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**TripleAiM1: a nationwide registry of de novo metastatic hormone sensitive prostate cancer with prospective quality-of-life assessment**

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TripleAiM1: a nationwide registry of de novo metastatic hormone sensitive prostate cancer with prospective quality-of-life assessment

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KEYWORDS

De novo metastatic hormone sensitive prostate cancer – Health-related quality of life– Treatment strategies – Real-world data – Value-based healthcare
ABSTRACT

Introduction

The treatment landscape for de novo metastatic hormone sensitive prostate cancer (mHSPC) is rapidly evolving. With an abundance of available treatment strategies, selecting the optimal strategy for an individual patient is becoming increasingly challenging. TripleAiM1 aims to evaluate the impact of mHSPC treatments on health-related quality of life (HRQoL) and to provide real-world data insights on diagnostics, treatment strategies, patient subgroups and related healthcare expenditure for mHSPC. The aspirational target of TripleAiM1 is that in the near future, a more tailored therapy can be offered based on the individual patient’s wishes and needs in accordance with the overarching principle of value-based healthcare.

Methods and analysis

We describe the TripleAiM1 study design; a nationwide registry comprising a retrospective and prospective cohort of patients with de novo mHSPC. Starting in May 2020, eligible patients are identified, selected and recruited in 14 participating hospitals in the Netherlands. Our hypothesis is that, in a real-world setting, differences in clinically meaningful HRQoL deterioration will be observed for treatment strategies over time. HRQoL data, assessed with patient-reported outcome measures, costs, and clinical data will be collected for 24 months.

For the retrospective cohort, all patients diagnosed with de novo mHSPC from January 2017 onwards are eligible for inclusion. Patient and tumour characteristics, imaging modalities, and treatment patterns will be analysed descriptively to provide a real-world overview. Time-to-event endpoints will be assessed using the Kaplan-Meier method and regression models will be employed to analyse
baseline characteristics associated with an increased likelihood of death, progression, and HRQoL
deterioration. Longitudinal mixed effects models will be employed to assess change of patient-
reported outcome scores from baseline until the end of follow-up.

**Ethics and dissemination**

Ethical approval was obtained from the Medical Research Ethics Committee Twente). Study results will
be published in peer-reviewed journals.

**Registration details**

The Netherlands Trial Register (NL9719)

**ARTICLE SUMMARY**

**Strengths and limitations of this study**

- Retrospective and prospective real-world data registry facilitating multiple studies within
  these cohorts
- Extensive health-related quality of life (HRQoL) data in multiple treatment subgroups
- Complete overview of all costs related to care activities on patient level during the full cycle
  of care
- Unique consolidation of data collection methods to improve data quality and enrich the
database
- Lack of power to compare HRQoL outcomes between treatment subgroups and risk of bias
  (non-randomised trial)
INTRODUCTION

Yearly, more than 13,000 Dutch men are confronted with a diagnosis of prostate cancer[1]. Of these, approximately 15% have metastatic disease at the time of diagnosis[2,3]. For decades, androgen deprivation therapy (ADT), consisting of bilateral orchiectomy, anti-androgens or luteinizing hormone-releasing (LHRH) (ant)agonist, has been the standard-of-care for patients with de novo metastatic hormone sensitive prostate cancer (mHSPC). However, treatment strategies combining ADT with upfront palliative radiotherapy to the prostate, docetaxel and/or an Androgen Receptor Targeting Agent (ARTA e.g., abiraterone, apalutamide or enzalutamide) have challenged ADT monotherapy as standard-of-care, ever since several randomised controlled trials (RCTs) concluded a survival benefit when adding either one, or multiple agents, to ADT[4-10]. These new treatment schedules have lengthened the time of hormone-sensitivity and delayed the time to clinical symptoms and deterioration with a comparable impact on overall survival, yet with different side effects and impact on health-related quality of life (HRQoL). Nevertheless, the prognosis of de novo mHSPC remains poor[11,12].

In this population where curation is not feasible, HRQoL is a critical outcome parameter for patients and clinicians [13,14]. Several patient-reported outcome measurements (PROMs) have been validated to objectify and monitor HRQoL in men with prostate cancer (e.g., Expanded Prostate Cancer Index Composite-26 (EPIC-26), European Organisation for Research and Treatment of Cancer (EORTC)-QLQ-C30, and Functional Assessment of Cancer Therapy (FACT)-prostate[13,15]. These PROMs are increasingly being used in mHSPC care to assess the patient’s perspective on disease symptoms, treatment tolerance and impact on HRQoL, as it has been postulated that both quantity and quality of life should be taken into account when tailoring therapy[16].
Nevertheless, with an abundance of treatment strategies to choose from, selecting the right strategy for the right patient is becoming increasingly challenging. There is a need for more detailed insights in real world data that reflect how treatments are initiated, combined and sequenced, how treatments impact a patient’s quality of life, and how their relative effectiveness profiles emerge outside clinical trial setting. Additionally, efforts should be made to predict which patient, considering both patient and tumour characteristics, responds better to which treatment strategy, to mitigate treatment side effects whilst improving survival outcomes and preserving HRQoL[16].

In this paper we describe TripleAiM1, a nationwide registry for patients with de novo mHSPC, which has been constructed to accelerate research on optimising patient care. We aim to evaluate the impact of mHSPC treatments on HRQoL and to provide real-world data insights on diagnostics, treatment strategies, detailed patient characteristics, and related healthcare expenditure for mHSPC. The aspirational target of TripleAiM1 is that in the near future, a more tailor-made therapy can be offered based on the individual patient’s wishes and needs.

METHODS AND ANALYSIS

Study design

TripleAiM1 has been initiated to uniformly obtain real-world clinical data, patient reported outcomes (PROs), and healthcare costs of de novo mHSPC patients in the Netherlands. As we aim to include overview data, survival data, and HRQoL data, we chose to incorporate a retrospective and prospective cohort in our registry, facilitating multiple studies within these cohorts (Figure 1). Due to the observational character of TripleAiM1, participation in either of the cohorts will not influence medical care, as treatment decisions are made at the discretion of the treating physician.
Patient population

Patients eligible for inclusion are men diagnosed with de novo mHSPC in one of the 14 participating regional, teaching and academic hospitals throughout the Netherlands. Prostate cancer diagnosis must be histologically confirmed by either biopsy of the prostate or, in absence of prostate biopsy, a serum PSA level >100 ng/ml and metastatic lesions on imaging suspect for metastatic prostate cancer. Moreover, patients must have had the complete radiological workup to confirm distant lymphogenous, bone or visceral metastasis.

Retrospective cohort

Eligibility criteria

For the retrospective cohort, patients diagnosed with de novo mHSPC from January 2017 onwards are eligible for inclusion. Patients will be excluded if they have one of the following: (1) a history of prostate cancer, irrespective of whether they received treatment or not; (2) histologically confirmed neuroendocrine small cell tumour; (3) lack of follow-up records within 6 months after diagnosis in one of the TripleAiM1 hospitals; (4) total follow-up of less than 6 months.

Sampling

Initial patient sampling will be performed by CTcue, a text mining programme which recruits eligible patients and collects additional patient data by using neurolinguistics programing and artificial intelligence to analyse electronic health records[17]. We will extend this sample with patients registered in the National Cancer Registry (NCR) of the Netherlands Comprehensive Cancer Organisation (IKNL) who were not found with CTcue[18]. More details on these data acquisition types can be found in the section “Data sources and collection methods”.
Sample size

Due to the retrospective study design, no specific sample size is required. Yet, we anticipate that we will include around 3000 patients who have been diagnosed with de novo mHSPC between January 2017 and January 2023. This estimate is based on a preliminary search conducted in one TripleAiM1 hospital, where 250 patients were found to be eligible for inclusion in this cohort. Extrapolating this number to the 14 participating hospitals, we expect to include around 3500 patients. However, when taking into account the varying size of the participating centres and the corresponding patient numbers, we expect that the final sample size will be around 3000.

Prospective cohort

Eligibility criteria

Patients are eligible if diagnosed with *de novo* mHSPC from May 2020 onwards in one of the participating hospitals. Eligible patients are older than 18 years, have no prior history of prostate cancer nor have they received initial treatment for prostate cancer >30 days prior to inclusion. No additional inclusion criteria comprising treatment strategy or patient characteristics were instated as we aim to assess real-world data. However, cognitively impaired patients and patients with an insufficient understanding of the Dutch language will be excluded, as their PROMs data may be less reliable.

Sampling

For the prospective cohort of the TripleAiM1 registry, patients will be identified, selected and recruited by treating physicians in participating hospitals.
Sample size

The registry has been designed to generate data for informative purposes and therefore, sample size is determined by pragmatic considerations based on the number of mHSPC patients in the national ProZib registry[1,2]. Included patients will be subdivided according to treatment strategy (e.g., ADT monotherapy, ADT + docetaxel (Doc), ADT + radiotherapy (RTx), ADT + abiraterone (Abi), ADT + enzalutamide (Enza), ADT + apalutamide (Apa), and triple therapies) and we aim to include at least 75 patients in each treatment arm. Moreover, as the treatment landscape for mHSPC will continue to change over the years, we will incorporate an ‘other treatment’ category which includes all types of treatment strategies of which group sizes are not substantial.

At the time of writing, 337 patients have been enrolled.

Data sources and collection methods

Clinical data, including patient and tumour characteristics, treatment information, survival outcomes (i.e., progression and overall survival data), adverse events, and data on costs and utilisation will be collected for both the retrospective and the prospective cohort. While HRQoL data will solely be collected from patients included in the prospective cohort. A multitude of data collection methods will be employed to collect all data (Figure 2). The consolidation of these data collection methods and sources will be performed in order to improve data quality and to enrich the database. In this section, we provide detailed information on the data sources and collection methods used.

Clinical data

IKNL

IKNL is an independent knowledge institute for oncological care in the Netherlands. IKNL facilitates nationwide identification of prostate cancer patients and independent data managers collect clinical
data from patient records [18]. As this clinical dataset did not encapsulate all the patient characteristics and clinical outcomes that we aim to assess, based on the *International Consortium for Health Outcomes Measurement* (ICHOM) *Standard Set for Advanced Prostate Cancer*, more data sources and data collection methods were employed to extract relevant data[14].

**Costs and utilisation data**

In the Netherlands, diagnosis-treatment-code (DBC) products form the basis of healthcare finance. Healthcare costs are not based on single activities, but on DBC products comprising a standard care path for each specific diagnosis. The price calculated for this DBC product is an abstraction of all costs and activities associated with the respective treatment[19]. Since all imaging, assessments, consultations, and hospital visits are related to a DBC product, healthcare expenditure and utility data regarding a specific diagnosis can easily be collected per patient from hospital systems and used for research.

LOGEX, a healthcare analytics company, will collect individual utility and expenditure data related to DBCs from hospital records to calculate real-world expenditure for single activities (e.g., diagnostic assessments and hospital visits) using mean costs, as there are substantial differences in diagnostic care pathways between patients. Notably, administrative healthcare data will be routinely validated using automated algorithms and a manual validation of outliers will be performed.

**CTcue**

CTcue uses data queries containing descriptive words to text mine patient records. As more than 70% of all data in patient records are stored as free text, CTcue can be used to find eligible patients and to collect patient data more easily and therefore, enrich the IKNL and DBC data 17].
Based on our data dictionary, we will search patient records with CTcue to obtain the desired data in a pseudo-anonymised and uniform matter. Each data query will be optimised with the help of a data scientist from CTcue to increase reliability. For validation of the query, we will compare patient level data acquired from hospital records with that from CTcue in two hospitals. Following automatic data extraction, all data items will be manually validated within CTcue to assure the quality of the acquired data.

**HRQoL data**

Multiple PROMs, addressing several aspects of quality of life (QoL), have been validated to quantify HRQoL in men with prostate cancer[13]. The EORTC-QLQ-C30 questionnaire is one of the most widely used cancer specific questionnaires to assess HRQoL. It comprises five functioning scales (physical, role, cognitive, emotional, and social), three symptom scales (fatigue, pain, and nausea and vomiting) and several single items regarding other symptoms and financial status[20]. Importantly, the EORTC-QLQ-C30 describes the patient’s global health status, representing their overall QoL.

While the EORTC-QLQ-C30 measures cancer specific QoL, the EPIC-26 provides prostate cancer specific QoL outcomes. It is recommended that both PROMs are administered simultaneously in patients with metastatic prostate cancer according to the *ICHOM Standard Set of Advanced Prostate Cancer*[14]. The EPIC-26 questionnaire measures function and bother on four domains (urinary, bowel, sexual, and hormonal) relevant to (metastatic) prostate cancer[21]. Furthermore, in patients receiving Taxane therapy, the FACT-Taxane is commonly used to assess HRQoL based on five subscales: physical, social/family, emotional, functional well-being, and Taxane related symptoms[22]. Moreover, to gain better insights into common symptoms of metastatic prostate cancer, symptom specific questionnaires will be used in addition to the EORTC-QLQ-C30, EPIC-26 and FACT-Taxane. The Brief Pain Inventory-Short Form (BPI-SF) includes four questions regarding pain intensity, seven on the level of pain that has interfered with the patient’s life, and a diagram to locate the pain[23]. The Functional
Assessment of Chronic Illness Therapy (FACIT)-Fatigue is a 40-item measure to assess fatigue and its impact on daily activities and function, and the FACT-Cognitive is a 37-item measure to assess cognitive function issues in cancer patients, and comprises four subscale domains (perceived cognitive impairments, impact of perceived cognitive impairments on QoL, comments from others, and perceived cognitive abilities)[24,25].

Following inclusion, prospectively included patients will receive the six previously stated questionnaires at predefined time intervals from the start up to 24 months to assess their HRQoL (Table 1). Efforts, such as a dashboard for patients tracking their HRQoL and conditionally administered questionnaires, are instated in an attempt to increase response rates and the patient’s willingness to respond.

Table 1- PROMs administration schedule

<table>
<thead>
<tr>
<th></th>
<th>Baseline (T=0)</th>
<th>Follow-up 1 (T=3)</th>
<th>Follow-up 2 (T=6)</th>
<th>Follow-up 3 (T=9)</th>
<th>Follow-up 4 (T=12)</th>
<th>Follow-up 5 (T=18)</th>
<th>Follow-up 6 (T=24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EORTC-QLQ-C30</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
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<tr>
<td>EPIC-26</td>
<td>x</td>
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<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
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<tr>
<td>FACT-Taxane</td>
<td>x</td>
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<tr>
<td>BPI-SF</td>
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<td>FACIT-Fatigue</td>
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<td>FACT-Cognitive</td>
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</tbody>
</table>

PROMs= Patient Reported Outcome Measures; T= time interval (in months); EORTC-C30= European Organisation for Research and Treatment of Cancer- QLQ-C30; EPIC-26- Expanded Prostate Cancer Index Composite-26; FACT= Functional Assessment of Cancer Therapy; FACIT= Functional Assessment of Chronic Illness Therapy; BPI-SF= Brief Pain Inventory- Short Form

* These questionnaires are administered conditionally

Table 1 shows that the BPI-SF, FACIT-fatigue and FACT-cognitive are conditionally administered in cases when patients positively answered predefined questions in regard to pain, fatigue and/or cognition on EORTC-QLQ-C30 and EPIC-26. These predefined questions are shown in Appendix 1.

The PROMs will be sent digitally to the participants via Questmanager, Brightfish, onlinePROMS, HiX or EPIC. This multitude in PROMs vendors is ascribed to the preference of participating hospitals,

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depending on local practice. Moreover, as the use of digital platforms may cause selection bias, written or verbal PROMs are allowed for patients with no email address and/or cell phone. The latter is necessary because most PROM vendors require obligatory two-step authentication to ensure patient data safety.

Data consolidation

All data will be collected and consolidated by trained employees from Medical Research Data Management (MRDM), a trusted third-party intermediary. MRDM will operate as a data processor for all TripleAiM1 data coming from participating hospitals. MRDM has official processor relations with all Dutch hospitals and a growing number of private clinics and first-line care, enabling them to collect and process medical data as if they were part of the institution itself. For data collection and consolidation, we have taken into account that some clinical data items will be extracted with both CTcue and IKNL. Therefore, when data of both is available, CTcue will be considered as the primary data collection method for clinical data. Subsequently, MRDM will process patient-identity data which they anonymise and encrypt before sending it in fully anonymised CSV files to the TripleAiM1 study team.

Study endpoints

The primary endpoint for the prospective cohort study is clinically meaningful change of global health/QoL, derived from EORTC-QLQ-C30 item 29/30, 12 months after treatment initiation. Secondary endpoints include patient compliance, defined as the percentage of expected questionnaires versus those received, and descriptive statistics (e.g., number of observations, mean, standard deviation, minimum, and maximum) of PRO scores at baseline and follow-up for each treatment group and prognostic patient group. Furthermore, deterioration and time to PRO progression, defined as the time interval from treatment initiation to the date the patient experiences a clinically meaningful change,
will be measured for all functioning domains and symptom scales of the EORTC-QLQ-C30; all domains of the EPIC-26; worst pain, average pain, and pain interference (BPI-SF); fatigue severity and fatigue interference (FACIT-Fatigue); cognitive impairment and impact of cognitive impairment (FACT-Cognitive); and Taxane-related symptoms (FACT-Taxane). This clinically meaningful threshold is defined for each PROM in accordance with the existing literature (Appendix 2a-b). HRQoL deterioration and time to PRO progression analysis will solely be performed in prospectively included patients that completed baseline PROMs within 30-days of treatment initiation, defined as the start date of either ADT or add-on treatment, whichever was initiated first.

Potential endpoints for studies within the retrospective cohort can be found in Table 2.

<table>
<thead>
<tr>
<th>Table 2- Potential endpoints for retrospective cohort studies</th>
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<tr>
<td><strong>Definition</strong></td>
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<td><strong>Descriptive endpoints</strong></td>
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<tr>
<td>ADT landscape for <em>de novo</em> mHSPC</td>
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<tr>
<td>Treatment landscape for <em>de novo</em> mHSPC</td>
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<tr>
<td>Patient- and tumour characteristics</td>
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<tr>
<td>Overview of imaging modalities</td>
</tr>
<tr>
<td>Real-world versus clinical trial</td>
</tr>
<tr>
<td><strong>Survival endpoints</strong></td>
</tr>
<tr>
<td>Overall survival</td>
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<tr>
<td>Progression-free survival</td>
</tr>
<tr>
<td>Clinical progression</td>
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<tr>
<td>Radiographic progression</td>
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</tbody>
</table>
Statistical analysis

Data collected at baseline will be descriptively analysed to provide an overview of the mHSPC patient population, disease characteristics, imaging strategies and mHSPC treatment landscape. For all continuous variables, descriptive statistics will include the number of patients, mean, standard deviation, median, minimum, maximum, and 95% confidence interval. All categorical variables will be summarised using frequencies and percentages. An interim analysis is planned for the prospective cohort after 450 inclusions.

Furthermore, all data will be analysed according to the intention-to-treat (ITT) principle, meaning that patients will be included in the statistical analysis of the predefined groups according to their initial treatment strategy. In this registry study, principal investigators have no control over the treatment assignment and therefore, treatment groups may show large differences on their observed covariates and these differences can lead to biased estimates of treatment effects. The propensity score, defined as the conditional probability of being treated given the covariates, can be used to balance the covariates, in the groups and therefore, reduce bias. To estimate the propensity score, the distribution
of the treatment indicator variable given the observed covariates will be modelled. Once estimated, the propensity score can be used to reduce bias through matching, stratification regression adjustment, or a combination of all three.

Time-to-event endpoints (e.g., progression-free survival, overall survival, change in HRQoL scores, time-to-deterioration) will be assessed for each treatment group using the Kaplan-Meier method with hazard ratios and 95% confidence intervals calculated using Cox’s proportional hazards model. Regression models will be employed to analyse baseline characteristics associated with an increased likelihood of death, progression (i.e., clinical, biochemical, and radiographic), QoL deterioration and (serious) adverse events. Longitudinal mixed effects models will be employed to assess change of PRO scores from baseline until the end of follow-up. Significance will be held at the standard value of \( P<0.05 \) in two-sided tests. Statistical analyses will be performed in IBM SPSS version 27.

PATIENT AND PUBLIC INVOLVEMENT STATEMENT

The Dutch Prostate Cancer Foundation and an independent patient were involved in the design and conduct of TripleAiM1. During the design, they critically reviewed potential PROMS and usability of one of the PROMS providers (i.e., Brightfish). Additionally, a patient participated in the steering committee of TripleAiM1. Once the interim analysis of the prospective cohort has been published, participants can request a patient summary of the results.

ETHICS AND DISSEMINATION

Ethical approval was obtained from the nWMO Medical Research Ethics Committee (MREC), Twente, The Netherlands (NWMO18.11.051). All patients eligible for inclusion in the prospective trial will provide written informed consent and will be made aware they may withdraw from the study at any
given time. The prospective trial is registered at the Netherlands’ Trial Register (www.trialregister.nl; NL9719). Study results of both the retrospective as well as the prospective cohort will be published in peer-reviewed journals and presented at international conferences. MRDM will retain the data for at least 15 years after the completion of the final study report. Data will be retained for a longer period if required by applicable regulatory requirements or by agreement with the sponsor.

AUTHOR CONTRIBUTIONS

Study design: JB, NM, ZL, TE
Drafting of manuscript: TE
Critical review of manuscript: JB, NM, SB, AV, RB, JD, MH, BW, OK, LR, AL, PM, ZL, PB, HB, DL, EV, GV
Principal investigators participating in the conduct of the study: JB, NM, AV, EV, BW, SK, DL, GV, JD, MH, AL, RB, PB, LR

Academic authorship for TripleAiM1 related articles will be based on international authorship criteria as defined by the International Committee of Medical Journal Editors (ICJME) in which is stated that recruitment of patients alone is not enough[26]. Individuals who collaborate in the trial, yet who do not fulfil the ICJME criteria for authorship, will be listed as part of the ‘TripleAiM1 Scientific Working Group’.

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All figures were created with BioRender.com

COMPETING INTERESTS STATEMENT

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AL reports grants and personal fees from Bayer, Clovis, Eisai, Ipsen, Janssen-Cilag and Pfizer.

Other authors report no competing interests.

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**Figure Legends**

**Figure 1:** Graphic display of the study lay-out

*mHSPC* = metastatic hormone sensitive prostate cancer; *HRQoL* = Health-related Quality of Life

**Figure 2:** Graphic display data sources and collection methods

*IKNL* = Netherlands Comprehensive Cancer Organisation; *HRQoL* = Health-related Quality of Life;

*PROMs* = Patient Reported Outcome Measures; *DBC* = Diagnosis Treatment Code; *MRDM* = Medical Research Data Management

*Research Data Management*
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16 Ng, K. et al. Metastatic hormone-sensitive prostate cancer (mHSPC): Advances and treatment strategies in the first-line setting. Oncol Ther 2020; 8: 209-230
17 Official CTcue website, visited March 2022 https://ctcue.com/solutions/
18 Official IKNL website, visited March 2022 https://iknl.nl/over-iknl/wat-we-doen
Figure 1- Graphic display of the study lay-out

645x334mm (118 x 118 DPI)
Graphic display data sources and collection methods

651x406mm (118 x 118 DPI)
SUPPLEMENTARY MATERIALS

Appendix 1

Conditional PROM Will be administered if...

<table>
<thead>
<tr>
<th>PROM</th>
<th>Scale</th>
<th>Definition threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td>EORTC-QLQ-C30</td>
<td>EORTC-QLQ-C30 item 9 “Have you had pain?” is scored ≥2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>EORTC-QLQ-C30 item 19 “Did pain interfere with your daily activities?” is scored ≥2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>EPIC-26 item 4b is scored ≥1</td>
<td></td>
</tr>
</tbody>
</table>

FACIT- Fatigue

<table>
<thead>
<tr>
<th>PROM</th>
<th>Scale</th>
<th>Definition threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td>EORTC-QLQ-C30</td>
<td>EORTC-QLQ-C30 item 10 “Did you need to rest?” is scored ≥2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>EORTC-QLQ-C30 item 18 “Were you tired?” is scored ≥2</td>
<td></td>
</tr>
</tbody>
</table>

FACT- Cognitive

<table>
<thead>
<tr>
<th>PROM</th>
<th>Scale</th>
<th>Definition threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td>EORTC-QLQ-C30</td>
<td>EORTC-QLQ-C30 item 20 “Have you had difficulty in concentrating on things, like reading a newspaper or watching television?” is scored ≥2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>EORTC-QLQ-C30 item 25 “Have you had difficulty remembering things?” is scored ≥2</td>
<td></td>
</tr>
</tbody>
</table>

PROM= Patient Reported Outcome Measure; BPI-SF= Brief Pain Inventory- Short Form; EORTC-QLQ-C30= European Organisation for Research and Treatment of Cancer- QLQ-C30; EPIC-26= Expanded Prostate Cancer Index Composite-26; FACIT= Functional Assessment of Cancer Therapy

Appendix 2

Appendix 2a- Threshold for clinical importance (single time point)

<table>
<thead>
<tr>
<th>PROM</th>
<th>Scale</th>
<th>Definition threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td>EORTC-QLQ-C30</td>
<td>Physical functioning</td>
<td>Threshold for clinical importance: 83 (0-100) (^1)</td>
</tr>
<tr>
<td></td>
<td>Role functioning</td>
<td>Threshold for clinical importance: 58 (0-100) (^1)</td>
</tr>
<tr>
<td></td>
<td>Social functioning</td>
<td>Threshold for clinical importance: 58 (0-100) (^1)</td>
</tr>
<tr>
<td></td>
<td>Emotional functioning</td>
<td>Threshold for clinical importance: 71 (0-100) (^1)</td>
</tr>
<tr>
<td></td>
<td>Cognitive functioning</td>
<td>Threshold for clinical importance: 75 (0-100) (^1)</td>
</tr>
<tr>
<td></td>
<td>Fatigue</td>
<td>Threshold for clinical importance: 39 (0-100) (^1)</td>
</tr>
<tr>
<td></td>
<td>Pain</td>
<td>Threshold for clinical importance: 25 (0-100) (^1)</td>
</tr>
<tr>
<td></td>
<td>Nausea/ vomiting</td>
<td>Threshold for clinical importance: 8 (0-100) (^1)</td>
</tr>
<tr>
<td></td>
<td>Sleep disturbances</td>
<td>Threshold for clinical importance: 50 (0-100) (^1)</td>
</tr>
<tr>
<td></td>
<td>Dyspnoea</td>
<td>Threshold for clinical importance: 17 (0-100) (^1)</td>
</tr>
<tr>
<td></td>
<td>Appetite loss</td>
<td>Threshold for clinical importance: 50 (0-100) (^1)</td>
</tr>
<tr>
<td></td>
<td>Constipation</td>
<td>Threshold for clinical importance: 50 (0-100) (^1)</td>
</tr>
<tr>
<td></td>
<td>Diarrhoea</td>
<td>Threshold for clinical importance: 17 (0-100) (^1)</td>
</tr>
<tr>
<td></td>
<td>Financial impact</td>
<td>Threshold for clinical importance: 17 (0-100) (^1)</td>
</tr>
</tbody>
</table>

PROM= Patient Reported Outcome Measure; EORTC-QLQ-C30= European Organisation for Research and Treatment of Cancer- QLQ-C30
Appendix 2b- Threshold for definition of clinically meaningful PRO progression/deterioration

<table>
<thead>
<tr>
<th>PROM</th>
<th>Scale/ subscale</th>
<th>Definition threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td>EORTC-QLQ-C30</td>
<td>Global health/ QoL</td>
<td>≥4 point change is considered clinically relevant&lt;sup&gt;2,3&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Physical functioning</td>
<td>≥5 point change is considered clinically relevant&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Role functioning</td>
<td>≥6 point change is considered clinically relevant&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Social functioning</td>
<td>≥5 point change is considered clinically relevant&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Cognitive functioning</td>
<td>≥3 point change is considered clinically relevant&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Fatigue</td>
<td>≥5 point change is considered clinically relevant&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Pain</td>
<td>≥6 point change is considered clinically relevant&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Nausea/ vomiting</td>
<td>≥3 point change is considered clinically relevant&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Sleep disturbances</td>
<td>≥4 point change is considered clinically relevant&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Dyspnoea</td>
<td>≥4 point change is considered clinically relevant&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Appetite loss</td>
<td>≥5 point change is considered clinically relevant&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Constipation</td>
<td>≥5 point change is considered clinically relevant&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Diarrhoea</td>
<td>≥3 point change is considered clinically relevant&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Financial impact</td>
<td>≥3 point change is considered clinically relevant&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td>EPIC-26</td>
<td>Bowel; vitality/hormonal</td>
<td>≥4 point change is considered clinically relevant&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Sexual</td>
<td>≥10 point change is considered clinically relevant&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Urinary irritation/ obstruction</td>
<td>≥5 point change is considered clinically relevant&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Urinary incontinence</td>
<td>≥6 point change is considered clinically relevant&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
<tr>
<td>BPI-SF</td>
<td>Pain progression</td>
<td>&gt;30% increase (of baseline)&lt;sup&gt;5,6,7&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Increase worst pain</td>
<td>≥2 point difference (from baseline) without a reduction in pain medication&lt;sup&gt;5,6&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Pain interference</td>
<td>Difference of ≥0.5 SD (from baseline)&lt;sup&gt;5,6&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Average pain</td>
<td>≥2 point difference (from baseline) without a reduction in pain medication&lt;sup&gt;5,6&lt;/sup&gt;</td>
</tr>
<tr>
<td>FACIT- Fatigue</td>
<td>All scales</td>
<td>≥3 point difference (from baseline)&lt;sup&gt;7,8&lt;/sup&gt;</td>
</tr>
<tr>
<td>FACT- Cognitive</td>
<td>All scales</td>
<td>Difference of ≥0.5 SD (from baseline)&lt;sup&gt;9&lt;/sup&gt;</td>
</tr>
<tr>
<td>FACT- Taxane</td>
<td>All scales</td>
<td>Difference of ≥0.5 SD (from baseline)&lt;sup&gt;9&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

PROM= Patient Reported Outcome Measure; BPI-SF= Brief Pain Inventory- Short Form; EORTC-QLQ-C30= European Organisation for Research and Treatment of Cancer- QLQ-C30; EPIC-26= Expanded Prostate Cancer Index Composite-26; FAC(I)T= Functional Assessment of Cancer Therapy
Appendix 2c- References


TripleAiM1: a nationwide registry of de novo metastatic hormone sensitive prostate cancer with prospective quality-of-life assessment

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Primary Subject Heading: Urology
Secondary Subject Heading: Oncology
Keywords: Quality of Life, Urological tumours < UROLOGY, Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT
TripleAiM1: a nationwide registry of de novo metastatic hormone sensitive prostate cancer with prospective quality-of-life assessment

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Word count of abstract: 300
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KEYWORDS

De novo metastatic hormone sensitive prostate cancer – Health-related quality of life– Treatment strategies – Real-world data – Value-based healthcare
ABSTRACT

Introduction

The treatment landscape for de novo metastatic hormone sensitive prostate cancer (mHSPC) is rapidly evolving. With an abundance of available treatment strategies, selecting the optimal strategy for an individual patient is becoming increasingly challenging. TripleAiM1 aims to evaluate the impact of mHSPC treatments on health-related quality of life (HRQoL) and to provide real-world data insights on diagnostics, treatment strategies, patient subgroups and related healthcare expenditure for mHSPC.

The aspirational target of TripleAiM1 is that in the near future, a more tailored therapy can be offered based on the individual patient’s wishes and needs in accordance with the overarching principle of value-based healthcare.

Methods and analysis

We describe the TripleAiM1 study design; a nationwide registry comprising a retrospective and prospective cohort of patients with de novo mHSPC. Starting in May 2020, eligible patients are identified, selected and recruited in 14 participating hospitals in the Netherlands. Our hypothesis is that, in a real-world setting, differences in clinically meaningful HRQoL deterioration will be observed for treatment strategies over time. HRQoL data, assessed with patient-reported outcome measures, costs, and clinical data will be collected for 24 months.

For the retrospective cohort, all patients diagnosed with de novo mHSPC from January 2017 onwards are eligible for inclusion. Patient and tumour characteristics, imaging modalities, and treatment patterns will be analysed descriptively to provide a real-world overview. Time-to-event endpoints will be assessed using the Kaplan-Meier method and regression models will be employed to analyse
baseline characteristics associated with an increased likelihood of death, progression, and HRQoL deterioration. Longitudinal mixed effects models will be employed to assess change of patient-reported outcome scores from baseline until the end of follow-up.

Ethics and dissemination

Ethical approval was obtained from the Medical Research Ethics Committee Twente. Study results will be published in peer-reviewed journals.

Registration details

The Netherlands Trial Register (NL9719)

ARTICLE SUMMARY

Strengths and limitations of this study

- Retrospective and prospective real-world data registry facilitating multiple studies within these cohorts
- Extensive health-related quality of life (HRQoL) data in multiple treatment subgroups
- Complete overview of all costs related to care activities on patient level during the full cycle of care
- Unique consolidation of data collection methods to improve data quality and enrich the database
- Lack of power to compare HRQoL outcomes between treatment subgroups and risk of bias (non-randomised trial)
INTRODUCTION

Yearly, more than 13,000 Dutch men are confronted with a diagnosis of prostate cancer[1]. Of these, approximately 15% have metastatic disease at the time of diagnosis[2,3]. For decades, androgen deprivation therapy (ADT), consisting of bilateral orchiectomy, anti-androgens or luteinizing hormone-releasing (LHRH) (ant)agonist, has been the standard-of-care for patients with de novo metastatic hormone sensitive prostate cancer (mHSPC). However, treatment strategies combining ADT with upfront palliative radiotherapy to the prostate, docetaxel and/or an Androgen Receptor Targeting Agent (ARTA e.g., abiraterone, apalutamide or enzalutamide) have challenged ADT monotherapy as standard-of-care, ever since several randomised controlled trials (RCTs) concluded a survival benefit when adding either one, or multiple agents, to ADT[4-10]. These new treatment schedules have lengthened the time of hormone-sensitivity and delayed the time to clinical symptoms and deterioration with a comparable impact on overall survival, yet with different side effects and impact on health-related quality of life (HRQoL). Nevertheless, the prognosis of de novo mHSPC remains poor[11,12].

In this population where curation is not feasible, HRQoL is a critical outcome parameter for patients and clinicians [13,14]. Several patient-reported outcome measurements (PROMs) have been validated to objectify and monitor HRQoL in men with prostate cancer (e.g., Expanded Prostate Cancer Index Composite-26 (EPIC-26), European Organisation for Research and Treatment of Cancer (EORTC)-QLQ-C30, and Functional Assessment of Cancer Therapy (FACT)-prostate)[13,15]. These PROMs are increasingly being used in mHSPC care to assess the patient’s perspective on disease symptoms, treatment tolerance and impact on HRQoL, as it has been postulated that both quantity and quality of life should be taken into account when tailoring therapy[16].
Nevertheless, with an abundance of treatment strategies to choose from, selecting the right strategy for the right patient is becoming increasingly challenging. There is a need for more detailed insights in real world data that reflect how treatments are initiated, combined and sequenced, how treatments impact a patient’s quality of life, and how their relative effectiveness profiles emerge outside clinical trial setting. Additionally, efforts should be made to predict which patient, considering both patient and tumour characteristics, responds better to which treatment strategy, to mitigate treatment side effects whilst improving survival outcomes and preserving HRQoL[16].

In this paper we describe TripleAiM1, a nationwide registry for patients with de novo mHSPC, which has been constructed to accelerate research on optimising patient care. We aim to evaluate the impact of mHSPC treatments on HRQoL and to provide real-world data insights on diagnostics, treatment strategies, detailed patient characteristics, and related healthcare expenditure for mHSPC. The aspirational target of TripleAiM1 is that in the near future, a more tailor-made therapy can be offered based on the individual patient’s wishes and needs.

METHODS AND ANALYSIS

Study design

TripleAiM1 has been initiated to uniformly obtain real-world clinical data, patient reported outcomes (PROs), and healthcare costs of de novo mHSPC patients in the Netherlands. As we aim to include overview data, survival data, and HRQoL data, we chose to incorporate a retrospective and prospective cohort in our registry, facilitating multiple studies within these cohorts (Figure 1). The registry started in May 2020 and will continue indefinitely. For the prospective cohort our aim is a minimum of 450 valid inclusions. Patients are deemed valid when they completed the baseline questionnaires and at least one follow-up moment (T=12 months after treatment initiation). An interim analysis will be performed to assess the validity and outcomes of patients included until 31 May 2023. Due to the
observational character of TripleAiM1, participation in either of the cohorts will not influence medical care, as treatment decisions are made at the discretion of the treating physician.

**Patient population**

Patients eligible for inclusion are men diagnosed with *de novo* mHSPC in one of the 14 participating regional, teaching and academic hospitals throughout the Netherlands. Prostate cancer diagnosis must be histologically confirmed by either biopsy of the prostate or, in absence of prostate biopsy, a serum PSA level >100 ng/ml and metastatic lesions on imaging suspect for metastatic prostate cancer. Moreover, patients must have had the complete radiological workup (e.g., magnetic resonance imaging (MRI), computed tomography (CT), prostate-specific membrane antigen positron emission tomography-CT (PSMA PET-CT), and/or bone scintigraphy) to confirm distant lymphogenous, bone or visceral metastasis.

**Retrospective cohort**

*Eligibility criteria*

For the retrospective cohort, patients diagnosed with *de novo* mHSPC from January 2017 onwards are eligible for inclusion. Patients will be excluded if they have one of the following: (1) a history of prostate cancer, irrespective of whether they received treatment or not; (2) histologically confirmed neuro-endocrine small cell tumour; (3) lack of follow-up records within 6 months after diagnosis in one of the TripleAiM1 hospitals; (4) total follow-up of less than 6 months.

*Patient identification*

Initial identification will be performed by CTcue, a text mining programme which recruits eligible patients and collects additional patient data by using neurolinguistics programing and artificial intelligence to analyse electronic health records[17]. We will extend this sample with eligible patients
registered in the National Cancer Registry (NCR) of the Netherlands Comprehensive Cancer Organisation (IKNL) who were not found with CTcue[18]. More details on these data acquisition types can be found in the section “Data sources and collection methods’.

Sample size

We anticipate that we will include around 3000 patients who have been diagnosed with de novo mHSPC between January 2017 and January 2023. This estimate is based on a preliminary search conducted in one TripleAiM1 hospital, where 250 patients were found to be eligible for inclusion in this cohort. Extrapolating this number to the 14 participating hospitals, we expect to include around 3500 patients. However, when taking into account the varying size of the participating centres and the corresponding patient numbers, we expect that the final sample size will be around 3000. As primary outcomes are descriptive rather than comparative, no power calculation was performed.

Prospective cohort

Eligibility criteria

Patients are eligible if diagnosed with de novo mHSPC from May 2020 onwards in one of the participating hospitals. Eligible patients are older than 18 years, have no prior history of prostate cancer nor have they received initial treatment for prostate cancer >30 days prior to inclusion. No additional inclusion criteria comprising treatment strategy or patient characteristics were instated as we aim to assess real-world data. However, severe cognitively impaired patients (i.e., patients with dementia or mental impairment) and patients with an insufficient understanding of the Dutch language will be excluded, as this might impact the quality of answers given in the questionnaires and therefore, affecting the reliability of HRQoL data.
Patient identification

For the prospective cohort of the TripleAiM1 registry, patients will be identified, selected and recruited by treating physicians in participating hospitals.

Sample size

The registry has been designed to generate data for informative purposes and therefore, sample size is determined by pragmatic considerations based on the number of mHSPC patients in the national ProZib registry[1,2]. Included patients will be subdivided according to treatment strategy (e.g., ADT monotherapy, ADT + docetaxel (Doc), ADT + radiotherapy (RTx), ADT + abiraterone (Abi), ADT + enzalutamide (Enza), ADT + apalutamide (Apa), and triple therapies) and we aim to include at least 75 patients in each treatment arm. Moreover, as the treatment landscape for mHSPC will continue to change over the years, we will incorporate an ‘other treatment’ category which includes all types of treatment strategies of which group sizes are not substantial.

At the time of writing, 337 patients have been enrolled.

Data sources and collection methods

Clinical data, including patient and tumour characteristics, treatment information, survival outcomes (i.e., progression and overall survival data), adverse events, and data on costs and utilisation will be collected for both the retrospective and the prospective cohort. While HRQoL data will solely be collected from patients included in the prospective cohort. A multitude of data collection methods will be employed to collect all data (Figure 2). The consolidation of these data collection methods and sources will be performed in order to improve data quality and to enrich the database. In this section, we provide detailed information on the data sources and collection methods used.
Clinical data

**IKNL**

IKNL is an independent knowledge institute for oncological care in the Netherlands. IKNL facilitates nationwide identification of prostate cancer patients and independent data managers collect clinical data from patient records [18]. As this clinical dataset did not encapsulate all the patient characteristics and clinical outcomes that we aim to assess, based on the *International Consortium for Health Outcomes Measurement (ICHOM) Standard Set for Advanced Prostate Cancer*, more data sources and data collection methods were employed to extract relevant data [14].

Costs and utilisation data

In the Netherlands, diagnosis-treatment-code (DBC) products form the basis of healthcare finance. Healthcare costs are not based on single activities, but on DBC products comprising a standard care path for each specific diagnosis. The price calculated for this DBC product is an abstraction of all costs and activities associated with the respective treatment [19]. Since all imaging, assessments, consultations, and hospital visits are related to a DBC product, healthcare expenditure and utility data regarding a specific diagnosis can easily be collected per patient from hospital systems and used for research.

LOGEX, a healthcare analytics company, will collect individual utility and expenditure data related to DBCs from hospital records to calculate real-world expenditure for single activities (e.g., diagnostic assessments and hospital visits) using mean costs, as there are substantial differences in diagnostic care pathways between patients. Notably, administrative healthcare data will be routinely validated using automated algorithms and a manual validation of outliers will be performed.
CTcue uses data queries containing descriptive words to text mine patient records. As more than 70% of all data in patient records are stored as free text, CTcue can be used to find eligible patients and to collect patient data more easily and therefore, enrich the IKNL and DBC data.

Based on our data dictionary, we will search patient records with CTcue to obtain the desired data in a pseudo-anonymised and uniform matter. Each data query will be optimised with the help of a data scientist from CTcue to increase reliability. For validation of the query, we will compare patient level data acquired from hospital records with that from CTcue in two hospitals. Following automatic data extraction, all data items will be manually validated within CTcue to assure the quality of the acquired data.

HRQoL data

Multiple PROMs, addressing several aspects of quality of life (QoL), have been validated to quantify HRQoL in men with prostate cancer[13]. The EORTC-QLQ-C30 questionnaire is one of the most widely used cancer specific questionnaires to assess HRQoL. It comprises five functioning scales (physical, role, cognitive, emotional, and social), three symptom scales (fatigue, pain, and nausea and vomiting) and several single items regarding other symptoms and financial status[20]. Importantly, the EORTC-QLQ-C30 describes the patient’s global health status, representing their overall QoL.

While the EORTC-QLQ-C30 measures cancer specific QoL, the EPIC-26 provides prostate cancer specific QoL outcomes. It is recommended that both PROMs are administered simultaneously in patients with metastatic prostate cancer according to the ICHOM Standard Set of Advanced Prostate Cancer[14]. The EPIC-26 questionnaire measures function and bother on four domains (urinary, bowel, sexual, and hormonal) relevant to (metastatic) prostate cancer[21]. Furthermore, in patients receiving Taxane
therapy, the FACT-Taxane is commonly used to assess HRQoL based on five subscales: physical, social/family, emotional, functional well-being, and Taxane related symptoms[22]. Moreover, to gain better insights into common symptoms of metastatic prostate cancer, symptom specific questionnaires will be used in addition to the EORTC-QLQ-C30, EPIC-26 and FACT-Taxane. The Brief Pain Inventory- Short Form (BPI-SF) includes four questions regarding pain intensity, seven on the level of pain that has interfered with the patient’s life, and a diagram to locate the pain[23]. The Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue is a 40-item measure to assess fatigue and its impact on daily activities and function, and the FACT-Cognitive is a 37-item measure to assess cognitive function issues in cancer patients, and comprises four subscale domains (perceived cognitive impairments, impact of perceived cognitive impairments on QoL, comments from others, and perceived cognitive abilities)[24,25].

Following inclusion, prospectively included patients will receive the six previously stated questionnaires at predefined time intervals from the start up to 24 months to assess their HRQoL (Table 1). Efforts, such as a dashboard for patients tracking their HRQoL and conditionally administered questionnaires, are instated in an attempt to increase response rates and the patient’s willingness to respond.

<table>
<thead>
<tr>
<th>Table 1- PROMs administration schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong> (T=0)</td>
</tr>
<tr>
<td>----------------------</td>
</tr>
<tr>
<td>EORTC-QLQ-C30</td>
</tr>
<tr>
<td>EPIC-26</td>
</tr>
<tr>
<td>FACT-Taxane</td>
</tr>
<tr>
<td>BPI-SF</td>
</tr>
<tr>
<td>FACIT-Fatigue</td>
</tr>
<tr>
<td>FACT-Cognitive</td>
</tr>
</tbody>
</table>

PROMs= Patient Reported Outcome Measures; T= time interval (in months); EORTC-C30= European Organisation for Research and Treatment of Cancer- QLQ-C30; EPIC-26= Expanded Prostate Cancer Index Composite-26; FACT= Functional Assessment of Cancer Therapy; FACIT= Functional Assessment of Chronic Illness Therapy; BPI-SF= Brief Pain Inventory- Short Form

* These questionnaires are administered conditionally
Table 1 shows that the BPI-SF, FACIT-fatigue and FACT-cognitive are conditionally administered in cases when patients positively answered predefined questions in regard to pain, fatigue and/or cognition on EORTC-QLQ-C30 and EPIC-26. These predefined questions are shown in Appendix 1.

The PROMs will be sent digitally to the participants via Questmanager, Brightfish, onlinePROMS, HiX or EPIC. This multitude in PROMs vendors is ascribed to the preference of participating hospitals, depending on local practice. Moreover, as the use of digital platforms may cause selection bias, written or verbal PROMS are allowed for patients with no email address and/or cell phone. The latter is necessary because most PROM vendors require obligatory two-step authentication to ensure patient data safety.

Data consolidation

All data will be collected and consolidated by trained employees from Medical Research Data Management (MRDM), a trusted third-party intermediary. MRDM will operate as a data processor for all TripleAiM1 data coming from participating hospitals. MRDM has official processor relations with all Dutch hospitals and a growing number of private clinics and first-line care, enabling them to collect and process medical data as if they were part of the institution itself. For data collection and consolidation, we have taken into account that some clinical data items will be extracted with both CTcue and IKNL. Therefore, when data of both is available, CTcue will be considered as the primary data collection method for clinical data. Subsequently, MRDM will process patient-identity data which they anonymise and encrypt before sending it in fully anonymised CSV files to the TripleAiM1 study team.
Study endpoints

The primary endpoint for the prospective cohort study is clinically meaningful change of global health/QoL, derived from EORTC-QLQ-C30 item 29/30, 12 months after treatment initiation. Secondary endpoints include patient compliance, defined as the percentage of expected questionnaires versus those received, and descriptive statistics (e.g., number of observations, mean, standard deviation, minimum, and maximum) of PRO scores at baseline and follow-up for each treatment group and prognostic patient group. Furthermore, deterioration and time to PRO progression, defined as the time interval from treatment initiation to the date the patient experiences a clinically meaningful change, will be measured for all functioning domains and symptom scales of the EORTC-QLQ-C30; all domains of the EPIC-26; worst pain, average pain, and pain interference (BPI-SF); fatigue severity and fatigue interference (FACIT-Fatigue); cognitive impairment and impact of cognitive impairment (FACT-Cognitive); and Taxane-related symptoms (FACT-Taxane). This clinically meaningful threshold is defined for each PROM in accordance with the existing literature (Appendix 2a-b). HRQoL deterioration and time to PRO progression analysis will solely be performed in prospectively included patients that completed baseline PROMs within 30-days of treatment initiation, defined as the start date of either ADT or add-on treatment, whichever was initiated first.

Potential endpoints for studies within the total cohort can be found in Table 2.

Table 2- Potential endpoints for cohort studies

<table>
<thead>
<tr>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Descriptive endpoints</strong></td>
</tr>
<tr>
<td>ADT landscape for de novo mHSPC</td>
</tr>
<tr>
<td>Descriptive overview of ADT (i.e., orchiectomy, LHRH (ant)agonists, AR-inhibitors), combinations and sequence</td>
</tr>
<tr>
<td>Treatment landscape for de novo mHSPC</td>
</tr>
<tr>
<td>Descriptive overview of initial treatment strategy (e.g., ADT monotherapy, ADT+Doc, ADT+Abi, ADT+Apa, ADT+Enza, ADT+RTx, and other treatment strategies) and subsequent therapies for the total population and population subgroups (e.g., M1a disease)</td>
</tr>
</tbody>
</table>
### Statistical analysis

Data collected at baseline will be descriptively analysed to provide an overview of the mHSPC patient population, disease characteristics, imaging strategies, and mHSPC treatment landscape. For all continuous variables, descriptive statistics will include the number of patients, mean, standard deviation, median, minimum, maximum, and 95% confidence interval. All categorical variables will be

<table>
<thead>
<tr>
<th>Patient- and tumour characteristics</th>
<th>Descriptive overview of patient- and tumour characteristics in the total de novo mHSPC population and predefined treatment subgroups, and identification of prognostic characteristics associated with a favourable treatment response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overview of imaging modalities</td>
<td>Descriptive overview of imaging modalities being used to confirm metastatic disease and radiology conclusions</td>
</tr>
<tr>
<td>Real-world versus clinical trial</td>
<td>Descriptive overview of patient characteristics and outcomes of the real-world versus landmark clinical trials</td>
</tr>
<tr>
<td><strong>Survival endpoints</strong></td>
<td></td>
</tr>
<tr>
<td>Overall survival</td>
<td>Overall survival is defined as the time from diagnosis to the date of death from any cause</td>
</tr>
<tr>
<td>Progression-free survival</td>
<td>Progression-free survival was defined as the time from diagnosis to progression, either biochemical, radiographic or clinical, or death, whichever occurred first</td>
</tr>
<tr>
<td>Clinical progression</td>
<td>Clinical progression is defined as a procedure for local progression and/or the presence of a skeletal event</td>
</tr>
<tr>
<td>Radiographic progression</td>
<td>Radiographic progression is defined as the first conclusion of radiographic progression in MDT consultation, as defined according to RECIST 1.1 criteria, or, when the MDT form is lacking, when progression is mentioned in radiology report</td>
</tr>
<tr>
<td>Biochemical progression</td>
<td>Biochemical progression is defined as an increase in PSA greater than 25% and &gt;2 ng/ml above nadir, confirmed by progression at 2 time points at least 3 weeks apart, as defined by PCWG3 criteria, and/or when biochemical progression is concluded in MDT consultation</td>
</tr>
<tr>
<td>Time to first-line CRPC treatment</td>
<td>Time to first-line CRPC treatment was defined as the time from diagnosis to first new treatment strategy after progression was concluded</td>
</tr>
<tr>
<td><strong>(Additional) VBHC endpoints</strong></td>
<td></td>
</tr>
<tr>
<td>Utilisation</td>
<td>Utilisation is defined as number of hospital/ ER visits, hospital admissions and diagnostics (e.g., laboratory tests and imaging) related to prostate cancer from time of diagnosis until end of follow-up or death, whichever occurred first</td>
</tr>
<tr>
<td>Relative costs</td>
<td>Costs are defined as prostate cancer related expenditure (e.g., treatments, hospital visits/ admissions, diagnostics) from time of diagnosis until end of follow-up or death, whichever occurred first</td>
</tr>
<tr>
<td><strong>Exploratory endpoints</strong></td>
<td></td>
</tr>
<tr>
<td>(Serious) Adverse Events</td>
<td>(S)AE’s are defined as reported cardiovascular toxicity, cytopenias, GI toxicity (e.g., vomiting, diarrhea, constipation), infection (e.g., fever, high infection parameters), and neuropathy; ER visits related to prostate cancer; unexpected hospital admissions related to prostate cancer</td>
</tr>
</tbody>
</table>

ADT= Androgen Deprivation Treatment; mHSPC= metastatic Hormone Sensitive Prostate Cancer; LHRH= Luteinizing Hormone-Releasing Hormone; AR= Androgen Receptor; Doc= Docetaxel; Abi= Abiraterone; Apa= Apalutamide; Enza= Enzalutamide; RTx= prostate radiotherapy; RECIST= Response Evaluation Criteria in Solid Tumours; MDT= Multidisciplinary Team; PSA= Prostate-Specific Antigen; PCWG3= Prostate Cancer Working Group 3; CRPC= Castration Resistant Prostate Cancer; VBHC= Value Based Health Care; (S)AE= (Serious) Adverse Event; GI= Gastrointestinal; ER= Emergency Room
summarised using frequencies and percentages. An interim analysis is planned for the prospective
cohort after 450 inclusions.

Furthermore, all data will be analysed according to the intention-to-treat (ITT) principle, meaning that
patients will be included in the statistical analysis of the predefined groups according to their initial
treatment strategy. In this registry study, principal investigators have no control over the treatment
assignment and therefore, treatment groups may show large differences on their observed covariates
and these differences can lead to biased estimates of treatment effects. The propensity score, defined
as the conditional probability of being treated given the covariates, can be used to balance the
covariates, in the groups and therefore, reduce bias. To estimate the propensity score, the distribution
of the treatment indicator variable given the observed covariates will be modelled. Once estimated,
the propensity score can be used to reduce bias through matching, stratification regression
adjustment, or a combination of all three.

Time-to-event endpoints (e.g., progression-free survival, overall survival, change in HRQoL scores,
time-to-deterioration) will be assessed for each treatment group using the Kaplan-Meier method with
hazard ratios and 95% confidence intervals calculated using Cox’s proportional hazards model.
Regression models will be employed to analyse baseline characteristics associated with an increased
likelihood of death, progression (i.e., clinical, biochemical, and radiographic), QoL deterioration and
.serious) adverse events. Prostate cancer related expenditure will be summarised descriptively for
each treatment strategy encompassing medication expenses and utilisation costs. Utilisation costs will
entail expenses of hospital and emergency room visits, hospital admissions and various diagnostics
(e.g., laboratory tests and imaging) related to prostate cancer. Longitudinal mixed effects models will
be employed to assess change of PRO scores from baseline until the end of follow-up. Significance will
be held at the standard value of P<0.05 in two-sided tests. Statistical analyses will be performed in IBM
SPSS version 27.
PATIENT AND PUBLIC INVOLVEMENT STATEMENT

The Dutch Prostate Cancer Foundation and an independent patient were involved in the design and conduct of TripleAiM1. During the design, they critically reviewed potential PROMS and usability of one of the PROMS providers (i.e., Brightfish). Additionally, a patient participated in the steering committee of TripleAiM1. Once the interim analysis of the prospective cohort has been published, participants can request a patient summary of the results.

ETHICS AND DISSEMINATION

Ethical approval was obtained from the nWMO Medical Research Ethics Committee (MREC), Twente, The Netherlands (NWMO18.11.051). All patients eligible for inclusion in the prospective trial will provide written informed consent and will be made aware they may withdraw from the study at any given time. The prospective trial is registered at the Netherlands’ Trial Register (www.trialregister.nl; NL9719). Study results of both the retrospective as well as the prospective cohort will be published in peer-reviewed journals and presented at international conferences. MRDM will retain the data for at least 15 years after the completion of the final study report. Data will be retained for a longer period if required by applicable regulatory requirements or by agreement with the sponsor.

AUTHOR CONTRIBUTIONS

T. van Elst Conceptualization, Methodology, Investigation, Writing-Original draft, Project administration, J.P.A. van Basten Conceptualization, Methodology, Resources, Writing-Review & Editing, Supervision P.L. van den Berg Resources, Writing- Review & Editing R.C.N. van den Bergh Resources, Writing-Review & Editing S. Bloem Conceptualization, Writing-Review & Editing J.M. van
Academic authorship for TripleAiM1 related articles will be based on international authorship criteria as defined by the International Committee of Medical Journal Editors (ICJME) in which is stated that recruitment of patients alone is not enough[26]. Individuals who collaborate in the trial, yet who do not fulfil the ICJME criteria for authorship, will be listed as part of the ‘TripleAiM1 Scientific Working Group’.

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All figures were created with BioRender.com

COMPETING INTERESTS STATEMENT

NM reports grants, institutional and personal fees from Janssen-Cilag. Outside of the submitted work

NM reports grants and personal fees from MSD, AstraZeneca, Astellas, BMS, Pfizer and Bayer.

MH reports grants from Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb,

Clovis Oncology, Eisai, Ipsen, Merck Sharp & Dohme, Novartis, Pfizer and Roche.

AL reports grants and personal fees from Bayer, Clovis, Eisai, Ipsen, Janssen-Cilag and Pfizer

Other authors report no competing interests.
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Figure Legends

Figure 1: Graphic display of the study lay-out

mHSPC = metastatic hormone sensitive prostate cancer; HRQoL = Health-related Quality of Life

Figure 2: Graphic display data sources and collection methods

IKNL = Netherlands Comprehensive Cancer Organisation; HRQoL = Health-related Quality of Life;
PROMs = Patient Reported Outcome Measures; DBC = Diagnosis Treatment Code; MRDM = Medical Research Data Management
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   https://ctcue.com/solutions/
18 Official IKNL website, visited March 2022
   https://iknl.nl/over-iknl/wat-we-doen
26 ICMJE author guidelines, visited February 2022
Figure 1 Graphic display of the study lay-out

645x334mm (118 x 118 DPI)
Figure 2 - Graphic display data sources and collection methods

651x406mm (118 x 118 DPI)
SUPPLEMENTARY MATERIALS

Appendix 1

<table>
<thead>
<tr>
<th>Conditional PROM</th>
<th>Will be administered if...</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BPI-SF</strong></td>
<td></td>
</tr>
<tr>
<td>EORTC-QLQ-C30 item 9 “Have you had pain?” is scored ≥2</td>
<td></td>
</tr>
<tr>
<td>EORTC-QLQ-C30 item 19 “Did pain interfere with your daily activities?” is scored ≥2</td>
<td></td>
</tr>
<tr>
<td>EPIC-26 item 4b is scored ≥1</td>
<td></td>
</tr>
<tr>
<td><strong>FACIT- Fatigue</strong></td>
<td></td>
</tr>
<tr>
<td>EORTC-QLQ-C30 item 10 “Did you need to rest?” is scored ≥2</td>
<td></td>
</tr>
<tr>
<td>EORTC-QLQ-C30 item 18 “Were you tired?” is scored ≥2</td>
<td></td>
</tr>
<tr>
<td><strong>FACT- Cognitive</strong></td>
<td></td>
</tr>
<tr>
<td>EORTC-QLQ-C30 item 20 “Have you had difficulty in concentrating on things, like reading a newspaper or watching television?” is scored ≥2</td>
<td></td>
</tr>
<tr>
<td>EORTC-QLQ-C30 item 25 “Have you had difficulty remembering things?” is scored ≥2</td>
<td></td>
</tr>
</tbody>
</table>

PROM= Patient Reported Outcome Measure; BPI-SF= Brief Pain Inventory- Short Form; EORTC-QLQ-C30= European Organisation for Research and Treatment of Cancer- QLQ-C30; EPIC-26= Expanded Prostate Cancer Index Composite-26; FACIT= Functional Assessment of Cancer Therapy

Appendix 2

Appendix 2a- Threshold for clinical importance (single time point)

<table>
<thead>
<tr>
<th>PROM</th>
<th>Scale</th>
<th>Definition threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td>EORTC-QLQ-C30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical functioning</td>
<td>Threshold for clinical importance: 83 (0-100)</td>
<td></td>
</tr>
<tr>
<td>Role functioning</td>
<td>Threshold for clinical importance: 58 (0-100)</td>
<td></td>
</tr>
<tr>
<td>Social functioning</td>
<td>Threshold for clinical importance: 58 (0-100)</td>
<td></td>
</tr>
<tr>
<td>Emotional functioning</td>
<td>Threshold for clinical importance: 71 (0-100)</td>
<td></td>
</tr>
<tr>
<td>Cognitive functioning</td>
<td>Threshold for clinical importance: 75 (0-100)</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>Threshold for clinical importance: 39 (0-100)</td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>Threshold for clinical importance: 25 (0-100)</td>
<td></td>
</tr>
<tr>
<td>Nausea/ vomiting</td>
<td>Threshold for clinical importance: 8 (0-100)</td>
<td></td>
</tr>
<tr>
<td>Sleep disturbances</td>
<td>Threshold for clinical importance: 50 (0-100)</td>
<td></td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>Threshold for clinical importance: 17 (0-100)</td>
<td></td>
</tr>
<tr>
<td>Appetite loss</td>
<td>Threshold for clinical importance: 50 (0-100)</td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>Threshold for clinical importance: 50 (0-100)</td>
<td></td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>Threshold for clinical importance: 17 (0-100)</td>
<td></td>
</tr>
<tr>
<td>Financial impact</td>
<td>Threshold for clinical importance: 17 (0-100)</td>
<td></td>
</tr>
</tbody>
</table>

PROM= Patient Reported Outcome Measure; EORTC-QLQ-C30= European Organisation for Research and Treatment of Cancer- QLQ-C30
<table>
<thead>
<tr>
<th>PROM</th>
<th>Scale/ subscale</th>
<th>Definition threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EORTC-QLQ-C30</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Global health/ QoL</td>
<td>≥4 point change is considered clinically relevant 2,3</td>
</tr>
<tr>
<td></td>
<td>Physical functioning</td>
<td>≥5 point change is considered clinically relevant 3</td>
</tr>
<tr>
<td></td>
<td>Role functioning</td>
<td>≥6 point change is considered clinically relevant 3</td>
</tr>
<tr>
<td></td>
<td>Social functioning</td>
<td>≥5 point change is considered clinically relevant 3</td>
</tr>
<tr>
<td></td>
<td>Cognitive functioning</td>
<td>≥3 point change is considered clinically relevant 3</td>
</tr>
<tr>
<td></td>
<td>Fatigue</td>
<td>≥5 point change is considered clinically relevant 3</td>
</tr>
<tr>
<td></td>
<td>Pain</td>
<td>≥6 point change is considered clinically relevant 3</td>
</tr>
<tr>
<td></td>
<td>Nausea/ vomiting</td>
<td>≥3 point change is considered clinically relevant 3</td>
</tr>
<tr>
<td></td>
<td>Sleep disturbances</td>
<td>≥4 point change is considered clinically relevant 3</td>
</tr>
<tr>
<td></td>
<td>Dyspnoea</td>
<td>≥4 point change is considered clinically relevant 3</td>
</tr>
<tr>
<td></td>
<td>Appetite loss</td>
<td>≥5 point change is considered clinically relevant 3</td>
</tr>
<tr>
<td></td>
<td>Constipation</td>
<td>≥5 point change is considered clinically relevant 3</td>
</tr>
<tr>
<td></td>
<td>Diarrhoea</td>
<td>≥3 point change is considered clinically relevant 3</td>
</tr>
<tr>
<td></td>
<td>Financial impact</td>
<td>≥3 point change is considered clinically relevant 3</td>
</tr>
<tr>
<td><strong>EPIC-26</strong></td>
<td>Bowel; vitality/hormonal</td>
<td>≥4 point change is considered clinically relevant 4</td>
</tr>
<tr>
<td></td>
<td>Sexual</td>
<td>≥10 point change is considered clinically relevant 4</td>
</tr>
<tr>
<td></td>
<td>Urinary irritation/ obstruction</td>
<td>≥25 point change is considered clinically relevant 4</td>
</tr>
<tr>
<td></td>
<td>Urinary incontinence</td>
<td>≥6 point change is considered clinically relevant 4</td>
</tr>
<tr>
<td><strong>BPI-SF</strong></td>
<td>Pain progression</td>
<td>&gt;30% increase (of baseline)5,6,7</td>
</tr>
<tr>
<td></td>
<td>Increase worst pain</td>
<td>≥2 point difference (from baseline) without a reduction in pain medication5,6</td>
</tr>
<tr>
<td></td>
<td>Pain interference</td>
<td>Difference of ≥0.5 SD (from baseline)5,6</td>
</tr>
<tr>
<td></td>
<td>Average pain</td>
<td>≥2 point difference (from baseline) without a reduction in pain medication5,6</td>
</tr>
<tr>
<td><strong>FACT- Fatigue</strong></td>
<td>All scales</td>
<td>≥ 3 point difference (from baseline)7,8</td>
</tr>
<tr>
<td><strong>FACT- Cognitive</strong></td>
<td>All scales</td>
<td>Difference of ≥0.5 SD (from baseline)9</td>
</tr>
<tr>
<td><strong>FACT- Taxane</strong></td>
<td>All scales</td>
<td>Change of ≥1 SE of measurement7</td>
</tr>
</tbody>
</table>

PROM= Patient Reported Outcome Measure; BPI-SF= Brief Pain Inventory- Short Form; EORTC-QLQ-C30= European Organisation for Research and Treatment of Cancer- QLQ-C30; EPIC-26= Expanded Prostate Cancer Index Composite-26; FAC(I)T= Functional Assessment of Cancer Therapy
Appendix 2c - References


