***ZINNIGE ZORG* ROOM FOR IMPROVEMENT REPORT**

Appropriate use of pharmaceutical products for patients with castration-refractory prostate cancer

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Zorginstituut Nederland* and *Zinnige Zorg

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Summary

Reason
Within the framework of the *Zinnige Zorg Programme, Zorginstituut Nederland* systematically assesses the Dutch minimal and mandatory package of health care that Dutch health care insurers must provide. There are four phases to this systematic assessment: screening, in-depth assessment, implementation and monitoring. In 2015 we published a screening report: 'Systematic analysis of neoplasms'. During the screening phase, one of the topics mentioned by the parties for in-depth assessment was 'appropriate use of pharmaceutical products on people with castration-refractory prostate carcinoma'. The aim of the in-depth phase is to gain insight into the potential for improving the use of pharmaceutical products. We engaged an external party to carry out research into possibilities for appropriate use of pharmaceutical products on these patients.

Background
Castration-refractory prostate carcinoma (CRPC) is the final phase of prostate cancer. The disease has generally spread by then. Curative interventions are no longer possible. Treatments are therefore palliative in nature, with the main goal being retaining or optimising quality of life. Oncolytics are generally used in this final phase of the disease. The treatment arsenal for patients with CRPC has grown considerably during the past decade. There is a lack of clarity about the choices underlying the use of these medicines to realise the greatest effectiveness in relation to adverse effects.

Room for Improvement Report
Research has shown that it is possible to arrive at more appropriate use of medicines based on:
- appropriate diagnosis
- good harmonisation between care professionals
- reduced use of active treatments in the final life-phase

Appropriate diagnosis
Due to the increasing complexity of a rapidly changing treatment landscape, we see that a broader range of characteristics are used to make treatment choices than the criteria listed in the guidelines. Using this broader range of characteristics has narrowed the range of indications for using docetaxal. This does not necessarily result in under-treatment, but does imply that for every patient careful consideration should be given to whether he is eligible for chemotherapy despite the considerable burden this entails. These broader characteristics can offer a basis for appropriately opting for systemic therapy treatment in cases lacking evidence on the optimum sequence of treatment. Patient preferences can also play a role, though they could not be involved in the research.

To arrive at a more appropriate diagnosis, the *Zorginstituut* argues in favour of including in the guidelines – alongside initiation criteria – these broader criteria for not giving systemic treatment. Patient and tumour characteristics that help in practice to determine fitness for chemotherapy can be explicitly defined in the guidelines. First it is necessary to demonstrate whether this practice does describe the most appropriate use of pharmaceutical products. From the patient's perspective it is important that transparency exists about which criteria offer a valid basis for discussing treatment choices. This can help patients when discussing an appropriate choice of treatment with their care provider.

Good harmonisation between care professionals
An analysis of normal practice shows that, in most cases, patients whose diagnosis forms an indication for chemotherapy are referred to a medical oncologist. The role of the multidisciplinary consultation (MDO) could not be included in the study. Patients who were not referred to a medical oncologist were older, had several comorbidities or their disease showed a milder progression. In half of the cases, patients with an indication for systemic therapy but who were not treated with chemotherapy were never referred to a medical oncologist. It seems therefore that referral policy affects prescriptive behaviour in relation to the use of pharmaceutical products. The effect this has on survival could not be traced using the available data.

A multidisciplinary consultation structure, e.g. in an MDO, should play a clear role in decision-making on treatment and referral policy. Such a consultative structure can contribute allowing the urologist to remain the physician in charge of treatment for as long as possible, up to the moment that the medical oncologist has to assess the indication for systemic therapy.

Recognising the final life-phase and starting a timely dialogue.
Care consumption, e.g. hospital admissions and supportive treatment, is high in the final life-phase of CRPC patients. It is even higher among patients who started a new active treatment in the final life-phase. However, we were unable to find a causal relationship between starting systemic treatments in the final life-phase and increased care consumption.

In general, consensus exists in the Netherlands that starting new active therapies in the final life-phase serves no further purpose. The resulting dilemma is that identifying a patient in his final life-phase is complex. In the opinion of the *Zorginstituut,* it is essential that research is designed for recognising the final life-phase and initiating a timely dialogue with patients about what to do during this final life-phase.

Use of pharmaceutical products within the context of treatment and the disease
Oncolytics are generally used in the palliative phase of cancer. The primary objective is to retain or improve quality of life. Appropriate care is essential in order to realise this: no more and no less than is necessary. Our Room for Improvement Report is in line with this. This will guarantee the accessibility of these products for patients who are eligible for them. Recognising the final life-phase is important due to the need to reduce the burden of active treatment in the light of its probably limited effectiveness in the final life-phase. This requires a re-assessment of the treatment perspective in the final life-phase. In all stages of the disease, patients' preferences and desires must be explicitly taken into account in making treatment choices.

1 Introduction

Within the framework of the *Zinnige Zorg Programme, Zorginstituut Nederland* systematically assesses the Dutch minimal and mandatory package of health care that Dutch health care insurers must provide. There are four phases to this systematic assessment: screening, in-depth assessment, implementation and monitoring.
This report is a Room for Improvement Report within the framework of the in-depth phase and is about the use of pharmaceutical products on patients with castration-refractory prostate cancer (CRPC). This is one of the in-depth topics studied by the *Zorginstituut* in response to the screening phase of the systematic analysis of the ICD 10-field Neoplasms.[1] This topic was chosen at the suggestion of parties in health care. They expected quality improvement would be possible in the use of pharmaceutical products on people with this stage of prostate cancer.[1]

Points for attention for improving care as suggested by the parties
After the screening phase and the systematic analysis, the *Zorginstituut* joined forces with the parties to come up with research questions for this in-depth analysis. The *Zorginstituut* subsequently carried out research into these topics. We focussed on whether appropriate use is made of chemotherapy and treatment with new anti-hormone products, whether referrals by urologists to medical oncologists are appropriate, and what care looks like in the final life-phase.

Aim of this Room for Improvement Report
The purpose of this Room for Improvement Report is – based on in-depth studies – to shed light on how care with pharmaceutical products can be improved for patients with castration-refractory prostate cancer.

Methods
Eight elements of good care
The *Zorginstituut* describes eight approaches in the form of eight elements of good and appropriate care. These are quality-related and package-related elements (appendix 2). In an appendix we present additional research that was carried out (externally). By analysing use in practice, we are taking an integral look at the use of pharmaceutical products in caring for CRPC. As this Room for Improvement Report was prompted by explicitly defined questions, the *Zorginstituut* did not carry out additional systematic reviews of the evidence or cost-effectiveness analyses of individual pharmaceutical products.

External research
For the external research, the *Zorginstituut* commissioned the *Institute for Medical Technology Assessment* (iMTA), a research institute of the Erasmus University of Rotterdam. For replying to the research questions, the iMTA made use of data provided by the CAPRI-study ("Castration-resistant prostate cancer registry: an observational study in The Netherlands"). This was a retrospective observational study that collected information on CRPC patients based on anonymised patient files.

Structure of this report
Section 2 describes what castration-refractory prostate cancer is, what it means to a patient and what costs are involved. **Section 3** discusses the relevant background to treatment. We also discuss the choice of drawing up a Room for Improvement Report on care using pharmaceutical products to treat CRPC and potential bottlenecks surrounding care as suggested by the parties in the field.

Section 4 describes our Room for Improvement Report and our motive: we paint a clear picture based on where room for improvement exists based on the external research results. We discuss the input from the systematic analysis of the elements of good and appropriate care in **section 5**. The external research carried out has been added to the relevant appendix. Finally, in **section 6** we discuss implementation of the Room for Improvement Report.

2 Castration-refractory prostate cancer: background

This section describes exactly what castration-refractory prostate cancer is, its incidence and possible consequences for patients. This description demarcates this in-depth analysis:

- Castration-refractory prostate carcinoma (CRPC) is the final phase of prostate cancer. At this stage the disease is no longer sensitive (refractory) to classic hormonal treatment.
- The disease has generally already spread. Curative interventions are no longer possible: only palliative treatment remains.

2.1 What is castration-refractory prostate cancer?

Prostate cancer is the genesis and development of a malignant tumour in the prostate. Prostate cancer is one of the forms of cancer with the highest incidence among men and one of the five most prevalent forms of cancer in the Netherlands. In 2013 about 74,000 men had prostate cancer in the Netherlands. Prostate cancer is diagnosed more frequently in older men. The risk of developing prostate cancer before the age of 60 is very small.

The disease is characterised by various stages. In most men prostate cancer is discovered when the tumour is limited to the prostate. This is known as stages with localised disease; stages I and II. The prognosis is very good and most patients survive the disease (5-year survival 100%). In these early stages of prostate cancer, various treatments are possible, comprised of local treatment by removing the prostate, or radiotherapy, whether or not in combination with hormonal treatment and in the event that the disease is a mild form, a good option can be to wait and see.

Prostate cancer often develops slowly. In the early stages the disease is accompanied by few symptoms if any, as a result of which it may go unnoticed for a long time. Eventually the disease can return, with or without metastases.

If the disease returns or has spread, cure is no longer possible. In that case treatment is palliative and focusses on relieving symptoms. Retaining quality of life is the primary objective. Treatment may involve surgical castration or hormonal products that repress testosterone (also referred to as androgen deprivation or ADT). The objective of ADT is to reduce testosterone concentrations in the blood to a level comparable with what can be achieved with surgical castration. This is because the growth of prostate cancer cells depends on testosterone. A tumour that develops further and becomes progressive, despite testosterone repression, is referred to as castration-refractory prostate cancer.[2,3] This in-depth study is specifically about castration-refractory prostate cancer.

2.2 What is the incidence of CRPC?

The number of new cases of CRPC in the Netherlands is estimated to be about 3,000 per year.[4] After starting anti-hormone therapy, about 10-20% of the patients will develop CRPC within five years. 85% of the patients have metastases by the time CRPC is diagnosed. Another 5% will develop metastases within two years.[5,6] Without active treatment, survival is generally no longer than 12 to 14 months.

The survival of men with CRPC has improved in recent decades due to the arrival of new treatment possibilities: chemotherapies (docetaxel and cabazitaxel), new hormonal products (abiraterone and enzalutamide) and radionuclides (radium-223). These are discussed in more detail in section 2.

2.3 Cost developments

In 2011 the total care costs for prostate cancer were €254 million. In 2012 total claims for pharmaceutical products for the diagnosis prostate cancer (docetaxel, cabazitaxel, abirateron, enzalutamide and radium-223) amounted to €21 million. This increased to €52 million in 2014. In 2012 claims for abiraterone amounted to about €11 million (with no claims as yet for enzalutamide). In 2014 the combined claims for enzalutamide and abiraterone were €38 million[7,8].

Based on provisional statistics for 2015, total costs seem to have risen to more than €56 million. Apparently, about three-quarters of this amount (€43 million) was spent on abiraterone and enzalutamide.

Although the number of patients treated with docetaxel increased slightly between 2012 and 2014, the costs per patient actually decreased. As a result, the total costs for docetaxel in cases of prostate cancer fell from almost €7.5 million per year in 2012 to €5 million in 2014.

2.4 What do these patients experience?

When CRPC has been diagnosed

A patient who has been diagnosed with CRPC usually undergoes an intensive course of treatment: treatment of the primary tumour (surgery of the prostate or radiation therapy) and anti-androgenous therapy in the event of progression following primary treatment. After the primary tumour has been treated, monitoring generally takes place during five to ten years. These treatments and monitoring usually take place under the guidance of a urologist. Hormone therapy can affect a patient's well-being and sexuality drastically. Guidance in explaining to patients the consequences of the primary treatment are important objectives of monitoring. Sooner or later the prostate cancer becomes refractory. This may be asymptomatic or it may be accompanied with symptoms if metastases have developed. Prostate cancer spreads mainly into bones, which can be accompanied by a lot of pain. Prostate cancer can also spread into the lymph glands and other tissues and organs. Although this occurs less frequently than bone metastases, these too can cause symptoms, but metastases do not always cause symptoms. Metastases can be asymptomatic or cause few symptoms and only cause problems at a later stage. Once CRPC has been diagnosed, the moment has arrived to consider whether treatment should be given. If there are no symptoms, one might decide to wait until the disease becomes castration-refractory. In view of the palliative setting of castration-refractory disease, retaining quality of life is an important objective. Delaying the disease by means of treatment has also become an important objective for preventing symptoms and thus retaining quality of life.

Use of pharmaceutical products: choice of treatment

Choosing between retaining quality of life and possible health gains always plays a role when choosing a treatment. Factors that influence the choice of treatment are the patient's fitness and his prognosis, as well as the patients' preferences. Treatment may include chemotherapy, which is often accompanied by adverse effects such as loss of hair, tiredness, nausea and vomiting. New hormonal pharmaceutical products are often well-tolerated and have their own adverse effects.

As mentioned earlier, the treatment arsenal for CRPC has grown profusely during the last decade. The new pharmaceutical products all lead to a proven, but fairly similar, survival gain. As several treatment options are available with the same survival gain, the value a patient attaches to other aspects of treatment will increasingly play a role in the choice of treatment and/or pharmaceutical product. Aspects such as the adverse events involved or the intensity of the treatment (for instance treatment via infusion versus tablets, or treatment with hospital admission versus treatment in an out-patient clinic) will become increasingly important. Also very important is that patients' personal preferences are an integral part of these complex treatment choices. This complex decision-making process is also referred to as shared decision-making. This often proves difficult in daily practice. Patients are not always aware of the possibility of making choices about treatment options. It is not always easy for doctors to involve patients in this decision-making process.

The final life-phase: re-assessing the use of active treatment

The final life-phase is a special life-phase due to the need to re-assess the treatment perspective: the treatment perspective shifts from disease-oriented palliation (potentially life-extending) to symptom-oriented and patient-oriented palliation. As the disease progresses, the burden of treatment can increase and no longer be in proportion to the health gains achieved. In this case treatment should stop in good time to limit as far as possible the degree to which a patient is burdened. It is even more important to give a patient an opportunity to (re-)assess what is important to him and his loved ones during the remainder of his life. However, defining this moment is complex: with the new treatment possibilities, survival is extremely variable and treatments are relatively well tolerated. As a result the physician in charge may find it difficult to estimate the actual degree to which a patient can be burdened. There are no clear criteria for recognising that a patient has reached the final life-phase. The remaining life expectancy is generally a few months. Most doctors regard active, potentially burdensome and intensive treatment as serving little purpose. Discussing this in good time with the patient is essential in the final life-phase. Patients take precedence in this complex decision-making process.

The terminal phase

The focus in the terminal phase shifts from symptom-oriented palliation to trying to ensure the best possible quality of death. In practice, these are the last days preceding death, in which it is clear that death is inevitable.

Harmonisation between care professionals

If possibilities exist for treatment with pharmaceutical products, a patient is generally referred to a medical oncologist who determines whether, and in what sequence, follow-up therapy is indicated and draws up a treatment plan together with the patient. However, good communication and harmonisation with other care professionals involved in the treatment of CRPC is crucial for continuity and for optimum therapeutic effect of the treatment. Good communication is crucial, for both the patient and his family, about agreements made and about the patient's preferences. Effective communication increases the patient's sense of security and of being in charge.

3 What form of care is given for castration-refractory prostate carcinoma?

This section describes what care in the form of pharmaceutical products looks like in cases of castration-refractory prostate cancer and where this has been recorded. This is where we describe the context of the research questions.

- Chemotherapy with docetaxel is the first line treatment for symptomatic CRPC patients indicated for treatment. Patients without symptoms or with mild symptoms, or patients who are not fit enough for chemotherapy, can also be treated with new anti-hormonal products (abiraterone and enzalutamide)

- Currently there are no precise data on the best sequence for docetaxel and products such as abiraterone and enzalutamide

- Intensive treatment is often avoided in the final life-phase, from the patient's perspective, and from the perspective of quality of care

3.1 Treatment with pharmaceutical products

Treatment possibilities for patients with metastatic CRPC have increased considerably during the past 12 years. As metastatic CRPC is regarded as an incurable disease, the purpose of treatment is palliative. This shifts the objective from cure to retaining or improving quality of life by treating the burden of the symptoms. Palliative treatment, specifically disease-orientated treatment, can potentially extend a patient's life. Appendix 1 shows the moment of introducing pharmaceutical products in cases of prostate carcinoma. Table 2 contains a summary of the most important pharmaceutical products for treating CRPC.

3.1.1 Classic anti-hormonal products

A number of hormonal interventions are also possible in cases of CRPC. For example, ending the use (temporarily) of anti-hormonal products (anti-androgenous withdrawal), or the addition of an anti-androgen to treatment, if not already given. The guidelines recommend continuing treatment with LHRH.[2]

3.1.2 Chemotherapy

In 2005 treatment with chemotherapy (docetaxel), supplemented with prednisolone, became possible for patients with metastatic CRPC. Until then, standard treatment was mitoxantrone (with prednisolone). As docetaxel increases survival by almost 3 months in comparison with mitoxantrone, docetaxel is the new standard treatment for CRPC patients. Docetaxel was also mentioned as recommended treatment for these patients in the first version of the Dutch guidelines on prostate carcinoma from 2007.[9] In practice, mitoxantrone was often used next in the event of progression (e.g. measured tumour growth or repeatedly increased PSA) after treatment with docetaxel, although there was no evidence that mitoxantrone was effective in this setting.[10] However, this option was not mentioned in the guidelines as recommended treatment after docetaxel.

In 2011 a second chemotherapeutic drug, cabazitaxel, came onto the market for patients with progression after docetaxel and those who were not fit enough to be able to tolerate a course of chemotherapy. The effectiveness of cabazitaxel was

studied in comparison with mitoxantrone and a difference in survival of about 3 months was found in these patients. In practice this meant that the first choice for patients who had become castration-refractory was a course of chemotherapy with docetaxel (first line drug). If tumour progression occurred during or after the course with docetaxel, but a patient was not fit enough, a second course of treatment could be given with cabazitaxel (second line drug).

The 2014 guidelines advise only to start chemotherapy if the disease is symptomatic.[2] Recent research shows that the use of docetaxel on patients with locally advanced or metastatic prostate cancer who are not castration-refractory, leads to a longer survival.[11,12] The BOM committee recently concluded that six courses of chemotherapy, added to ADT, particularly in patients with prognostically unfavourable characteristics, seems to have a major added value.[13] The guidelines, which were updated in September 2016, do recommend this treatment.[14]

When to start treating CRPC patients with few or no symptoms is not clear, and according to the guidelines this should be discussed with the patient. According to the guidelines, a patient who is castration-refractory, but whose disease is not metastatic and who has no unfavourable prognostic factors, is not eligible for treatment with chemotherapy.[2] The following box sums up the indication criteria described in the current guidelines.

- Good performance score (WHO 0-2) and
- Symptomatic: with lymphatic, bone or visceral metastases, or
- Asymptomatic: with visceral metastases or with signs of rapid progression (time to CRPC less than one year after starting anti-hormone treatment)

In addition to patient characteristics and disease characteristics, patient preferences also play an important role in choosing whether or not to give chemotherapy. These were not included here.

3.1.3 New anti-hormone products

In 2011 and 2013 two new anti-hormone products became available for patients with metastatic CRPC who had already been treated with docetaxel. In clinical trials these products, abiraterone and enzalutamide, led to an extended survival, about the same for both products. The advantage these have over chemotherapy is that they can be given orally. The BOM committee issued a positive assessment for abiraterone at the start of 2012 and for enzalutamide in 2013, though the BOM committee stated that the study did not answer the question of whether one should opt for cabazitaxel, abiraterone or enzalutamide after progression on docetaxel.

At the end of 2012 and 2014 respectively, it became possible to use abiraterone and enzalutamide for patients with no symptoms, or only mild symptoms, if given prior to docetaxel. The first study results indicated that the use of abiraterone did not lead to improved survival and this was one of the reasons why, initially, the BOM committee did not issue positive advice for this treatment. However, new study results eventually became available which showed that abiraterone could improve survival for these patients. At the end of 2015 the BOM committee therefore issued a revised assessment. Although a lot is still not clear about the optimum use of the various products, the BOM committee did indicate that prior to chemotherapy, the choice for patients with few or no symptoms was between abiraterone and enzalutamide. For chemotherapy-naive patients, the market registration of abiraterone and enzalutamide is limited to patients who are asymptomatic or those with few symptoms, for whom treatment with chemotherapy is still not clinically

indicated.[15,16]

The 2014 guidelines state that in second line treatment, i.e. patients with CRPC after treatment with Docetaxel, the choice is between cabazitaxel, abiraterone and enzalutamide. According to the guidelines, in first line treatment abiraterone is only an option if chemotherapy is not possible. Enzalutamide and the additional data on abiraterone regarding survival when treatment precedes chemotherapy were not discussed in the guidelines.[2] The revised 2016 guidelines recommend as first line treatment chemotherapy for progressive CRPC in patients who are "chemo-fit". Alternatives for patients who are not chemo-fit, or for other reasons are not eligible for docetaxel, are abiraterone or enzalutamide. Opting for chemotherapy or new anti-hormone products depends in part on symptoms and diagnostics.

3.1.4 Radium-223

Radium-223 is a pharmaceutical product with a radioactive substance that is mainly absorbed in bones. As a result it can be effective on CRPC patients with bone metastases. This product arrived on the market at the end of 2013 and is intended for the treatment of patients with bone metastases but no metastases in the abdominal organs. The BOM committee issued positive advice for treating these patients if they are not eligible for treatment with docetaxel, or after treatment with docetaxel. The 2016 guidelines indicates a place for radium-223 as first or second line treatment for patients with bone metastases but without visceral metastases.

Table 2: Summary of the most important (expensive) pharmaceutical products for the treatment of CRPC

Treatment	**Marketing authorisation date**	**Survival gains (months) new treatment versus control**	**BOM committee advice**	**Place in Dutch guidelines (2014)[17]**	**Place in Dutch guidelines (2016)[14]**
Docetaxel	2004	19.2 vs 16.3 (mitoxantrone + prednisolon)[18,19]	Positive	First line	First line (progressive and "chemo-fit")
Cabazitaxel	2011	15.1 vs 12.7 (mitoxantrone + prednisolone)[20]	Positive	Second line	Second line
Abiraterone (in combination with prednisolone, after chemotherapy)	2011	15.8 vs 11.2 (prednisolone)[21]	Positive (fit patients)	Second line	Second line
Enzalutamide (after chemotherapy)	2013	18.4 vs 13.6 (placebo)[22]	Positive	Second line	Second line
Abiraterone (prior to chemotherapy)	2012	34.7 vs 30.3 (placebo + prednisolone)[23,24]	Negative; (implicit) positive upon reassessment	First line treatment patients in a good clinical state of health, only if chemotherapy is not an option	First line (progressive and "chemo-fit")
Enzalutamide (prior to	2014	35.3 vs 31.3 (placebo)[25]	Positive	-	First line (progressive and "chemo-fit")

chemotherapy)					
Radium-223	2013	14.4 vs 11.3 (placebo)[26]	Positive	-	First line Second line (without visceral metastases)

3.1.5 Place determination and sequence of treatment

There are currently four treatment options for treating CRPC patients after progression while on docetaxel: cabazitaxel, abiraterone, enzalutamide, and radium-223 if the disease has caused bone metastases. These treatments came onto the market in rapid succession, and clinical studies involving the products took place simultaneously to an extent. For this reason we do not know which of these three products is the best choice in respect of efficacy after chemotherapy. No research has been carried out into whether the products are effective when given sequentially, nor into how many treatments are effective. There are signs that the effects of enzalutamide are reduced when it is given after docetaxel and abiraterone, in comparison with the effects seen when given after only docetaxel. The same applies to abiraterone after treatment with docetaxel and enzalutamide.[27-35] As abiraterone and enzalutamide can now also be given before chemotherapy, this raises the question as to how these products can be used effectively on the same patient after chemotherapy. The guidelines have no recommendations for treatments subsequent to second line treatment. The BOM committee has the following to say on the matter:

> "Now that various new products have become available for the treatment of CRPC, there is growing uncertainty about the (optimum) sequence for treatments. It is not possible to indicate the exact positioning of abiraterone in relation to enzalutamide or to docetaxel."

The report on standard-setting of the Oncological Cooperation Foundation (SONCOS) described cooperation between various specialists. On the matter of the treatment of prostate carcinoma, the said report states that as soon as the status of castration-refractory prostate carcinoma has been reached, policy relating to care of the patient must be discussed in a multidisciplinary setting. This should include at least a urologist, a medical oncologist experienced in the treatment of prostate carcinoma, and a radiotherapist-oncologist. The guidelines agree with this.[2,36]

3.2 Palliative therapeutic treatment options

Bone metastases may go hand-in-hand with complications that can cause severe pain and limit function. External radiotherapy is highly effective for local pain caused by a limited number of bone metastases. In the event more extensive and more diffuse bone metastases, radionuclides (e.g. strontium-89, radium-223) are indicated.[37] If there are severe complications, e.g. the threat of a bone lesion or a pathological vertebral fracture, palliative surgery may be necessary (orthopaedic or neuro-surgery).[38] Pharmaceutical products capable of preventing skeletal complications, are products that affect bone metabolism, like bis-phosphonates (zoledronate or clodronate) and denosumab. Starting such products depends in part on the chemotherapy and hormone therapy that is still available for the patient.[2]

3.3 Topics suggested for improving care

At an initial meeting organised by the *Zorginstituut*, the parties in health care suggested three topics for in-depth research. These relate to the rapidly changing treatment landscape and the lack of clarity regarding the sequence of treatment. The parties feel that improvement is possible in relation to these three topics. The *Zorginstituut* translated them into the following research questions:

- Is systemic therapy being used appropriately: are patients with an indication for treatment with systemic therapy actually receiving this treatment?
- Are urologists referring patients with an indication for systemic treatment to a medical oncologist?
- Are pharmaceutical products being used appropriately for CRPC patients in the final life-phase?

4 Room for Improvement: insights based on the study results

The *Zorginstituut* has examined the form that pharmaceutical care takes in cases of castration-refractory carcinoma and where improvements are possible in the care of CRPC patients. The results of this study are presented in detail in the relevant appendix. As we were only able to look at patients diagnosed with CRPC during the period 2010-2012, the analysis cannot apply in full to current daily practice due to the continually changing treatment landscape. Nevertheless, discussing the outcomes, and how these relate to the treatment guidelines and advice that applied at the moment of prescribing medicines, does lead to insights that can be used to make recommendations that are relevant for current practice. The analysis also illustrates how various new treatments have found their way into daily practice.

Due to the increasing complexity of a rapidly changing treatment landscape, we see that a broader range of characteristics are used to make treatment choices than those stated in the guidelines. In cases lacking evidence on the optimum sequence of treatment, these broader characteristics can offer a basis for opting appropriately for systemic therapy treatment. No current guidelines are available that combine evidence-based and consensus-based recommendations (e.g. based on feedback information). The *Zorginstituut* concludes specifically in this situation – which is characterised by a complex, continually changing treatment landscape and an important place for the MDO – that professional groups are responsible for determining the choices based on which systemic treatment should or should not be initiated.

4.1 Use of systemic therapy

The introduction of new pharmaceutical products and the wider use of existing products has boosted the number of patients being treated with systemic therapy over the past few years.

What does the study show?

Of all patients included in the CAPRI-study, 46% received docetaxel. Of the patients who were indicated for treatment with docetaxel, 60% of them were actually treated with docetaxel (table 3). The data suggest that though these patients were fitter, the course of their disease was more progressive than that of patients with an indication for treatment with docetaxel but who were not treated with docetaxel. This difference between these groups of patients gives indications about which tumour characteristics and patient characteristics were weighed up in determining whether or not a patient is fit enough for chemotherapy.

Table 3: Docetaxel, indication and treatment

Number of patients		**Docetaxel treatment**		
		Yes	No	Total
Indication for docetaxel	Yes	646 (42%)	437 (29%)	1,083 (71%)
	No	53 (3.5%)	388 (26%)	441 (29%)
	Total	699 (46%)	825 (54%)	1,524

In practice we see that characteristics which are not formalised in the guidelines, though they cannot be described as inappropriate care, are being taken into account in the decision on chemotherapy treatment. Patients' preferences also increasingly play a role in choosing whether or not chemotherapy is given.

The 2014 guidelines state that abiraterone can be used as an alternative for patients with a good clinical condition and progressive CRPC if they are not eligible for docetaxel.[17] Abiraterone was not yet available in 2007, when the last version of the guidelines was published. According to the analyses, abiraterone was used on 19% of the patients who were never treated with chemotherapy, despite having an indication for docetaxel. We expect the use of abiraterone and denzalutamide for chemotherapy-naive patients to have increased considerably by now, because enzalutamide (before chemotherapy) became available in 2014, and abiraterone (the final analysis showing the survival advantage) in 2015.

At the moment, abiraterone or enzalutamide can be considered for patients with progressive CRPC who have no symptoms if any, and whose condition is good (WHO performance score 0-1). Docetaxel is indicated for fit (WHO 0-2), symptomatic patients or asymptomatic patients with signs of rapid progression. Thus, according to these criteria, patient with few symptoms are indicated for treatment with either abirateron/enzalutamide or docetaxel. The optimum treatment strategy for these patients is now clear, based on the evidence currently available. The revised 2016 guidelines recommend that patients who are "chemo-fit" are treated with chemotherapy, and emphatically states that all patients should be discussed in an MDO.

Thus, when docetaxel is indicated, there are three possibilities for using docetaxel, based on the current treatment on offer. First, initial treatment can be docetaxel. After docetaxel (post second line treatment), second line treatment can start with chemotherapy (cabazitaxel), or hormone treatment with abiraterone or enzalutamide can be considered.

Second, despite the docetaxel indication, one can choose not to treat using docetaxel. This is a possibility if a patient is not eligible for docetaxel (e.g. if the patient is not "chemotherapy-fit") or if the patient has personal reasons for not wanting chemotherapy. In this situation, assuming the patient is eligible, abiraterone or enzalutamide can be an alternative to chemotherapy.

Third, treatment with docetaxel can be delayed, e.g. due to conservative, wait-and-see policy or because pre-docetaxel treatment is given first, to patients who are eligible, with abiraterone or enzalutamide. Possible post-docetaxel treatments include cabazitaxel or a new treatment with abiraterone or enzalutamide.

Now that, according to the recently revised modular guidelines, in some cases

docetaxel can also be added to treatment with ADT in the hormone-sensitive stage, the use of docetaxel for CRPC may decrease. It is therefore highly likely that the treatment landscape will change again in the near future.

Firm evidence is not always available to answer the question of whether, in order to realise the best efficacy, a patient is eligible for chemotherapy, and if so when. Based on data from daily practice, the findings do suggest that implicit choices made in the past which ignore the guidelines may provide a footing for the future. In particular these provide insight into which characteristics play a role in determining whether a patient is "chemotherapy-fit". In that case, whether the use of these characteristics describes the most appropriate use of pharmaceutical products still has to be validated.

At the moment registers are used almost exclusively for feedback. This in-depth analysis is based on that feedback. However, the added value would increase enormously, specifically for insight into the treatment of CRPC, if – in addition to feedback – registers could also provide insight into relative effectiveness. This requires a more far-reaching demand-oriented collection of data and analysis methods than currently provided by observational studies. At the moment this shortcoming limits the use of observational studies to feedback and a lower level quality of evidence.

What can be concluded based on the study findings?
We conclude that for every patient a decision needs to be made as to whether he is eligible for chemotherapy, despite its heavy burden. The fact is that this involves making choices that cannot be substantiated with the highest level of evidence. Nevertheless, we feel that the considerations currently being made in practice, namely regarding the fitness of the patient and certain tumour characteristics, are an important addition to the guidelines and advice on treatment. Preferably, explicit patient characteristics and tumour characteristics should be recorded to help determine fitness for chemotherapy. This need is increased by the fact that treating CRPC is highly complex due to the various treatment possibilities, uncertainties regarding substantiation, patient characteristics and external factors. This transparency about treatment decisions is highly desirable from the perspective of patients.

Therefore, the *Zorginstituut* argues in favour of formulating start criteria, or criteria for foregoing treatment. Consensus-based considerations can be added to evidence-based considerations in cases in which a high level of evidence is lacking. The systematic collection of insights, e.g. based on the CAPRI-study, can be invaluable, despite the fact that current treatment strategy has evolved in the meantime in comparison with the CAPRI-study.

Improvement activity
An appropriate diagnosis can be realised by formulating start criteria, or criteria for foregoing treatment with chemotherapy, which gives greater certainty when determining fitness for chemotherapy. Signs based on feedback can be used, as long as they are consensus-based, to supplement existing evidence-based criteria. First it is necessary to demonstrate whether this practice does describe the most appropriate use of pharmaceutical products. It is essential that the guidelines are updated soon.

4.2 Referrals

What does the study show?
In half of the cases, patients with an indication for systemic therapy but who were not treated with docetaxel, were never referred to a medical oncologist. The fact that these patients were less likely to receive systemic therapy does not necessarily mean that they were under-treated because the patient characteristics and disease characteristics may also differ. Another possibility is to involve the medical oncologist in treatment strategy via a multidisciplinary consultation. We cannot delve more deeply into this because data to answer this question were not collected. Patients with an indication for chemotherapy (and thus for a referral) and who were actually referred, were often younger than 75 years and had fewer co-morbidities than patients who were not referred.

In the Netherlands, chemotherapy for CRPC is almost exclusively prescribed by a medical oncologist. Oncologists have more experience with undesired effects that can occur due to chemotherapy. When assessing who is eligible for which treatment, whether this is chemotherapy, or another systemic therapy such as abiraterone and enzalutamide, the input of a medical oncologist is essential for making a choice of therapy.
Moreover, these patients must be discussed in a multidisciplinary consultation in which a medical oncologist participates who is experienced in treating prostate cancer. It is therefore difficult to trace the exact input of the medical oncologist based only on a referral.

Conversely, more intensive collaboration is needed. This is closely linked to the lack of clarity about the optimum treatment strategy, all the more now that pre-chemotherapy treatments are available. It is important to carefully consider all treatment options, including ending treatment, and to involve the medical oncologist when a patient has an indication for both chemotherapy and a pre-chemotherapy treatment, of if he may not (yet) be eligible for chemotherapy.

What can be concluded based on the study findings?
In view of the work territory of the medical oncologist in relation to treatment with chemotherapy, in the opinion of the *Zorginstituut* it is essential that a patient with an indication for systemic therapy is assessed by a medical oncologist. Treatment – and determining who is in charge of treatment – can be agreed in consultation with the patient, the urologist, the medical oncologist and the radiotherapist.

Recent evidence shows that certain patients whose prostate cancer is still hormone-sensitive may benefit when docetaxel is added to their treatment. The BOM committee recently issued positive advice on this treatment. This means that the input of a medical oncologist is desirable at a (much) earlier stage. It is in patients' interest to determine in the near future how collaboration between the urologist and the medical oncologist will take place and to ensure that patients who are eligible for this care receive it.

Improvement activity
A clear role of a multidisciplinary consultation structure, e.g. an MDO, should be updated with a place for the urologist as physician in charge as long as possible, until such time that the oncologist needs to assess the indication for systemic therapy.

4.3 Final life-phase

What does the study show?
A lot of care is consumed during the last three months of life. Care consumption is higher for patients who are started on a new active therapy than for patients who no longer received active treatment during this period. This is mainly about the number of patients admitted to hospital and the number of hospital admissions. The data suggest that patients for whom a new active treatment was started during the final life-phase were younger, but had a more aggressive disease. Using the available data, we were unable to gain insight into whether these patients benefited from the use of therapy during final three months of their life in comparison with patients with the same characteristics but who did not receive active treatment.

What can be concluded based on the study findings?
It is not clear whether patients benefited from the use of the therapy during the final life-phase. In general, consensus exists in the Netherlands that starting new active therapies in the final life-phase serves no further purpose. The question is whether one could predict, at the moment of starting therapy, that these patients were in the final life-phase.

Improvement activity
Although we could not find a causal relationship between the use of systemic treatment during the final life-phase and increased care consumption, we do feel that active systemic therapy is often used inappropriately in the final life-phase. It is important to manage the final life-phase, in dialogue with patients, based a far as possible on the patient's own wishes. The dilemma is that defining the final life-phase is complex.

5 Elements of good care

In sections 4 and 5 we described the use of CRPC care in practice. In this section we describe additional elements that the *Zorginstituut* regards as good care (see appendix 2 for more information about the eight elements of good care). The other elements do not lead to concrete improvement activities here, but are relevant for the next phases of the *Zinnige Zorg* programme's cycle of improvement.

Knowledge about good care
Knowledge about good care is about the availability of quality standards, information standards, patient information/decision aids and instruments of measurement (PREMs/PROMs). Quality standards are dynamic products that are continually being developed and if necessary adjusted. We include a summary in appendix 3. Our improvement activities relate specifically to the multidisciplinary treatment guidelines on castration-refractory prostate carcinoma. This criterion is therefore not discussed further here.

Application in practice
Application in practice is about the degree to which quality standards, decision aids and instruments of measurement are implemented: analyses of data on actual practice, the literature. We examined this based on research that was carried out externally, and which sheds light on where potential exists for improvement. The outcomes of this research are presented in the relevant appendices.

Care outcomes
When examining care outcomes, we look at whether quality information on outcomes is available and findable.

A set of indicators exists for prostate cancer in a curative setting. This instrument of measurement has been included in the *Zorginstituut*'s register of quality products.

Effectiveness
What do the analyses show?
The *Zorginstituut* (the former CVZ) assessed the post-docetaxel use of cabazitaxel and abiraterone. In 2011 it was concluded that, in comparison with mitoxantron, cabazitaxel has a therapeutic added value in fit patients (ECOG PS 0-1) with hormone-refractory, metastatic prostate cancer and disease progression despite earlier treatment with docetaxel, cabazitaxel.[4]
At the start of 2012 , CVZ concluded that the therapeutic value of abiraterone was equal to that of cabazitaxel for the second line treatment of CRPC patients.[39]
Currently there are no firm data on the best sequence for docetaxel and products such as abiraterone and enzalutamide (see Chapter 3).

High quality evidence is essential to arrive at 'evidence-based' recommendations on optimum treatment strategies. We see a great need to fill this 'evidence-gap'. On the one hand this could take the form of randomised research focussing on this question. On the other hand it would be valuable to examine the extent to which optimum effectiveness can be determined based on observational research (registers). Future registers could be designed with this in mind.

At the moment registers are used almost exclusively for feedback. This in-depth analysis is based on that feedback. However, the added value would increase

enormously, specifically for insight into the treatment of CRPC, if – in addition to feedback – registers could also provide insight into relative effectiveness. This requires a more far-reaching demand-oriented collection of data and analysis methods than currently provided by observational studies. At the moment this shortcoming limits the use of observational studies to feedback and a lower level quality of evidence.

Cost-effectiveness

What do the analyses show?

In its assessment of cabazitaxel and abiraterone, CVZ presented an estimate of the cost-effectiveness. For cabazitaxel the relationship between the incremental costs, compared to those of mitoxantrone, and the incremental benefits, compared to those of mitoxantrone (expressed as quality of life-adjusted life-years gained), were estimated at €120,819/QALY.

For abiraterone, the estimated cost-effectiveness was €61,171/QALY compared to treatment with cabazitaxel, and €104,454/QALY compared to prednisolone monotherapy.

At the moment of assessment, CVZ still did not use reference values for cost-effectiveness. For a disease with this burden of disease, the *Zorginstituut* currently uses a maximum reference value of €80,000/QALY. The *Zorginstituut* did not carry out a re-assessment to determine the cost-effectiveness in practice.

In order to estimate the current cost-effectiveness in practice, evaluations are needed based on information from daily practice that also measure quality of life. This is not currently possible, though the data will be collected in the follow-up to the CAPRI-study (PRO-CAPRI). We are currently unable to estimate whether the use of pharmaceutical products for CRPC is cost-effective in practice. A monitoring phase will follow after the implementation phase has ended that resulted from this in-depth assessment. In view of the signal that the cost-effectiveness of individual products may be unfavourable, this will emphatically play a role in considerations relating to the selection of follow-up analyses on this topic.

Necessity

The *Zorginstituut* includes burden of a disease in necessity (is the disease serious enough to insure) and considering whether treatment can be funded by patients themselves.

What do the analyses show?

Burden of disease is determined based on loss of quality of life and the possibility of life being shortened. The burden of disease of CRPC in the Netherlands is estimated at 0.640 on a scale of 0 to 1, where 1 is equal to mortality and 0 to 'perfect health'. This is 0.930 for terminal prostate cancer.[40] The *Zorginstituut* regards such a burden of disease as (very) high. The costs per patient are also very high: in 2015, per patient, docetaxel cost more than €3,000, cabazitaxel cost more than €20,000, enzalutamide cost more than €13,000, while abiraterone cost almost €20,000 and radium-223 cost almost €13,000.[8]

The *Zorginstituut* concludes that CRPC treatment with pharmaceutical products must be insured. No room for improvement exists here.

Feasibility

We use the criterion feasibility to examine whether there are factors that hinder the successful implementation of care. These could include, e.g. basis of support,

budget impact or the organisation of health care on a macro level. These are preconditions for successful use, rather than for the implementation and quality of implementing specific elements of care, as takes place with the *use in practice* quality criterion. For this reason, the responsibilities of the urologist and the medical oncologist are not part of the *feasibility* criterion.

A lot of experience has been gained in Dutch practice in organising oncological care and its funding in general, and the *Zorginstituut* detected no problems relating to this that indicate limited feasibility of using pharmaceutical products for CRPC. At the moment, thus, there is no potential for improvement here.

The costs of pharmaceutical products for CRPC rose sharply over the past few years, from €21 million in 2012 to €52 million in 2014. The most important reason for this is the availability of new pharmaceutical products, which can cost more than €20,000 per user, per year. The number of patients has also increased. At the moment it is difficult to estimate how costs will develop over the next few years. This is because the treatment arsenal is growing and the place of pharmaceutical products in treatment is changing.

We conclude that attention must be given to this trend of increasing costs. During the monitoring phase, the *Zorginstituut* will explicitly monitor the costs of the various individual products, and the costs of CRPC medicines in total.

Consistency in quality circles
Various parties in health care have paid a lot of attention to improving the quality of care for men with CRPC. The *Zorginstituut* can contribute to this by providing knowledge, data and research, and through its combined tasks in the field of package management and quality improvement. By choosing this topic, the *Zorginstituut* envisages possibilities for synergy with current initiatives, such as the Quality and Appropriateness Agenda of the partners in the Outline Agreement.

6 Implementation and monitoring

Implementing these improvement activities is the task of the parties in health care, based on their respective accountabilities within the health care system. Where necessary, further collaboration will be sought with other parties.

For this topic, the most important improvement activity is stronger evidence on guideline recommendations in relation to patient characteristics and disease characteristics and whether or not therapy should be offered. In our implementation and monitoring phases, we want to evaluate these choices based on effectiveness data, specifically on quality of life, to be able to make statements on the appropriate use of systemic therapies for CRPC. This will be possible, e.g, based on data currently being collected in the PRO-CAPRI-study.

About three months after publishing the Room for Improvement Report, the *Zorginstituut* will organise a meeting to discuss implementation and the role that each party can play. We will also facilitate implementation research or give advice.

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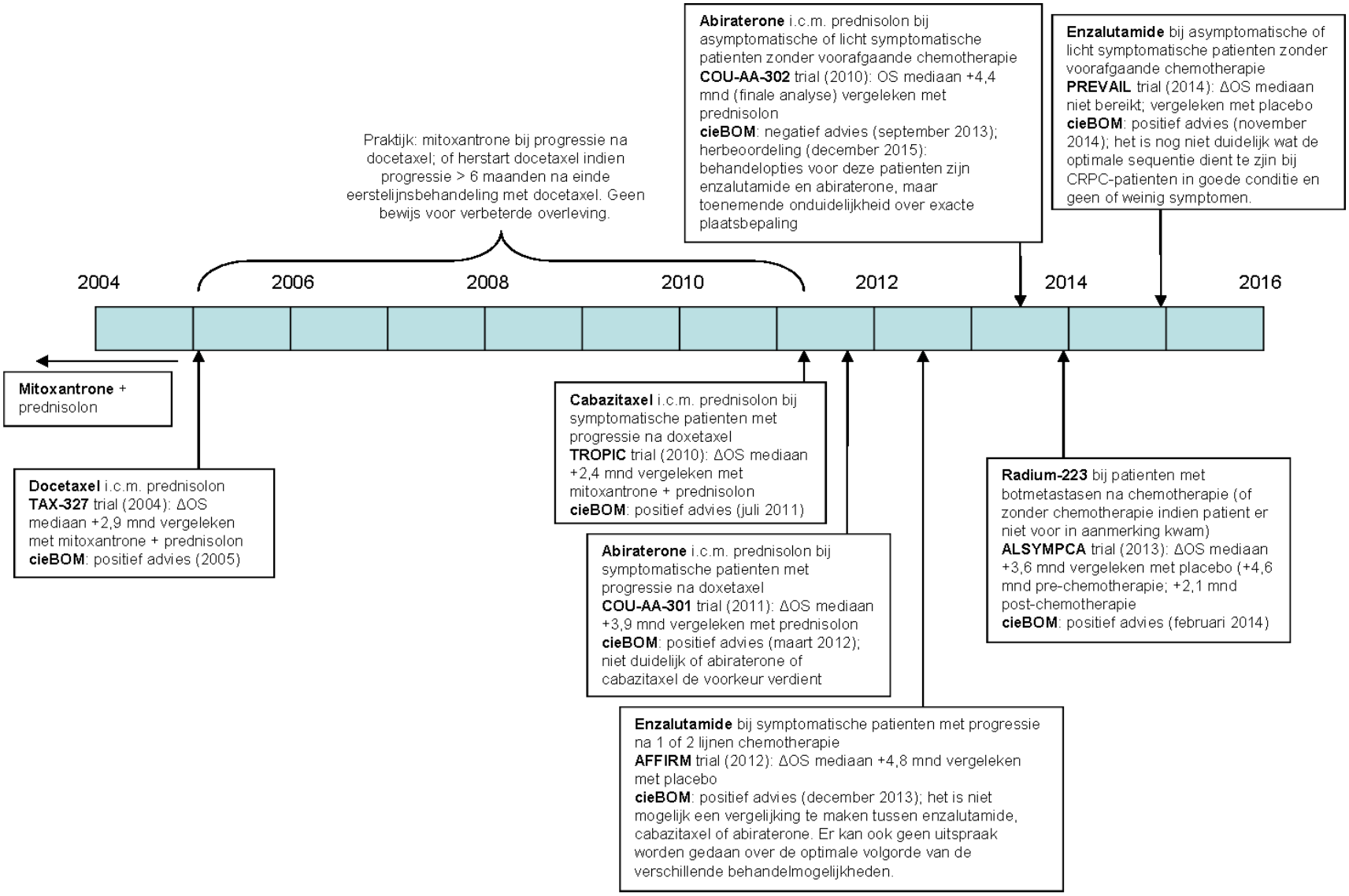
Appendix 1: Treatment of CRPC



Appendix 2: Accountability

In this 'Accountability' appendix we explain the main outline of how the *Zinnige Zorg* programme works, with attention to the quality elements and package criteria and the use of claim data in analyses, we provide a summary of the parties involved, describe how we have worked together with the parties and turn our attention to describing the process.

Working method of the *Zinnige Zorg* Programme

Points of Departure

The *Zorginstituut* designed a systematic working method for the *Zinnige Zorg* Programme for examining the use that is made of care in the insured package. The key is to identify and reduce ineffective and/or unnecessary care, in order to improve the quality of care for patients, increase health gains and avoid unnecessary costs. We carry out a systematic assessment for a field of disorders as defined in the ICD-10 classification system. A systematic assessment is carried out based on a number of points of departure:

Central role for patients
When assessing care, we give a central role to patients and the care pathway they follow. The underlying question is always how much does a patient benefit from the care given? Is he receiving care that is appropriate to his situation, or is he perhaps receiving too little care (under-treatment) or too much care (over-treatment)?

Shared decision-making
Care must be in keeping with patients' personal circumstances. In addition to the diagnosis, patient-related matters play a role in the choice of treatment, such as a patient's expectations, his professional situation, impact on social functioning, pain perception, motivation, etc. For some diagnoses it is clear which treatment options should be deployed. Often, however, various treatment options exist, each with their pros and cons, and opting for a given treatment will depend more on the preferences of the patient and his carer. Shared decision-making is a way of arriving at an optimum treatment pathway together with a patient. Various instruments exist that can support the shared decision-making of doctors and patients effectively – such as decision aids, option grids and patients' versions of guidelines – and which increase the quality of the decision-making process.

Stepped care
We assume that courses of treatment start based on the stepped care principle. According to this principle, care is offered based on a step-by-step plan: starting with the least burdensome effective treatment, and only when this gives insufficient results are more complex or more invasive interventions offered. Stepped care is a general point of departure, not a mandatory requirement. The 'start moment' is not necessarily step 1, as steps may be skipped, according to the symptoms with which a patient presents.

Parties in health care are involved throughout the entire process
The *Zorginstituut* wants to realise active agreement with the parties in health care. This will benefit the quality of the analyses and the basis of support for improvement measures. We involve the parties who bear responsibility in all phases of the systematic assessment.
The parties are invited to attend various consultations via umbrella arrangements.

They are also given an opportunity to participate in supervising the research of external research bureaus. Lastly, we ask parties for comments on draft versions of reports.

Phases of systematic assessment
In order to promote good care, we carry out a systematic assessment according to a quality circle, or improvement circle, as illustrated in the following figure. This circle is comprised of four sequential phases:
1. Screening phase
2. In-Depth Analysis Phase
3. Implementation phase
4. Evaluation phase

Figure 1: Zinnige Zorg's circle of improvement

Zinnige Zorg's circle of improvement starts with a screening phase, in which we analyse how care is currently being given ('snapshot'). Based on this, a number of topics are chosen for in-depth analysis. In the second phase, the in-depth phase, we determine the potential for improvement, per topic. In the third phase (implementation) it is mainly up to the parties in health care to implement the agreed improvement measures. Lastly, in the evaluation phase we examine the extent to which the goals set have been achieved and whether a new circle of improvement should start, possibly using different instruments for improvement. Where necessary, if insufficient results are realised, the *Zorginstituut* can make use of its statutory instruments (e.g., clarification, advising on inclusion in – or exclusion from – the package, power to overrule within the framework of the Multi-Year Agenda). The Multi-Year Agenda offers an overview of top-priority fields of care for which quality standards, measuring instruments and information standards (hereafter: quality products) are being developed. If the *Zorginstituut* sees that the parties involved are in default, after the periods specified in the Multi-Year Agenda have lapsed, the *Zorginstituut* will take over the initiative or the coordination of developing a quality product. This is referred to as the power to overrule. Below we describe the four phases of the circle of improvement in more detail.

<u>Screening phase</u>
The objective of the screening phase is to select a number of topics for in-depth analysis with a possible potential for improving the quality and effectiveness of care

by using care more appropriately. These topics are recorded in a report that is sent, together with the underlying analysis, to the parties in health care and to the Minister of Health Welfare and Sport.

Figure 2 shows how we obtain establish in-depth topics by consulting various sources in a systematic analysis. Sources include the quality standards (guidelines, care standards and care modules), scientific literature, claim data and other data, and the parties in health care. This involves not only collecting and analysing all the detailed information, but also searching for signals from daily practice in order to obtain a succinct picture of the care provided in the current situation. We look at the care pathway that a patient follows from the perspective of the *Zorginstituut*, with the elements that the *Zorginstituut* defines as good and appropriate care (see explanation below).

Figure 2: From sources to in-depth topics in the screening phase

The choice of in-depth topics is based on the systematic analysis (based on the elements of good and appropriate care), the size of the topic (number of patients, burden of disease, budget impact), possible improvements and what the parties in health care feel is important.

<u>In-Depth Analysis Phase</u>
The screening phase is followed by the in-depth phase. The objective of this phase is to make the method for achieving potential improvements in the selected topics as concrete as possible.

Per topic, based once again on the elements of good and appropriate care, we carry out an in-depth study and we supply any missing knowledge in the form of extra data-analyses, scientific reviews, studies of daily practice and/or literature studies.

The final results are recorded in a so-called Room for Improvement Report. This states which improvements in care and in health the *Zorginstituut* feels are possible, in respect of both content and amount, and provides an estimate of the total sum of costs involved (budget impact). We try to ensure that agreements with the parties on improvement measures are as concrete as possible. The Room for Improvement Report is also sent to the parties in health care and to the Minister of VWS.

Implementation phase
The implementation phase is primarily a task for the parties in health care: patients, care professionals, institutions and health insurers. It takes place based on agreements made in the in-depth phase. In the implementation phase the *Zorginstituut* can play a supportive and facilitative role, for instance, by organising meetings, providing data and feedback, and by carrying out additional research. In order to guarantee compliance with agreements, both in respect of content and time, the *Zorginstituut* can place action points from the Room for Improvement Report that relate to quality standards and measuring instruments on the Multi-Year Agenda.
Periodically, the *Zorginstituut* reports on progress booked to the accountable parties and to the Minister of VWS.

Evaluation phase
During the evaluation phase, the *Zorginstituut* examines, together with the parties involved, whether the results mentioned in the Improvement Report have been achieved. Based on this, we determine whether a new circle of improvement should start, possibly using different instruments for improvement. During this phase we also examine whether all necessary information is structurally available.

Elements of good and appropriate care
We carry out an analysis of care in both the screening phase and the in-depth phase. To do this, we use the "elements of good and appropriate care". Together, these give an idea of what the *Zorginstituut* regards as good and appropriate care. They are also in keeping with our quality and package management tasks. The following analysis scheme is used:

1. Knowledge about good care
A description of what we know about the availability of national and international quality standards (such as guidelines), measuring instruments (questionnaires and indicators) and information standards. We see whether these can be found in, e.g., the *Zorginstituut*'s Register. Their entry in the Register shows that they fulfil the procedural criteria of the Assessment Framework[41]. We try to ensure that everything that can be found is included in *Zorginzicht.nl*.
Does patients' information exist, such as a patients' version of guidelines, or information about diagnosis and treatment on the website of a patients' association or on *KiesBeter* or *thuisarts.nl*? Are there decision aids, option grids or outcome indicators which are relevant to patients, such as measures of quality of life, PROMs and PREMs?[42] On which websites (public database and public information) can they be found?

In addition to procedural matters, we also look at the content of standards and guidelines: what recommendations are made that are relevant to our topic and is there sufficient scientific evidence for (recommendations in the) guidelines? Lastly, we look at concordance between guidelines for first and second line treatment.

2. Application in practice
We use various sources (such as claim data, publications, formal and informal

consultations) to look at how care takes place in practice (including concordance between first and second line treatment) and what the experts think about it. We compare this to what we found in practice on recommendations in quality standards and guidelines.

3. Care outcomes
Do patients benefit from the treatment? Is information available about quality of care and care outcomes, and can it be found by care providers, patients and citizens? For instance, a registry of complications, mortality statistics after an operation, data from PROMs and PREMs. Where can this information be found, e.g., on such websites as *Kiesbeter.nl* or *Zorgkaartnederland.nl*.

4. Effectiveness
Is the care effective? If we feel that scientific substantiation of the guidelines (as assessed under 1, Knowledge about good care) is of sufficient quality, we take the recommendations in the guidelines as our point of departure. If the guidelines are of insufficient quality, or are dated, we can inform the parties that the guidelines need to be updated. A formal assessment based on the criteria established by the *Zorginstituut*, including a systematic review based on the GRADE system, only takes place if this is dictated by bottlenecks and there are no recommendations in the guidelines or there seems to be insufficient scientific evidence.

The primary questions, as described in the so-called PICOT, are an important part of an assessment of effectiveness: For which group of patients is the care intended and is that the group for which research is available? Which treatment or care is being offered and has this care been studied? With which control treatment (regular care, standard therapy) was that care compared and what is the added value of the recommended care? And which outcomes relevant to patients were examined in order to determine whether the care was effective and for how long?

5. Cost-effectiveness[44]
Cost-effectiveness shows whether the (added) costs incurred to achieve an effect are reasonably in proportion with a treatment's effectiveness. We look at whether the guidelines have anything to say about cost-effectiveness, we look at the (scientific) literature, and, if necessary, we carry out our own cost-effectiveness study.

6. Necessity[45]
This is where we examine whether a form of care should be part of the basic health insurance or whether it involves costs that people could pay for themselves. Weighing this up involves two different aspects: severity of the disease (burden of disease) and the societal necessity of actually insuring the treatment concerned. With burden of disease the emphasis is on medical necessity, while with 'necessity to insure' the emphasis is on whether insurance is actually necessary.

7. Feasibility[45]
Care that is not feasible cannot be supplied. The feasibility element indicates whether the preconditions have been fulfilled and how sustainable including an intervention in the basic package is. Relevant to this are, e.g., basis of support, how care is organised (indications and administration), funding, jurisdiction and ethics. This also involves, for instance, whether a funding formula (intervention description) exists for an intervention that should be included in the basic package.

8. Consistency in quality circles
This is where we look at whether quality circles are used that focus on improving care, who uses them, and the interdependence that exists between quality circles.

Difference in the screening phase and the in-depth phase
The spectacles with which we examine care are, in principle, the same for all phases of the assessment, based on the eight elements mentioned above. Sometimes the nature and intensity of the systematic analysis differs in the screening phase and in the in-depth phase. The terminology itself shows that the first involves a global inventory, at the level of a disorder (ICD-10), and that the selected topics are examined in more detail during the in-depth phase. This phase often also combines various data sources.

Parties involved

The following parties are involved in the in-depth phase:
- Prostate Cancer Foundation
- Dutch Federation of Cancer Patients Organisations (NFK)
- Dutch Patients' Federation
- Netherlands Association of Internal Medicine (NIV)
- Netherlands Association for Medical Oncology (NVMO)
- Netherlands Association for Urology (NVU)
- Federation of Medical Specialists (FMS)
- V&VN Oncology
- Association of Dutch Healthcare Insurers (ZN)
- Dutch Association of Hospitals (NVZ)
- Top Clinical Hospitals Association (STZ)
- Dutch Federation of University Medical Centres (NFU)

Third-party studies commissioned by *Zorginstituut Nederland*

Disclaimer
In realising this report, the *Zorginstituut* commissioned an external party to carry out research: the Institute for Medical Technology Assessment (iMTA), a research institute of the Erasmus University of Rotterdam. iMTA made use of the CAPRI-study ("Castration-resistant prostate cancer registry: an observational study in The Netherlands").

The iMTA is responsible for the data and analyses. The iMTA's data and conclusions were not always adopted in the *Zorginstituut*'s own reports. The *Zorginstituut* is responsible for the interpretations of the analyses included in this Room for Improvement Report.

Appendix 3: Summary of knowledge about care

Type	Date	Title	Accountability
Advisory	2016	Prostate cancer, national guidelines, version 2.1[14]	Dutch Association for Urology (NVU)
Guidelines (quality standard)	2014	Prostate cancer, national guidelines, version 2.0[17]	Dutch Association for Urology (NVU)
Advisory	2007	Prostate cancer, national guidelines, version 1.0[9]	Dutch Association for Urology (NVU)
Advisory	2014	Prostate cancer, national guidelines, version 2.0[2]	Dutch Association for Urology (NVU)
Advisory	2015	Guidelines on prostate cancer[46]	European Association of Urology
Advisory	2015	Cancer of the prostate: ESMO clinical practice guidelines for diagnosis, treatment and follow-up[47]	European Society For Medical Oncology
Standard	2013	Micturition complaints in men[48]	NHG
Patients' brochure	2015	Prostate cancer.[49]	KWF Kankerbestrijding
Patients' information	2014-2016	Prostate cancer.[50]	Kanker.nl
Patients' information	2014	Prostate cancer.[51]	NHG
Treatment advice	2005	Docetaxel for hormone-refractory prostate cancer[52]	Dutch Association for Medical Oncology
Treatment advice	2011	Cabazitaxel for docetaxel-refractory prostate cancer[10]	Dutch Association for Medical Oncology
Treatment advice	2012	Abiraterone for docetaxel-refractory prostate cancer[53]	Dutch Association for Medical Oncology
Treatment advice	2013	Abiraterone for metastatic castration-refractory prostate cancer without prior chemotherapy[54]	Dutch Association for Medical Oncology
Treatment advice	2013	Enzalutamide for metastatic prostate cancer after chemotherapy[55]	Dutch Association for Medical Oncology
Treatment advice	2014	Radium-223 for bone metastatic prostate cancer[56]	Dutch Association for Medical Oncology
Treatment advice	2014	Enzalutamide prior to chemotherapy for metastatic prostate cancer[57]	Dutch Association for Medical Oncology
Treatment advice	2015	The reassessment of abiraterone for metastatic castration-refractory prostate cancer without prior chemotherapy[58]	Dutch Association for Medical Oncology
Treatment	2016	Docetaxel added to androgen-deprivation	Dutch Association for Medical

advice		therapy for hormone-sensitive prostate cancer[13]	Oncology
Assessment of outcome	2011	Cabazitaxel for the indication 'hormone-refractory metastatic prostate cancer'[4]	*Zorginstituut Nederland*.
Assessment of outcome	2012	Abiraterone for the indication 'metastatic prostate cancer that has become hormone-resistant during or after treatment with docetaxel'[39]	*Zorginstituut Nederland*.

Appendix 4: Parties' responses

Patients' association: Dutch Federation of Cancer Patients' Organisations (NFK); Prostate Cancer Foundation

Treatment pathway

The patients' association feels that drawing up an indication/treatment protocol is superfluous because the current guidelines are already modular and they are regularly reviewed. Moreover, as the data from the CAPRI-study are dated they cannot play a role in making treatment decisions. The NFK also challenges the status of such a protocol, alongside guidelines, and expects it will be needlessly bureaucratic, confusing, scientifically impossible and expensive. The NFK suggests using the data from the CAPRI-study in the guidelines to make consensus-based recommendations.

Referrals

The NFK disagrees with the report's conclusion that patients should in any case be discussed in an MDO and should be seen by a medical oncologist and a urologist.

Final life-phase

The NFK emphasises that recognising the final life-phase is difficult. The patients' organisations feel that care during the final life-phase must be tailored to the patient, regarding contents, place, medical necessity/expected results and the patient's preference. The NFK refers to the decision aid of the KWF, which could assist in this, and emphasises that palliative care must be guaranteed in the insured package.

Zorginstituut Nederland's response

We note that the objectives of the patients' association and those of ZIN are largely the same. We see agreement in the desire of the patients' association to combine evidence-based considerations with consensus-based considerations. ZIN feels that this should take place systematically, preferably based on feedback from a patient register, such as the CAPRI-study. We regret that our proposal for rapid updating and combining evidence-based and consensus-based considerations in a treatment protocol specifically for CRPC cannot count on the support of the patients' associations.

We upgraded our Room for Improvement Report, partly as a result of the response of the patients' associations. Obviously, we will harmonise the proposed improvement measures with the relevant parties in health care. We would like to discuss concrete steps for improving health care for CRPC patients further during the implementation phase.

Dutch Association for Medical Oncology/Dutch Association of Internists

On the whole the NVMO and the NIV agree with the report and the improvement measures, and are of the opinion that the administration of expensive medicines and guidance of patients must be placed in the hands of internist-oncologists and that patients should regularly be discussed in an MDO. The NVMO and the NIV feel there is room for improving treatment in the final life-phase and will pay attention to this.

Zorginstituut Nederland's response

We are pleased that the NVMO and the NIV agree with the Room for Improvement Report. We would like to discuss concrete steps for improving health care for CRPC patients further during the implementation phase.

Dutch Association for Urology (NVU)
The NVU agrees with the conclusions that patients benefit from effective diagnosis and coordination between care professionals. The guidelines will be updated faster, according to the NVU, and activities to this end have already commenced. According to the SONCOS guidelines, the MDO works well on harmonisation between care professionals. The NVU does warn about the possibility of work being duplicated in relation to the guidelines. Furthermore, the NVU emphasises that the data from the CAPRI-study are limited to interpretation as they were collected in 2012, and that the potential under-treatment revealed by the study may no longer exist. According to the NVU, the study shows that urologists follow the guidelines well and the ADT is used appropriately.

Zorginstituut Nederland's response
The *Zorginstituut* supports the efforts of the NVU in the field of updating guidelines and harmonisation between care professionals. In the implementation phase we would like to discuss concrete steps for improving care for CRPC patients in more detail, in harmonisation with the parties.

Federation of University Medical Centres in the Netherlands (NFU)
The NFU points out that the results from the CAPRI study are somewhat dated. The NFU would have appreciated receiving more information about the reason why in more than half of all cases patients did not receive docetaxel. There are patient characteristics and tumour characteristics which can be decisive in starting chemotherapy, such as PSA doubling-time, genetic characteristics of the tumour, potential cross-resistance to products and the level of symptoms. The NFU feels that a treatment protocol for this is not feasible.

Zorginstituut Nederland's response
The *Zorginstituut* sees agreement between the NFU's response and the results of the Room for Improvement Report, that various patient characteristics play a role in deciding which systemic therapy to give. This is why the *Zorginstituut* argues for recording these insights in the form of a treatment protocol, or start-criteria, to be able to offer patients the most appropriate treatments. We would like to discuss concrete steps for improving health care for CRPC patients further during the implementation phase.