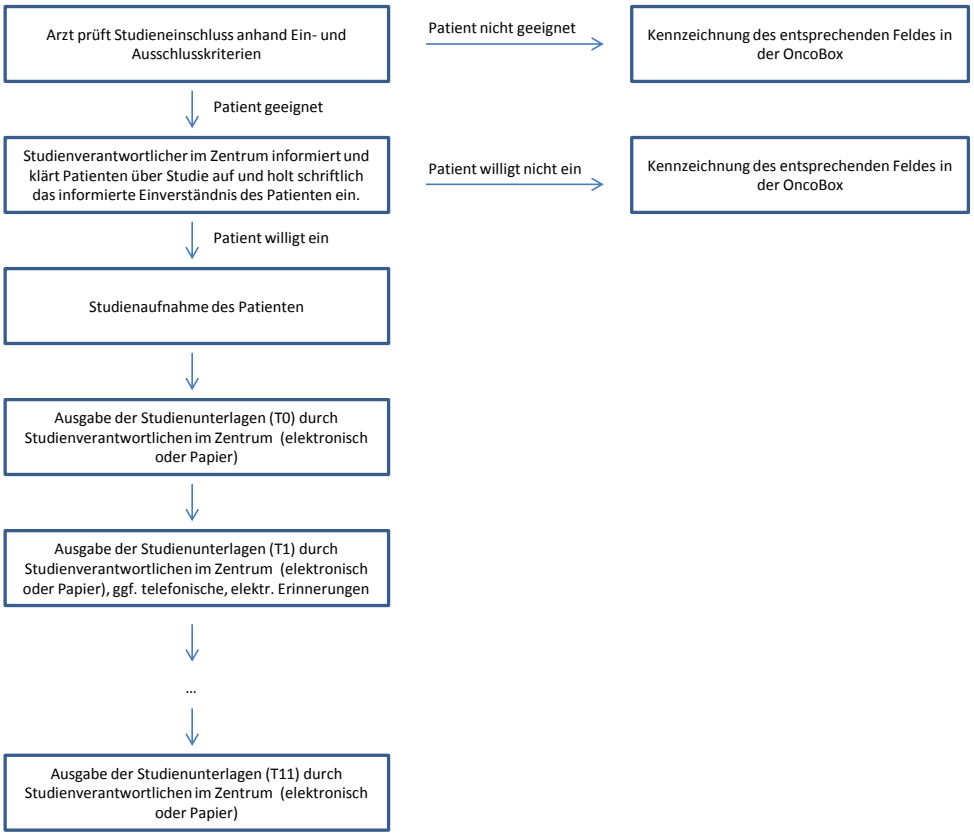


Fig. 1: Patient Flowchart

## 5.10. Duration of study, termination criteria

From 1 July 2016 patients will initially be consecutively included over a period of twenty-four months, with follow-up surveys for a period of up to ten years. It is planned that thereafter the procedure will be transferred into routine practice via a concurrent healthcare research project. Due to the non-interventional design, no risks to the patient are expected, a priori no defined termination criteria are laid down for the examination as a whole. In individual cases, the study is terminated in the event of the withdrawal of consent.

## 6. Undesired events

Study-induced events are not to be expected during this observational study. Every letter to the patient contains information (name, telephone number) for the following contact persons in the regular treatment centre for patients with acute needs: access to Prostate Cancer Centre, psycho-oncology, social work. An employee is also listed for queries (from 2.1./2.2.1./2.2.2.).

## 7. Data Management

### 7.1. Data collection

Collected are variables listed in the ICHOM set, plus a selection of other sociodemographic, disease and treatment related indicators that form part of the data gathered during the certification or the cancer registry, and further prospective respectively follow-up sociodemographic and patient experience measures. These are supplemented by structure and process parameters that are freely available or have been generated from the certification system of the treatment facilities. Patient-reported data is collected locally by participating centres through the online tool developed by OnkoZert or paper questionnaires. Invitation and reminders are the responsibility of the local staff who have personal data at their disposal. When using the online tool, data is retrieved by the centres. For the data matching survey on clinical parameters, an identification number (pseudonymisation) is generated for each patient. The other indicators (e.g. severity of illness, treatment regimens, year of birth, etc.) are taken from the patient's records and transferred locally into the OncoBox that performs the data matching process (survey - clinical parameters) via identification number (cf. Fig. 2: Individual Flowchart Data Management). Personalised data is then available to the centres so that they can take customised measures as required. Before transmitting the data to OnkoZert/DKG, references to persons and the identification number are removed so that the data leaves the centre anonymously. The matched data (survey + clinical parameters) is thus available to the evaluators, DKG and OnkoZert, in anonymous form, and is processed and stored in this form outside the centres. This anonymous data set is made available to the International Data Coordination Center.

Unlike existing approaches for linking PROs and registry data [22,35] , there is no transfer of personal PRO data from the clinics, i.e. merged personal data is only available locally in the centres, while the merged data leaving the centres is anonymised. This is shown schematically in Fig. 3.

Using OncoBox, data sets are checked for completeness and plausibility by the centre using OncoBox, anonymised (i.e. all references to persons and centres are removed) and transmitted to OnkoZert and the DKG office (dispatch trigger: centre). It should be noted that no data is stored in the OncoBox

- the only source of clinical information is the tumour documentation system, where merging with the structural and process parameters of the treatment centres takes place. The individual measurement instruments are comprehensively tested; for this reason, no additional piloting is performed. Should any changes occur during the study period, they are documented, these will be established and documented in an updated study protocol and immediately communicated to the participating centres.

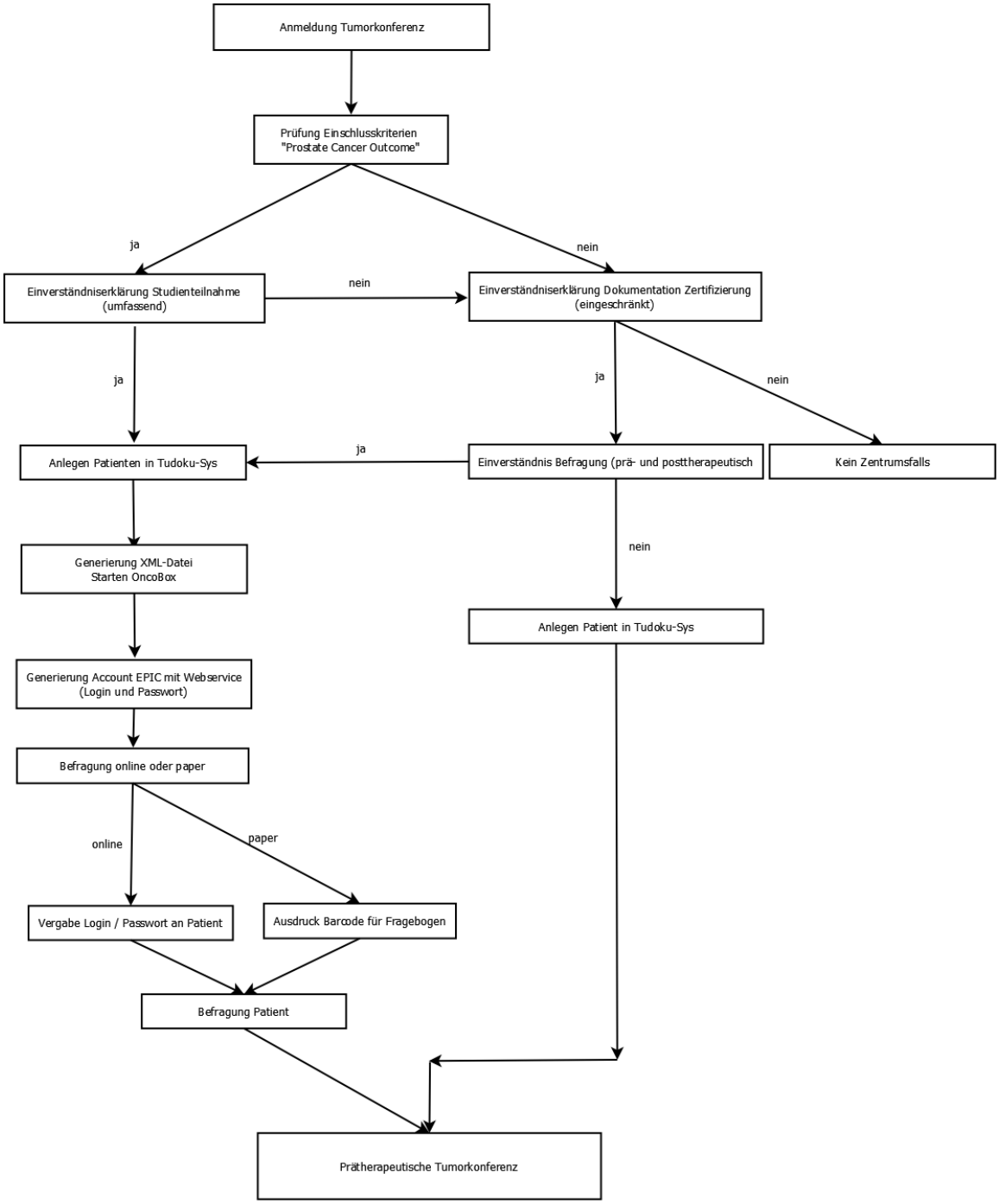


Fig. 2: Individual Flowchart Data Management

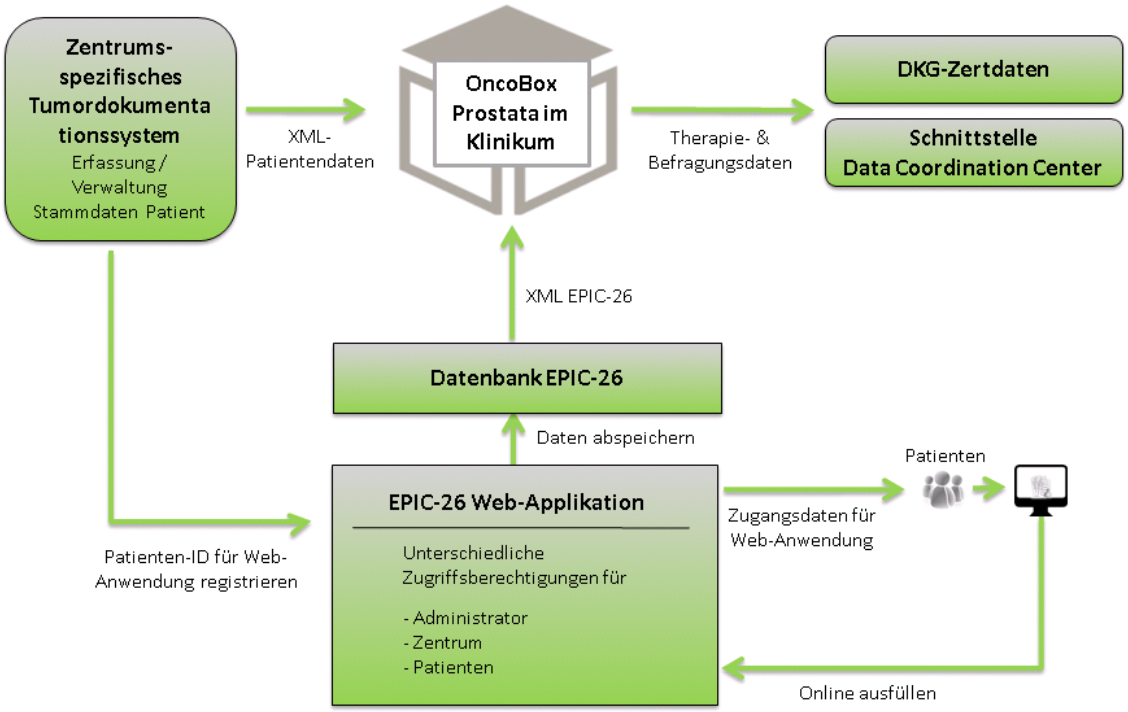


Fig. 3: Flowchart Data Management Centre - German Data Coordination Center (schematic)

Data collected is as follows, by data source:

a) Individual data I - registry/certification data: cf. data field specification Appendix 3. Registry data is collected electronically.

b) Individual data II - patient-reported outcomes (PROs): EPIC-26 [36-39] and additional items according to the ICHOM guide plus country-specific sociodemographics (cf. Appendix 2). Additionally, in the follow-up: current PSA value and, if applicable: date of relapse; PSA value in relapse; date of remote metastasis; PSA value for remote metastasis; secondary tumour; hormone therapy; radiotherapy; surgery; other treatment (cf. data field specification Appendix 3). During the project and/or in the follow-up and depending on the development of the international comparative project and the participating partners, five scales of the EORTC QLQ-C30 are used, if required, to retrieve information on physical, social, emotional and cognitive functionality and role function [40], fear of progression [41] , social distress [42] or the HCAHPS survey [43] on experiences of hospitalisation, giving further insight into patient-relevant differences in the reality of health care. Data is gathered at baseline, six and twelve months after the completion of primary treatment or inclusion in AS and WW, and then annually for a period of up to 10 years as described in 5.6. Individual Study. Data with reference to per-

sons shall only be stored locally in centres. Electronic questionnaires are transmitted to the centres via the web application, paper questionnaires are uploaded to the web application first locally and, over the course of the study and if required, centrally and then transmitted to the centres.

c) Hospital data: data on structures and processes of the certification system: e.g. case number, certification date and from structured quality reports: e.g. sponsorship, teaching status

### 7.2. Data transfer for the international study

For the international comparative project, anonymised data is additionally pseudonymised with regard to centres (key retained by competent OnkoZert and DKG employees) and transmitted to the International Data Coordination Center in accordance with Appendix 5, Chapter 6.4. Unlike in Appendix 5, Chapter 9, the German sub-study requires explicit consent (opt-in) rather than opt-out variant.

### 7.3. Quality assurance

Using OncoBox, data sets are checked for completeness and plausibility by the centre using OncoBox, anonymised (i.e. all references to persons and centres are removed) and transmitted to OnkoZert and the DKG branches (dispatch trigger: centre). The plausibility check performed by the OncoBox includes an immediate correction request to the relevant document and significantly reduces the risk of incorrect entries and the inadvertent delivery of incomplete data. Documentation quality processes and structures are reviewed in the annual certification audit, whereby random entries are taken from patient records (sample: ~10%) for validation by experts.

### 7.4. Data storage and data protection

Patient related data collected in centres is stored locally for at least ten years following completion of the maximum ten-year follow-up phase. The centres involved shall ensure that only authorised persons have access to personal data, e.g. by access control through technical measures in secure rooms, user controls via password control for legitimisation and automatic screen locking, as well as access control through the assignment of different authorisations and differentiated ways of accessing individual fields (confidentiality). They must additionally guarantee that personal data will remain intact, complete and current during processing, e.g. through the avoidance of unauthorised or accidental data processing by blocking access to operating systems and/or data encryption and that the

data is verified as current by regular monitoring (integrity); and additionally that personal data is available at the right time and can be properly processed for anonymisation and subsequent transmission, e.g. through the clear and concise alignment of the data set and assigning of access authorisation to the required extent (while weighing these against the principle of confidentiality) (availability). Furthermore, they shall ensure that personal data can be assigned to its origin at all times, e.g. by documentation of the original data and its origin and the traceability of processing steps (authenticity). They must also ensure that it can be determined who has processed data at what time and in what way, e.g. by establishing clear responsibilities and accountability, as well as the logging of input and further processing of data (auditability). The procedures for the processing of personal data must be documented so as to be complete and current, and such that it can be traced within a reasonable timeframe. Documentation is performed partially through the web application and partially through the OncoBox/tumour documentation systems (transparency).

## 8. Ethical and legal aspects

Acceptance to the study takes place once informed consent has been granted by the patient in accordance with the attached consent form (Appendix 2). Anonymised data sets transmitted to OnkoZert and DKG are the property of OnkoZert/DKG. Data must be gathered in accordance with data protection law. The study must be planned, implemented and assessed in accordance with the recommendations for good epidemiological practice and the Helsinki Declaration. The study must be initially compiled after a period of no more than eighteen months; interim reports must subsequently be compiled on an annual basis for use by the centres. Furthermore, additional publications are anticipated for medical practice and science.

## 9. Bibliography


1. Robert-Koch-Institut, e.V. GdeKiD, Hrsg. Krebs in Deutschland 2009/2010. 9. Aufl; 2013
2. Chen AB, D'Amico AV, Neville BA et al. Provider case volume and outcomes following prostate brachytherapy. J Urol 2009; 181: 113-118; discussion 118
3. Begg CB, Riedel ER, Bach PB et al. Variations in morbidity after radical prostatectomy. N Engl J Med 2002; 346: 1138-1144
4. Herden J, Ernstmann N, Schnell D et al. [The HAROW study: an example of outcomes research: a prospective, non-interventional study comparing treatment options in localized prostate cancer]. Urologe A 2014; 53: 1743-1752
5. Lee JK, Assel M, Thong AE et al. Unexpected Long-term Improvements in Urinary and Erectile Function in a Large Cohort of Men with Self-reported Outcomes Following Radical Prostatectomy. Eur Urol 2015; 68: 899-905
6. Resnick MJ, Barocas DA, Morgans AK et al. The Evolution of Self-Reported Urinary and Sexual Dysfunction over the Last Two Decades: Implications for Comparative Effectiveness Research. Eur Urol 2015; 67: 1019-1025
7. Gavin AT, Drummond FJ, Donnelly C et al. Patient-reported 'ever had' and 'current' long-term physical symptoms after prostate cancer treatments. BJU Int 2015; 116: 397-406
8. King AJ, Evans M, Moore TH et al. Prostate cancer and supportive care: a systematic review and qualitative synthesis of men's experiences and unmet needs. Eur J Cancer Care (Engl) 2015; 24: 618-634
9. Stockle M, Bussar-Maatz R. [Localised prostate cancer: the PREFERE trial]. Z Evid Fortbild Qual Gesundhwes 2012; 106: 333-335; discussion 335
10. Basch E, Deal AM, Kris MG et al. Symptom Monitoring With Patient-Reported Outcomes During Routine Cancer Treatment: A Randomized Controlled Trial. Journal of Clinical Oncology 2015, DOI: 10.1200/jco.2015.63.0830
11. Klinkhammer-Schalke M, Koller M, Steinger B et al. Direct improvement of quality of life using a tailored quality of life diagnosis and therapy pathway: randomised trial in 200 women with breast cancer. Br J Cancer 2012; 106: 826-838
12. Jha AK, Orav EJ, Zheng J et al. Patients' perception of hospital care in the United States. N Engl J Med 2008; 359: 1921-1931
13. Talcott JA, Manola J, Chen RC et al. Using patient-reported outcomes to assess and improve prostate cancer brachytherapy. BJU Int 2014; 114: 511-516
14. Deutsche Krebsgesellschaft. Jahresbericht der zertifizierten Prostatakrebszentren. Berlin; 2015
15. Kowalski C, Ferencz J, Albers P et al. Quality assessment in prostate cancer centers certified by the German Cancer Society. World J Urol 2015, DOI: 10.1007/s00345-015-1688-z
16. Steffens JA, Ting O, Schmidt S et al. [Certified prostate cancer centers of the German Cancer Society : Current status 2 years after certification and future developments]. Urologe A 2010; 49: 910-915
17. Mehnert A, Lehmann C, Graefen M et al. Depression, anxiety, post-traumatic stress disorder and health-related quality of life and its association with social support in ambulatory prostate cancer patients. Eur J Cancer Care 2010; 19: 736-745
18. Iezzoni L, Hrsg. Risk Adjustment for Measuring Healthcare Outcomes. 4. Aufl. Chicago, IL: Health Administration Press; 2012
19. Kowalski C, Kuhr K, Scholten N et al. Adjustierung für Patientenmerkmale bei der Auswertung von Befragungsdaten. Das Gesundheitswesen 2013; 75: 660-666
20. Berglund A, Garmo H, Robinson D et al. Differences according to socioeconomic status in the management and mortality in men with high risk prostate cancer. Eur J Cancer 2012; 48: 75-84
21. Martin NE, Massey L, Stowell C et al. Defining a Standard Set of Patient-centered Outcomes for Men with Localized Prostate Cancer. Eur Urol 2014, DOI: 10.1016/j.eururo.2014.08.075

22. Chawla N, Urato M, Ambs A et al. Unveiling SEER-CAHPS(R): A New Data Resource for Quality of Care Research. J Gen Intern Med 2015, DOI: 10.1007/s11606-014-3162-9
23. Scholten N, Pfaff H, Raabe N et al. [The Willingness to Consent to the Linkage of Primary and Secondary Data: An Analysis Based on a Survey of Patients with Primary Breast Cancer in Northrhine Westfalia]. Gesundheitswesen 2015, DOI: 10.1055/s-0035-1564182
24. Kowalski C, Würstlein R, Steffen P et al. Vier Jahre Patientinnenbefragung im Rahmen der (Re-)Zertifizierung der Brustzentren in Nordrhein-Westfalen. Geburtshilfe und Frauenheilkunde 2011; 71: 67-72
25. March S, Powietzka J, Stallmann C et al. [The Significance of a Large Number of Health Insurance Funds and Fusions for Health Services Research with Statutory Health Insurance Data in Germany - Experiences of the lidA Study.]. Gesundheitswesen 2014, DOI: 10.1055/s-0034-1390443
26. Scholten N, Pfaff H, Raabe N et al. Die Bereitschaft zum Datenlinkage von Routinedaten und Primärdaten - Eine Analyse auf Basis der Befragung von Patientinnen und Patienten mit primärem Mammakarzinom in NRW. Das Gesundheitswesen submitted, DOI:
27. Porter ME, Larsson S, Lee TH. Standardizing Patient Outcomes Measurement. New England Journal of Medicine 2016; 374: 504-506
28. Zertifizierungskommission Prostatakrebszentren der Deutschen Krebsgesellschaft. Erhebungsbogen für Prostatakrebszentren der Deutschen Krebsgesellschaft. Berlin: Deutsche Krebsgesellschaft; 2015
29. Hearld LR, Alexander JA, Fraser I et al. Review: how do hospital organizational structure and processes affect quality of care?: a critical review of research methods. Med Care Res Rev 2008; 65: 259-299
30. Kowalski C, Lee SY, Ansmann L et al. Meeting patients health information needs in breast cancer center hospitals: a multilevel analysis. BMC Health Serv Res 2014; 14: 601
31. Hox JJ. Multilevel analysis. Techniques and applications. New York: Routledge; 2010
32. Andersen PK, Perme MP. Pseudo-observations in survival analysis. Stat Methods Med Res 2010; 19: 71-99
33. Beyer B, Huland H, Feick G et al. ["Expanded prostate cancer index composite" (EPIC-26): Results of functional treatment in patients with localized prostate cancer]. Urologe A 2015; 54: 1591-1595
34. Dillman DA. Mail and telephone surveys: the total design method. New York: Wiley & Sons; 1978
35. Katz SJ, Lantz PM, Janz NK et al. Patient involvement in surgery treatment decisions for breast cancer. J Clin Oncol 2005; 23: 5526-5533
36. Chipman JJ, Sanda MG, Dunn RL et al. Measuring and predicting prostate cancer related quality of life changes using EPIC for clinical practice. J Urol 2014; 191: 638-645
37. Chang P, Szymanski KM, Dunn RL et al. Expanded prostate cancer index composite for clinical practice: development and validation of a practical health related quality of life instrument for use in the routine clinical care of patients with prostate cancer. J Urol 2011; 186: 865-872
38. Schmidt S, Garin O, Pardo Y et al. Assessing quality of life in patients with prostate cancer: a systematic and standardized comparison of available instruments. Qual Life Res 2014; 23: 2169-2181
39. Szymanski KM, Wei JT, Dunn RL et al. Development and validation of an abbreviated version of the expanded prostate cancer index composite instrument for measuring health-related quality of life among prostate cancer survivors. Urology 2010; 76: 1245-1250
40. Aaronson NK, Ahmedzai S, Bergman B et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 1993; 85: 365-376
41. Halbach SM, Enders A, Kowalski C et al. Health literacy and fear of cancer progression in elderly women newly diagnosed with breast cancer - A longitudinal analysis. Patient Education and Counseling, DOI: 10.1016/j.pec.2015.12.012

42. Wright P, Downing A, Morris EJA et al. Identifying Social Distress: A Cross-Sectional Survey of Social Outcomes 12 to 36 Months After Colorectal Cancer Diagnosis. Journal of Clinical Oncology 2015, DOI: 10.1200/jco.2014.60.6129
43. Giordano LA, Elliott MN, Goldstein E et al. Development, implementation, and public reporting of the HCAHPS survey. Med Care Res Rev 2010; 67: 27-37

## Appendix 1: Information and declaration of consent

- Placeholder -

## Appendix 2: Questionnaire - EPIC 26, additional items and items for Sociodemographics (DRV)

- Placeholder -

## Appendix 3: OncoBox Data Fields

- Placeholder -

## Appendix 4: ICHOM Standard Set Localized Prostate Cancer Data Collection Reference Guide

- Placeholder -

## Appendix 5: International study protocol - Prostate Cancer Outcomes Global Initiative to Compare and Reduce Variation ("PCO-CRV")

- Placeholder -

## Appendix 6: Scoring Manual EPIC-26

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