UNIVERSITY OF TWENTE.

The Health Economic Impact of Circulating Tumour Cells Analysis in Metastatic Castration Resistant Prostate Cancer Treatment

Master Thesis Report

Koen Degeling

2/7/2015

Author:
Koen Degeling, BSc.
Master Student, Industrial Engineering and Management

Johanna van Burenstraat 15
7552 VN Hengelo (Ov)
The Netherlands
+31 6 55 83 80 83
k.degeling@student.utwente.nl

Primary Supervisor:
Maarten J. IJzerman, PhD.
Professor, chair Health Technology & Services Research
Deputy dean, Health & Biomedical Technology

University of Twente
7500 AE Enschede
The Netherlands
+31 53 489 3684
m.j.ijzerman@utwente.nl

Secondary Supervisor:
Dr.ir. Ingrid M. H. Vliegen
Assistant professor, Industrial Engineering and Business Information Systems

University of Twente
7500 AE Enschede
The Netherlands
+31 53 489 4014
+31 53 489 3912
i.m.h.vliegen@utwente.nl

Management Summary

The survival rates for metastatic Castration Resistant Prostate Cancer (mCRPC) patients have improved significantly over the last decades, which is likely to be caused by technological improvements in diagnostics and treatment effectiveness. The analysis of Circulating Tumour Cells (CTC) as test for patients' response to treatment is assumed to be such a technological improvement, as it is expected to reduce the amount of overtreatment. Unfortunately, these technological improvements are accompanied by increasing costs and the cost-effectiveness of new technologies is becoming increasingly important.

The objective of this study is to explore the Health Economic Impact of the application of CTC Analysis in the treatment process of mCRPC, by building and analysing a Health Economic Model. Two possible applications of CTC Analysis are studied: CTC Analysis as additional test to treatment response and CTC Analysis as the only test to treatment response. The primary outcome measure is the Incremental Cost Effectiveness Ratio (ICER), expressed in Quality Adjusted Life Years and costs. Discrete Event Simulation was selected as primary modelling technique in order to simulate a total of 486 different experiments. Timed Automata was selected as secondary (exploratory) modelling technique.

The application of CTC Analysis as only test to treatment response turned out to be a cost-effective alternative in the base-case scenario. CTC Analysis lowers costs by €2.618,61 (12%), improves the effectiveness with 0.04 QALY (5%), reduces the average amount of overtreatment for the first line from 3.4 cycles in the control arm to 1.5 cycles in the experimental arm and from 2.5 to 1.3 cycles for second line treatment. The application of Circulating Tumour Cells Analysis as additional test to treatment response is not cost-effective in the base-case.

Sensitivity analysis showed that the outcome measures are most sensitive to changes in the treatment effectiveness, diagnostic performance of the CTC Analysis and the first allowed decision moment. The application of CTC Analysis as only test to treatment response reduces the amount of overtreatment in all experiments while being cost-effective in most of the experiments. The application of Circulating Tumour Cells Analysis as additional test to treatment response is not cost-effective in any of the experiments.

Comparison of the two modelling techniques, Discrete Event Simulation and Timed Automata, shows that both approaches yield comparable results, but with small differences. Modelling is considered easier using Timed Automata and the statistical model checking features is very helpful for validation of the model. However, performing different experiments and gathering outcomes was more easy using the Discrete Event Simulation Model.

According to this study, CTC Analysis should be the new standard for assessing mCRPC patients' response to treatment. This application of CTC Analysis is considered a large improvement to the currently used technology based on an increase in average utility and a decrease in overtreatment in all performed experiments, while being cost-effective in the vast majority of the performed experiments with regard to the ICER outcome measure.

Preface

In this report I present my master thesis research on the Health Economic Impact of using CTC Analysis as test for patients' response to treatment in metastatic Castration Resistant Prostate Cancer. This report is written in British English, as one of the contributing organisations is the Institute for Cancer Research that is established London.

During the course Clinical Efficacy and Medical Technology Assessment, of which Maarten IJzerman is the lecturer, I was introduced to the field of Health Economic Modelling. For me as an Industrial Engineering and Management student it was unimaginable that high impact decision on new technologies were based on rather simplified models. When I shared this thought with Maarten IJzerman, Ingrid Vliegen and Erwin Hans the research was founded.

While being quite an adventure, I really enjoyed my master thesis research. This, to a large extend, owes to all the people I met and with whom I had the pleasure to collaborate with. I really enjoyed the collaboration with my primary and secondary supervisors, Maarten IJzerman and Ingrid Vliegen, who provided very valuable feedback and steering during the research. Also the collaboration on the Times Automata Model with Erik Koffijberg, Stefano Schivo and Rom Langerak was very nice and instructive.

In the end I am very pleased with the result of this master thesis research and the enthusiasm of others about the thesis and the results. I learned that scientific research can be challenging and fun and I am glad that I am getting the opportunity to continue this research for the Health Technology and Services Research department of the University of Twente. I am curious about what the future will bring!

Koen Degeling

Enschede, June 2015

Table of Contents

1. Introduction

The Institute of Cancer Research in London is starting a Phase III Study on the application of Circulating Tumour Cells Analysis as test for treatment response in the treatment process of men with metastatic Castration Resistant Prostate Cancer. This report provides a cost-effectiveness analysis of this application of the analysis of Circulating Tumour Cells and explores different modelling techniques for today's complex and personalized treatment processes.

This first chapter provides a short introduction to Prostate Cancer and Circulating Tumour Cells, it introduces the research itself and describes the methods that are used for carrying out the research.

1.1. Prostate Cancer and Circulating Tumour Cells

Prostate Cancer (PCa) is the fourth most commonly diagnosed form of cancer worldwide and corresponds to 7.9 percent of all diagnoses (Ferlay et al., 2013). It takes account for 3.7 percent of the cancer related mortality (Stattin et al., 2010), which assumes it is relatively good treatable or not as life threatening as other forms of cancer. The disease becomes threatening when the tumour progresses. At that point, medical or surgical castration can stop further progressing of the disease for several years. When medical or surgical castration is no longer effective, the disease progresses to the metastatic Castration Resistant Prostate Cancer (mCRPC) phase with a median survival of thirty months (Dragomir, D., Vanhuyse, Cury, & Aprikian, 2014).

The one-, five- and ten-year survival rates of PCa increased significantly in the past decades, with an estimated ten-year survival rate of 84 percent ("Prostate cancer survival statistics," 2014). This improvement is considered to be the result of improved diagnostics (Parker, Muston, Melia, Moss, & Dearnaley, 2006) and more effective treatment (Kvale et al., 2007). However, these improved treatments are accompanied with increasing costs and the patients' response-to-treatment rates are often less than fifty percent (Dragomir et al., 2014). Therefore, the cost-effectiveness of new technologies has become very important.

The analysis of Circulating Tumour Cells (CTC) is such a technological improvement that could positively contribute to the treatment process of mCRPC. CTC are cells that were detached from a primary tumour and circulate in the blood system. When applied before and after the start of a treatment CTC Analysis can assess the effect of that treatment to the number of CTC in the blood and thereby the patient's response to that treatment (de Bono et al., 2008). The advantage of CTC Analysis compared to the currently used PSA test is that CTC Analysis could assess the response more accurately and earlier, namely two weeks instead of three months after the start of the treatment. Knowing whether the patient responses to the treatment earlier would reduce the amount of overtreatment and thereby reduce costs and improve the Quality of Life of the patient. Therefore, the application of CTC Analysis is expected to be highly cost-effective. However, so far no research has been done on the Health Economic Impact of this specific application of CTC Analysis.

1.2. The Research

1.2.1. Objective

The primary objective of this research is to determine the cost-effectiveness of CTC Analysis as test for response to treatment. This is a Health Technology Assessment (HTA) Study of which an important aspect is the modelling of the standard and alternative treatment process. Nowadays these treatment processes are becoming more and more difficult and personalized (Personalized Medicine) and currently used modelling techniques, like Decision Tree Analysis and Markov Modelling, are under discussion. The question is whether these modelling techniques should still be used for modelling in HTA studies, as they cannot longer include all relevant factors (Caro, Moller, & Getsios, 2010; Karnon, 2003). Therefore, a secondary objective of this research is to identify modelling techniques that can be used for the analysis of the Health Economic Impact of new technologies for today's advanced and personalized treatment processes and to select the one that is most appropriate for this case.

1.2.2. Research Question and Sub-Research Question

The research question is formulated according to the PICO format (Aslam & Emmanuel, 2010; Riva, Malik, Burnie, Endicott, & Busse, 2012) and is defined as follows:

'What is the Health Economic Impact of using CTC as a response marker for mCRPC treatment, compared to the current used standard?'

In order to answer the research question and assess which modelling method is suitable for HTA, several sub-research questions need to be answered. These are:

1. What is metastatic Castration Resistant Prostate Cancer, how does the disease progress and what is the most common treatment process?
2. What is CTC Analysis and how can it improve the treatment process of metastatic Castration Resistant Prostate Cancer?
3. What is the desired input for the Health Technology Assessment model and what are the desired outcomes of the model?
4. Which modelling techniques can be used to model the treatment process of metastatic Castration Resistant Prostate Cancer to assess the Health Economic Impact and which method is the most appropriate to use?
5. What is the Health Economic Impact of using CTC Analysis in the treatment process of metastatic Castration Resistant Prostate Cancer?

Sub-research questions 1 and 4 are answered by literature research, while Sub-research question 3 is mainly based on expert opinions. A combination of literature research and expert opinions are used to answer Sub-research question 2. Sub-research question 5 involves modelling the treatment process, which involves al information gathered in the other sub-research questions and which will result in an estimation of the cost-effectiveness of CTC Analysis in the treatment process of metastatic Castration Resistant Prostate Cancer.

1.3. Methodology

This section elaborates on the method used for performing literature studies, the expert panel, the research method used for carrying out the research and the structure of the report.

1.3.1. Literature Study Method

A well performed literature study is the basis for each research. A clear and appropriate literature study method can help clarifying the process and improve the result. The framework introduced by J. F. Wolfswinkel et al. (Wolfswinkel, Furtmueller, & Wilderom, 2011), turned out to be an extensive, but well-structured and effective framework for performing literature studies and therefore is selected as literature study method in this research. The framework exists out of five steps, which will be explained in this section: Define, Search, Select, Analyse and Present. To guide this section, the sample size during the search progress for cost-effectiveness studies on treatment or diagnosis of prostate cancer is presented in Figure 1.

Define

The first step is about defining the inclusion and exclusion criteria, identifying the fields of research, determining appropriate sources and deciding on the specific search terms.

Search

In the second step the actual search in the different sources is carried out. It is very likely that insights gained in this step result in adjustment of the search strategy defined in the first step. When this is the case, return to the first step and redefine the search strategy.

Select

Next, the sample of articles is refined by removing duplicates and reading titles and abstracts. Also forward and backward references should be checked to improve the quality of the sample.

Analyse

When the final sample of articles is selected, these articles need to be analysed. In this step the data, information or knowledge is extracted from the articles and ordered in such a way that it can provide new insights.

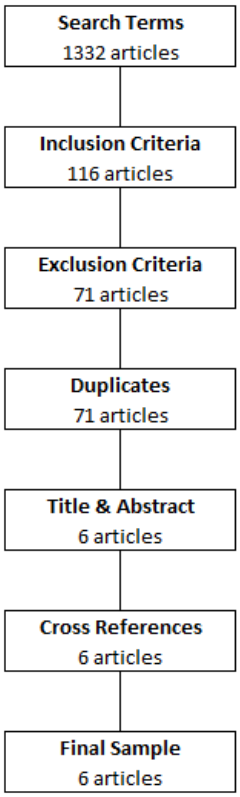


Figure 1. Number of articles during search and select process.

Present

The last step is about clearly representing the findings of the literature study. Most ideally this is done by supporting graphics.

1.3.2. Expert Panel

Experts need to be consulted when literature does not provide enough insights on a certain topic. The expert panel consists out of Prof. Dr. M. J. IJzerman and Dr. E. Koffijberg from the HTSR[1] Department of the University of Twente, Dr.ir. I. M. H. Vliegen from the IEBIS[2] Department of the University of Twente, Dr.ir. R. Langerak and Dr. S. Schivo from the EEC[3] department of the University of Twente and representatives of the Institute of Cancer Research in London[4]. These experts are selected in such a way that all the relevant expertise areas (clinical, health technology assessment and modelling) are covered.

1.3.3. Research Method and Report Structure

The research method is essential to a successful research and describes the steps that need to be taken and the way in which these should be reported. Articles and books can be found on the role of HTA studies like this (Gold, Siegel, Russell, & Weinstein, 1996) and on common pitfalls and good practices (Ramsey et al., 2005), but there is no written standard on the steps that need to be taken. A literature study on HTA studies is done to identify commonly used practices in these studies and prevent this research to be carried out without any guidance.

Scopus[5] is consulted for Journal Articles on Cost-Effectiveness Studies with regard to Prostate Cancer. Articles should be at most two years old, the full text of the article should be available and the article should be written in English, German or Dutch. Using this search strategy (see Figure 1), six articles were found on cost-effectiveness studies in the diagnosis or treatment of PCa (Carter et al., 2014; de Rooij et al., 2014; Koerber, Waidelich, Stollenwerk, & Rogowski, 2014; Pataky et al., 2014; Reed, Stewart, Scales, & Moul, 2014; Sher, Parikh, Mays-Jackson, & Punglia, 2014). The following sections were identified and will be used as guide in this research: Introduction, Methods, Results, Discussion and Conclusion.

In the introduction the authors introduce the topic of the article and describe the results of the literature study on that specific disease and the relevant technologies. In this report, the topic of the research in introduced in this first chapter and the literature study results will be presented in Chapter 2.

In the methods section, the model or trial is described together with the input and the output. Systematic Literature Reviews or Meta-Analyses are often used for the collection of the input data. As selecting an appropriate modelling technique is a secondary objective of this research, this will be described in Chapter 2 that is about the literature study. The input and output data will be described partly in Chapter 2 and in Chapter 3. In Chapter 2, Section 2.3 is about

[1] Health Technology and Services Research: http://www.utwente.nl/bms/htsr/
[2] Industrial Engineering and Business Information Systems: http://www.utwente.nl/bms/iebis/
[3] Electrical Engineering, Mathematics and Computer Science: http://www.utwente.nl/en/education/eemcs/
[4] http://www.icr.ac.uk/
[5] http://www.scopus.com/

the input data the modelling techniques need to use in order to model this case study and about the outcome measures the modelling techniques need to generate. The actual gathered input data and selected outcome measures are presented in Section 3.2.1 of Chapter 3.

In the articles, the outcomes of the model and the sensitivity analysis are presented in the results section, which is done in Chapter 3 which is about the model. All results will be summarized in order to answer the last sub-research question about the cost-effectiveness of CTC Analysis in Chapter 4.

Methods used and assumptions made are discussed, after which the research is summarized in the conclusion. There is no need for an separate Discussion chapter in this report, as in management reports assumptions and choices are argued when they are made. Conclusion and limitation will follow n in Chapter 5 and Chapter 6.

2. Literature Study

This chapter gives an overview of the literature studies performed in order to answer the four sub-research questions. For each of these questions, it is explained how the literature was found and what was found in the literature. For the questions regarding the added value of CTC and the modelling requirements, answered in section 2.2 and 2.3, also expert opinions are taken into account.

2.1. Metastatic Castration Resistant Prostate Cancer

What is metastatic Castration Resistant Prostate Cancer, how does the disease progress and what is the most common treatment process?

The first research question to be answered is about mCRPC in general. A literature study on the treatment guidelines is the first step in answering this question. Secondly, cross-references and obtained insights can be used to identify further and more specific search terms that can be used when additional literature research is required.

The used search terms are "metastatic Castration Resistant Prostate Cancer" or "Castration Resistant Prostate Cancer" and "Guidelines". The consulted sources are Scopus[6] and PubMed[7]; for Scopus the selected research fields are Life Sciences and Health Sciences. Articles are included when the full text version of the article is available, they are published in the last five years, and are available in English, German or Dutch. The search strategy resulted in 67 articles on Scopus and 15 articles on PubMed. Removing the duplicates resulted in 69 articles of which the title and abstract were assessed. Selection based on the title and abstract resulted in 13 articles. For one article the full text could not be obtained, which brings the final number of articles to be read to 12. Reading the articles did not result in additional articles, so the final sample contains 12 articles. See Figure 2 for a graphical representation of the search process.

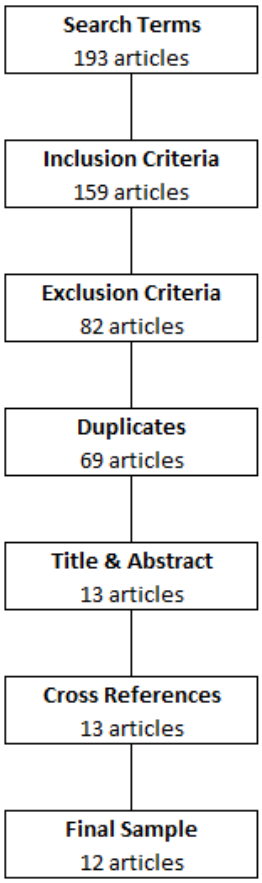


Figure 2. Number of articles during the search and select process.

The final sample of articles and the information found in those articles are presented in Table 1. In this table a "x" in a certain cell indicates that the topic mentioned in the column heading is discussed and confirmed in the article mentioned in the row heading.

There were no articles that described and explained the disease progression of prostate cancer, which might be caused by the inclusion criterion of a maximum age of 5 years. However, eleven out of the twelve articles mentioned

[6] http://www.scopus.com
[7] http://www.ncbi.nlm.nih.gov/pubmed

the disease progression as general knowledge (see Table 1, "Standard Disease Progression") and cross-referencing (including articles older than 5 years) did not result in an article that explained the disease progression of prostate cancer in detail. Since all these eleven articles described the same disease progression, this disease progression is assumed to be standard and generally accepted.

The described disease progression is as follows. When the patient is diagnosed with Prostate Cancer the disease is, most of the times, monitored until it progresses to the advanced phase. In the advanced phase progression of the disease is postponed by medical or surgical castration. Medical castration, or androgen deprivation therapy (ADT), is by far the most used method for castration and the current treatment standard is the Luteinising Hormone-Releasing Hormone (LHRH) (Dragomir et al., 2014). When the medical or surgical castration does not longer succeed in postponing disease progression, which is indicated by a rising Prostate-Specific Antigen (PSA) level (Heidenreich et al., 2014), the disease progresses to the metastatic Castration Resistant Prostate Cancer (mCRPC) phase. When the disease is in the mCRPC state the median survival is around 30 months and it is desirable to continue the ADT complemented with several lines of additional treatments (Dragomir et al., 2014). Over the last decade several new treatment options were approved for use by the Food and Drug Administration (FDA), the European Medicine Agency (EMA) and other governmental organizations. When no treatment options are left, the patient enters the Palladium Phase[8] in which continuation of ADT can reduce pain (Cassinello, Climent, Gonzalez del Alba, Mellado, & Virizuela, 2014; Heidenreich et al., 2014). See Figure 3 for a graphical representation of this disease progression.

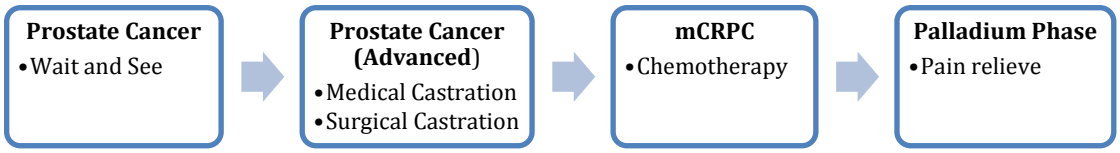


Figure 3. Graphical representation of the disease progression and treatments.

Regarding the treatment options, eleven out of the twelve articles discuss the several treatment options that are available. Ten out of these articles indicate Docetaxel as the standard first line treatment; two out of them also mention the relatively high toxic-level of Docetaxel (Basch et al., 2014; Heidenreich et al., 2014). After finishing the first line treatment with Docetaxel, or when treatment with Docetaxel is not effective, it is possible to start alternative treatment. To determine the effectiveness of the treatment the patient's PSA level is assessed, which can be done after two to three months of treatment (Bahl, Bellmunt, & Oudard, 2012). As alternative or second line treatment, Docetaxel can be combined Prednisone as a second line treatment, which is put forward in four articles (see Table 1, "Docetaxel Second Line"). For a long period of time, the only alternative to second line treatment with Docetaxel and Prednisone has been Mitoxantrone (El-Amm & Aragon-Ching, 2013). However, currently there are two alternatives to Mitoxantrone and Docetaxel with Prednisone for second line

[8] Palladium Phase = no other treatment options available.

treatment. The first and considered most appropriate alternative is Cabazitaxel, with nine of the ten articles recommending its use or presenting the improvement in cost-effectiveness compared to Mitoxantrone (see Table 1, "Cabazitaxel"). The second alternative is Abiterone. Three out of the ten articles mention that it is also possible to use Abiterone before Docetaxel, so as first line treatment. Cassinello et al. recommend the use of Abiterone only as second line treatment before Docetaxel (see Table 1, "Abiterone"). Other treatment options are Enzalutamide for second line treatment, Radium-223 for patients with bone metastasis and Sipuleucel-T for patients with asymptomatic [9] or semi-symptomatic[10] mCRPC.

Article	Standard Disease Progression[1]	Docetaxel (First Line)	Docetaxel (Second Line)	Cabazitaxel	Abiterone	Enzalutamide	Radium-223 (Bone Metastasis)	Sipuleucel-T (Asymptomatic)
(Bahl et al., 2012)	x	x		x				
(Basch et al., 2014)	x				x	x	x	x
(Cassinello et al., 2014)	x	x		x	x[2]	x[2]		x
(Climent et al., 2012)	x	x		x				x
(Dragomir et al., 2014)	x	x	x	x	x			
(El-Amm & Aragon-Ching, 2013)	x	x			x[3]			x
(Freedland, Richhariya, Wang, Chung, & Shore, 2012)	x							
(Heidenreich et al., 2014)		x	x	x	x	x		
(Horwich, Parker, de Reijke, Kataja, & Group, 2013)	x	x		x	x	x		
(Malik et al., 2013)	x	x		x	x[3]	x	x	
(Saad et al., 2013)	x	x	x	x	x	x		
(Wolff & Mason, 2012)	x	x	x	x	x			

Table 1. Literature study results.
1 = Disease Progress as presented as standard in this section.
2 = Applied before Docetaxel.
3 = Applied before and after Docetaxel.

[9] Asymptomatic = without disease symptoms.
[10] Semi-symptomatic = with few disease symptoms.

Additional literature on Docetaxel and Cabazitaxel was obtained in order to expand knowledge on the process.

Docetaxel is used for treatment of several sorts of cancer and belongs to the Taxane group of chemotherapy drugs, which interferes with microtubules (ACS, 2014). Microtubules are part of the internal structure of cells and are needed for cell dividing. As cancer cells divide faster than normal cells the cancer cells are suffering more from treatment than the normal cells. The TAX327 Study was the first Phase III Study that compared Docetaxel in combination with Prednisone to the previous first line treatment standard of Mitoxantrone in combination with Prednisone in the treatment of mCRPC patients (Tannock et al., 2004). Treatment with Docetaxel led to superior survival and improved rates of response in terms of pain, serum PSA level and Quality of Life. Docetaxel was given in a three week interval in combination with daily Prednisone.

Cabazitaxel also belongs to the Taxane group of chemotherapy drugs and is used only for treatment of advanced prostate cancer (ACS, 2014). Cabazitaxel is approved as second line chemotherapy in the EU and the USA in 2010 as result of the TROPIC Trial (Bahl et al., 2012). In this study Cabazitaxel plus Prednisone was compared to Mitoxantrone with Prednisone for second line treatment of mCRPC patients with progressive disease after Docetaxel-based treatment (de Bono et al., 2010). The trial proved that Cabazitaxel improved the overall survival and since then it is considered as the standard second line treatment for patients with progression during or after treatment with Docetaxel.

Summarizing, metastatic Castration Resistant Prostate Cancer is the phase of Prostate Cancer in which hormone therapy does not longer postpone progression and other treatments are required. It progresses out of the advanced or metastatic phase of Prostate Cancer. The most common treatment process of metastatic Castration Resistant Prostate Cancer exists out of continuation of the hormone therapy combined with first line treatment followed by second line treatment. The most common first line treatment is Docetaxel plus Prednisone and the most common second line treatment is Cabazitaxel plus Prednisone. This all leads to the most common treatment process presented in Figure 4.

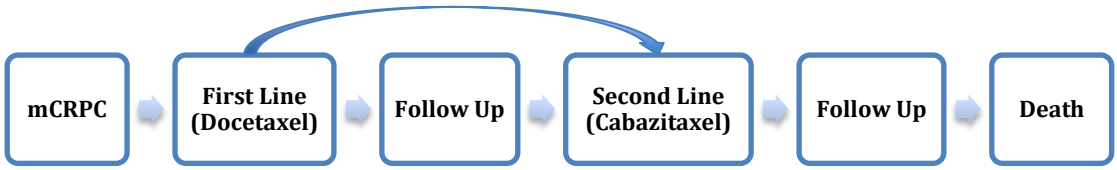


Figure 4. Common Treatment Process of mCRPC.

2.2. Circulating Tumour Cells Analysis

What is CTC Analysis and how can it improve the treatment process of metastatic Castration Resistant Prostate Cancer?

First some general information on CTC is presented, after which these obtained insights are used to perform more in depth research.

CTC are small parts that were detached from the primary and metastatic tumour and circulate in the blood of the patient. CTC can be filtered out of the blood and analysed as a biomarker and thereby influence medical decision making. Medical decision making includes: the detection of the disease, the prognosis of the disease and the prediction of the progression of the disease (Danila, Fleisher, & Scher, 2011).

There are two sorts of CTC Analysis, being molecular profiling of CTC and enumeration of CTC. According to literature, molecular profiling of CTC has the potential to provide a snapshot of the molecular makeup of the tumour they were detached from and predict the sensitivity or resistance to treatment (Danila et al., 2011). CTC enumeration simply is counting the number of CTC in the patient's blood. In literature, the CTC count is associated with the progression-free survival, overall survival and/or tumour response in Colorectal Cancer (Cohen et al., 2008), Breast Cancer (Bidard et al., 2012; Hayes et al., 2006; Jiang et al., 2013), Lung Cancer (Das et al., 2012), Ovarian Cancer (Poveda et al., 2011) and in Prostate Cancer (de Bono et al., 2008). In Prostate Cancer (PCa) CTC enumeration cannot only be used for prediction of progression-free and overall survival, but it could also assess the patient's benefit from treatment (Shaffer et al., 2007). The current standard for response to treatment is a 30% or 50% decrease in PSA (Armstrong et al., 2007), which can reliably be shown after several treatment cycles. The expectations are that CTC enumeration can be used earlier after the start of the treatment and thereby reduce the amount of overtreatment (de Bono et al., 2008) by reducing the treatment time of patients for whom the treatment is not effective.

Currently the only approved CTC Analysis technology is the CellSearch™, which was approved by the FDA in 2004 (FDA, 2004). It takes a sample of blood from the patient and treats that sample with the CellSearch™ Epithelial Cell Kit. Protein-coated magnetic balls mark the cancerous cells, which are strained with fluorescent markers for precise identification. The labelled sample then is dispensed into a cartridge for analysis and a strong magnetic field is applied to the mixture, attracting the marked cells. The result is analysed with the CellSpotter™ and checked by a medical professional ("How does the CELLSEARCH® System work?," 2014). A CTC count of less than 5 in a 7,5 mL sample of blood is considered as favourable and a CTC count equal to or more than 5 in a 7,5 mL sample of blood as unfavourable (Allard, Matera, et al., 2004; Cristofanilli et al., 2005).

A literature study is performed to obtain further insights in the application of CTC Analysis for assessing the patient's response to treatment. Effectiveness is considered to be too general for a search term and response to treatment as redundant to treatment response. The consulted sources are Scopus and PubMed; for Scopus the selected research fields are Life Sciences and Health Sciences. Articles are included when the full text is available, are about the human species, are published in the last ten years and are available in English, German or Dutch. This search strategy resulted in thousands of articles on Scopus and more than a hundred thousand articles on PubMed. A quick scan on some of these articles showed that many of these articles were about the use of CTC Analysis for response to treatment for different sorts of cancer and were reporting on positive results (Economos, Morrissey, & Vessella, 2012; Klinac et al., 2014; Miyamoto, Sequist, & Lee, 2014; Wallwiener et al., 2014). Therefore, a new search was done focusing on mCRPC, since the number of articles found was considered too large to study and indicates that there would also be enough articles available specific in mCRPC, which are more desirable.

The second literature search focusing on mCRPC resulted in 69 full text articles on Scopus and 30 articles on PubMed, so 99 articles in total. After removing duplicates and assessing the titles and abstracts 24 articles were left. For four of these articles the full text turned out to be not available, which brings the number articles to read to twenty. Reading the sample resulted in two extra articles by cross-referencing and one article being deleted from the sample. The final sample therefore was 21 articles, see Figure 5 for a graphical representation of this search process.

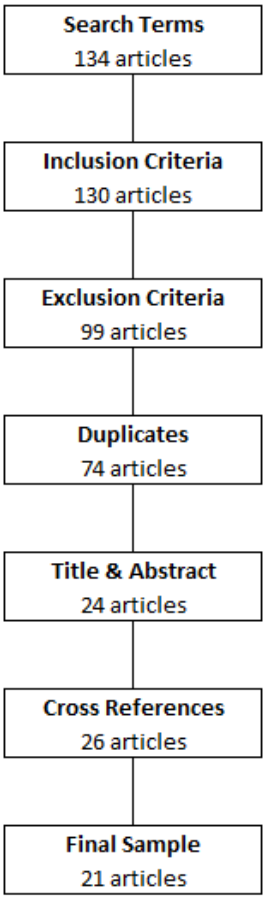


Figure 5. Number of articles during the search and select process.

Table 2 shows the results of analysing the final sample of articles. In this table the column in which the "x" is located indicates to which of the four categories the article in the row belongs. The four categories are about the use of CTC Analysis for assessing response to treatment and are distinguished as follows: positive without evidence, positive with weak evidence, positive with moderate evidence and no opinion on this appliance of CTC at all. In first instance also categories negative about CTC Analysis were included, but no articles could be categorized in one of these categories. Furthermore, weak evidence is considered as numerical and statistical substantiated associated with a small N (Phase I/II Studies). Strong evidence is considered as numerical and statistical substantiated associated with a large N (Phase II/III Study) or in which the use of CTC Analysis to assess treatment response did belong to the primary objective.

Five articles argued the possible benefits of continuous CTC enumeration as test for treatment response and overall survival, without providing additional evidence for this opinion. Continuous CTC enumeration is about performing CTC-enumeration several times in the treatment process: at baseline, before the start

of the treatment, in several intervals after the treatment and during follow-up. Ten articles substantiated their opinion with weak evidence, which exists for a large part of Phase II Studies using CTC enumeration as secondary or experimental endpoint. These studies show promising results regarding CTC enumeration and many of these studies will incorporate or are incorporating CTC enumeration in following Phase III Studies. Fortunately, there are also Phase II Studies that do investigate CTC counts as primary endpoint (Olmos et al., 2009; Scher et al., 2009) or compare it to the use of PSA Level (de Bono et al., 2008). However, these three studies' populations are not large enough to provide the requires scientific evidence and therefore Phase III Studies are required to confirm the benefit of using CTC count as primary endpoint in the assessment of treatment response and overall survival.

Furthermore, Shamash et al. (2012) and de Bono et al. (2008) report on a response to treatment in the number of CTC within two weeks, which contributes to the expectations about the suitability of CTC enumeration for earlier assessment of treatment response than the currently used PSA level. Nevertheless, Armstrong & Febbo mention that the low CTC counts before the start of the (chemo)therapy and the inaudibility about the cut-off point of 5 CTC per 7,5 mL of blood can be troublesome. As said before, large Phase III Studies need to be carried out to provide scientific evidence for the use of CTC count as primary endpoint for treatment response.

All of this favours the use of CTC Analysis, but nothing is said about the actual diagnostic performance of CTC Analysis. The performance of a test or analysis is very important, as it determines how good test or analysis is in showing the right results. In order to be cost-effective and improve the treatment process, CTC Analysis should at least have a comparable diagnostic performance compared to the current situation.

In diagnostics, the performance of a technology is assessed by the Sensitivity, Specificity, Positive Predictive Value (PPV), the Negative Predictive Value (NPV) and Accuracy (Bouter, van Dongen, & Zielhuis, 2005; Hunink et al., 2001). The sensitivity represents the percentage of ill patients that get diagnosed with the disease. The specificity regards to ruling out suspicions of disease, as it represents the percentages of patient who are not ill and indeed do not get diagnosed with the disease. Therefore, a high sensitivity results into a low amount of under treatment, while a high specificity results into a low amount of overtreatment. The PPV represent the percentage of patients who got diagnosed with the disease that indeed are ill, while the NPV represents the percentage of patients that who do not get diagnosed with the disease and indeed are not ill. The accuracy is about the patients who got diagnosed right as percentage of all patients.

Article	Positive on CTC (No Evidence)	Weak[1] Evidence for CTC	Strong[2] Evidence for CTC	Nothing on CTC / No opinion
(Ang, Olmos, & de Bono, 2009)		x		
(Antonarakis, Heath, Posadas, et al., 2013)	x			
(Antonarakis, Heath, Smith, et al., 2013)		x		
(Antonarakis et al., 2014)				x
(Armstrong & Febbo, 2009)	x			
(Armstrong et al., 2013)		x		
(Attard et al., 2009)		x		
(Bianchini et al., 2013)		x		
(Danila et al., 2010)		x		
(Danila et al., 2011)				
(Danila et al., 2011)	x			
(de Bono et al., 2008)			x	
(Dreicer et al., 2014)		x		
(Lee et al., 2013)		x		
(Miyamoto et al., 2014)	x			
(Morris et al., 2012)				x
(Olmos et al., 2009)			x	
(Reid et al., 2010)		x		
(Scher et al., 2009)			x	
(Shamash et al., 2012)		x		
(Shiota et al., 2013)	x			

Table 2. Literature study results.
1 = Weak evidence is considered as numerical and statistical substantiated with a small N or in which the use of CTC Analysis to assess treatment response did not belong to the primary objective.
2 = Strong evidence is considered as numerical and statistical substantiated with a large N or in which the use of CTC Analysis to assess treatment response did belong to the primary objective.

In order to obtain insight in the diagnostic performance of CTC Analysis, a systematic literature is performed. Most ideally, the obtained information could be combined in a Meta-Analysis. In order to perform such a Meta-Analysis, the research context should be comparable, so the first literature study attempt was on application of CTC Enumeration in mCRPC patients. This did not result in any articles, so a more general literature study needed to be performed. For this literature study, the search terms were "CellSearch", "sensitivity" and "specificity". The term "CellSearch" was chosen, because this is the only approved technology for carrying out the analysis. "Sensitivity" and "Specificity" were chosen, because those are the most important performance characteristics. Furthermore, no date restrictions were applied, only articles on the human species were included and the full text of the articles should be available. The result was a sample of 78 full text articles on Scopus and PubMed combined. Removing duplicates between the two sources resulted in a sample of 68 articles.

After reading the titles and abstracts, 21 articles remained to read. One of these articles turned out to be not available in full text and 8 articles were added by cross-referencing. The final sample therefore is 28 articles, see Figure 6 .

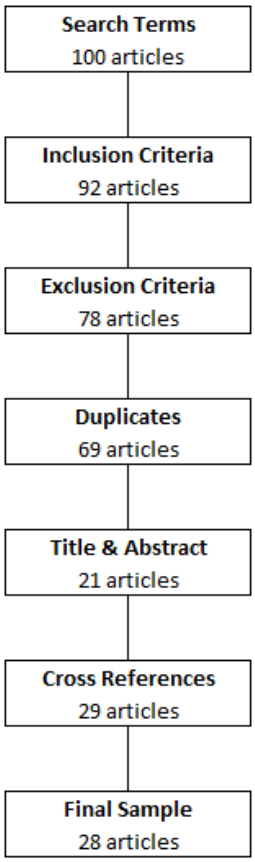


Figure 6. Number of articles during the search and select process.

Out of the 28 articles, 11 reported about the sensitivity, specificity, PPV, NPV and/or accuracy of CTC Analysis, see Table 3. In these articles the results of the performance characteristics were very different. Sensitivity ranged from 27% (Cohen et al., 2008; Guzzo et al., 2012) to 98% (Gazzaniga et al., 2010) and specificity ranged from 75% (Goodman et al., 2011) to 100% (Gazzaniga et al., 2010; Goodman et al., 2009). For the PPV the minimum and maximum found values were 27% (Bidard et al., 2010) and 97% (Gazzaniga et al., 2010), for the NPV respectively 80% (Schulze et al., 2013) and 100% (Gazzaniga et al., 2010) and for the accuracy 77% (Bidard et al., 2010) and 85% (Allard, Miller, et al., 2004).

The large difference in performance scores can be explained by the large heterogeneity between the studies. Regarding the population, only one article was about the application of CTC Analysis on Castration Resistant Prostate Cancer, one article was about Hormone-Sensitive (non-Castration Resistant) Prostate Cancer. Furthermore, three articles were about Carcinoma, two about Breast Cancer, one about Bladder Cancer, one about Colorectal Cancer, one about Lung Cancer and one about Urothelial Cancer.

There were also large differences regarding the application of CTC Analysis. Some articles assessed the performance characteristics looking at the expected and counted number of cells, while other focused on a certain threshold, for example 5 CTC per 7,5 mL blood sample, and assessed the performance characteristics regarding that outcome. Another observed application is the sensitivity and specificity of CTC Analysis in predicting overall survival. These different ways of assessing the performance of CTC Analysis indeed result in different outcomes. For example, Goodman et al. show that different threshold values lead to different performances (see Figure 7).

All these differences make it impossible to combine information and generalize results. Furthermore, it suggests that the usefulness and the performance of CTC Analysis is different for each of its applications for each individual disease and therefore should be studied separately when considered to be applied. Regarding mCRPC, Goodman et al. show promising results: a sensitivity of 61% and a specificity of 100% with regard to CTC Enumeration with a threshold of 4 CTC per 7,4 mL blood. However, the sample size of n=100 is not large enough to provide strong evidence. Therefore, Phase III Studies are required to provide the required evidence for the usefulness of CTC Analysis.

Even though the results cannot be combined, they do provide insight in what can be expected from CTC Analysis. Except for one article, all articles report a higher specificity than sensitivity. This suggests that the amount of under treatment is relatively low compared to the amount of overtreatment. The small amount of overtreatment is desirable, as one of the objectives of the application of CTC Analysis is to reduce overtreatment. Under treatment is not desirable, as effective treatment then is stopped and patients do not receive the treatment they need.

In the end it can be concluded that the application of CTC Analysis in the treatment process of mCRPC looks very promising, but there is a lack of strong evidence. Therefore, there is a urgent need for Phase III Studies to provide this evidence and put the implementation process of CTC Analysis in the mCRPC treatment process into higher gear.

Article	Sens.	Spec.	PPV	NPV	Accuracy	N	Cancer type
(Allard, Miller, et al., 2004)		99,7 %			85%	5	Carcinoma
(Beveridge, 2007)	70%	89%				50	Breast
(Bidard et al., 2010)	55%	81%	27%	91%	77%	115	Breast
(Cohen et al., 2008)	27%	93%	53%	81%	78%	334	Colorectal
(Gazzaniga et al., 2010)	98%	100%	97%	100 %		105	Carcinoma
(Goodman et al., 2009)	61%	100%				100	CRPC
(Goodman et al., 2011)	82%	75%				33	Non-CRPC
(Guzzo et al., 2012)	27%	88%	78%			43	Bladder
(Hiltermann et al., 2012)	41%	80%				59	Lung
(Naoe et al., 2007)	78,5 %					12	Urothelial
(Schulze et al., 2013)	58%	83%	61%	80%		78	Carcinoma

Table 3. Literature Study results.

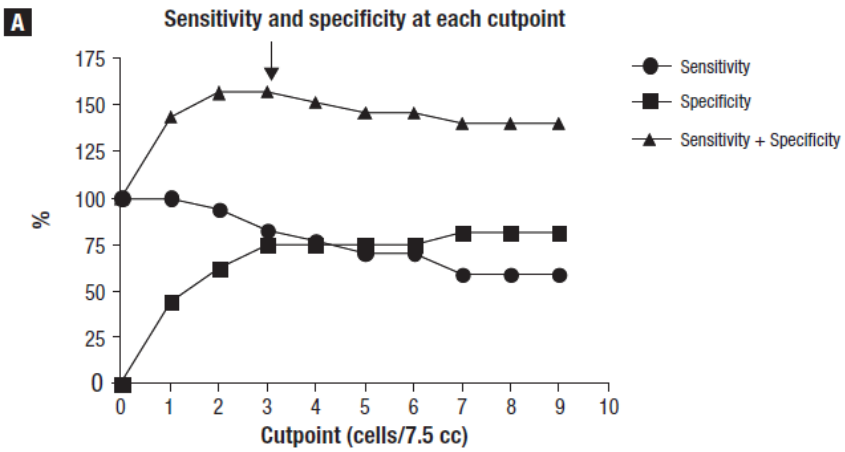


Figure 7. Retrieved from Goodman et al. (2011)

2.3. Model Requirements

What is the desired input for the Health Technology Assessment model and what are the desired outcomes of the model?

Like stated in the introduction, the modelling of different alternatives is a very important aspect in Health Technology Assessment (HTA) and the current used modelling techniques are under discussion (Caro et al., 2010; Karnon, 2003). This section elaborates on the requirements that a model should satisfy in order to represent current practice in a realistic way. Requirements, in this case, are mainly about the input and output that the model should use, respectively provide, but other obtained insights will also be taken into account.

In order to answer this question, two situations are distinguished: the current situation and the desired situation. The latter is of course the preferred situation, but is not current practice due to, for example, ethics, costs, difficulty of gathering the required information or model limitations. This report focusses on solving the restrictions due to model limitation by analysing different modelling techniques in order to select the best option. This will be done in the next section, but it first needs to be known what the current situation and the desired situation are.

2.3.1. The current situation

The current situation relates to what is currently done and has been done in practice. In order to provide insights into this, literature research is done on the used input and output of cost-effectiveness modelling studies. As these studies are published frequently a literature study will provide satisfying insights and no additional expert opinion is required.

2.3.1.1. Input

The input of a model determines what can be modelled. The used input depends on the data that is available or can be gathered and the desired output of the model. In order to obtain insights in the most frequently used inputs for mCRPC cost-effectiveness modelling, a literature study is performed using the search terms "Cost-Effectiveness" or "Health Economic Impact" and "Castration Resistant Prostate Cancer" and "Model". The term "Model" was added, because otherwise many cost-effectiveness studies without actual modelling would be included and those would not provide insights into input and output of modelling. No date restrictions were applied, only articles on the human species were included, the full text of the articles should be available and the articles should be written in English, German or Dutch. The consulted sources were Scopus and PubMed and the included research fields are Life Sciences and Health Sciences. See Figure 8 for the results of the search strategy.

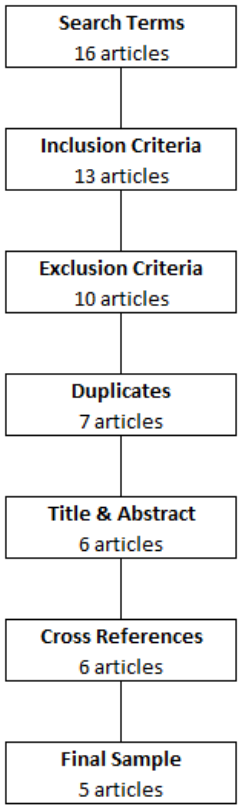


Figure 8. Number of articles during the search and select process.

The five articles in the final sample represented three different modelling techniques: Decision Tree Analysis Modelling (Wilson et al., 2014; Zhong et al., 2013), Markov Modelling (Snedecor, Carter, Kaura, & Botteman, 2013; Stopeck et al., 2012) and experimental use of Discrete Event Simulation (Lord et al., 2013). All articles used utilities (Quality of Life), costs and transition probabilities as input. Only Lord et al. (2013) used additional input for their model, namely: diagnostic accuracy for any tests in the pathway, clinical effectiveness of any treatments included in the pathway, treatment side effects, relationships between the parameters and individual patient characteristics. In the other models some of these additional inputs were integrated in the transition probabilities. For example, the diagnostic accuracy and effectiveness of treatments.

2.3.1.2. Output

The same articles that are used for obtaining insight in the currently used inputs are also used to obtain insights in the used outputs. All five articles focus on costs and utilities or Quality Adjusted Life Years (QALYs) regarding the output. This is obvious, as all articles are about cost-effectiveness studies and in those studies effectiveness is almost always expressed in QALYs. QALYs are calculated by multiplying the survival of a patient with the average utility of that patient. Only Snedecor et al. (2013) also explicitly mention the number of Skeletal Related Events (SREs) and survival as outcomes of their model.

Moreover, the separate cost and effectiveness outcomes can be combined into the Incremental Cost Effectiveness Ratio (ICER), which is the golden standard in the health economic research field (Ryen & Svensson, 2014). The ICER indicates how much it costs to gain one year of perfect health in the experimental arm of an experiment, compared to the control arm of the experiment. Results on this outcome measure are mostly presented in an ICER Plot.

An ICER Plot, as presented in Figure 9, shows the difference in costs between the experimental arm and the control arm on the vertical axis and the difference in effectiveness expressed in Quality Adjusted Life Years (QALYs) on the horizontal axis. Results in the lower right corner, indicated with a “D” in Figure 9, indicate that the experimental arm dominates the control arm, as the effectiveness is improved while the costs have decreased. When the results are in the upper right corner, indicated with a “B” in Figure 9, the experimental arm is considered as an improvement when the results are below the Willingness to Pay threshold (WTP). Result left of the vertical axis, indicated with an “A” or a “C” in Figure 9, or above the WTP are in favour of the control arm.

The WTP indicates how much society is willing to pay in order to gain one year of perfect health. For the Netherlands the WTP was estimated at €24.500,- in 2010 (Bobinac, Van Exel, Rutten, & Brouwer, 2010).

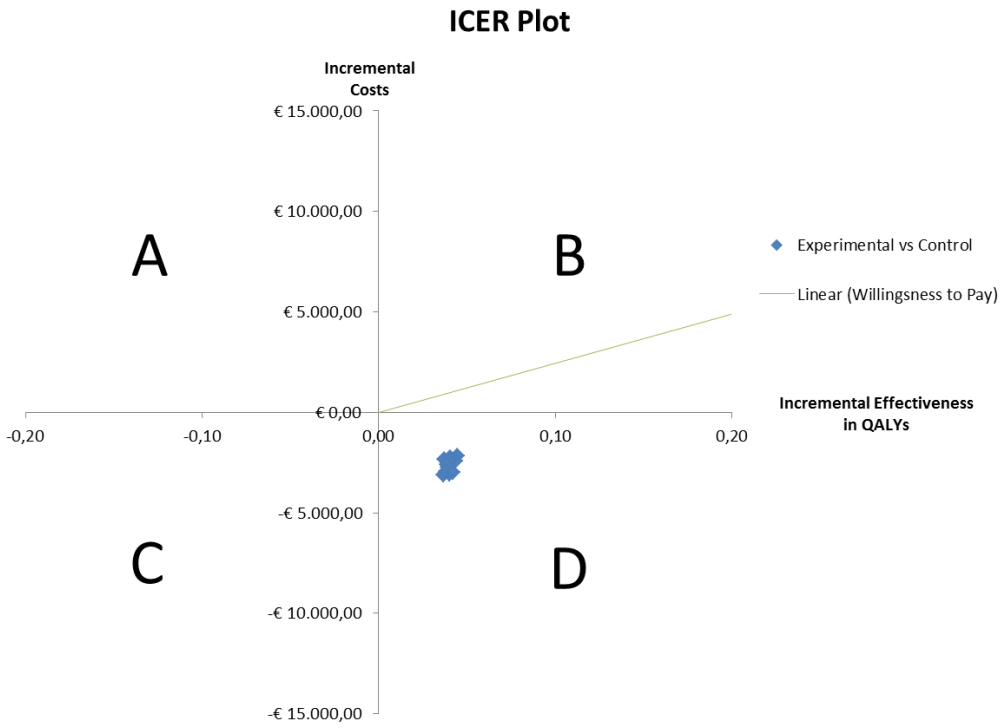


Figure 9. An example of an ICER Plot.

2.3.1.3. Conclusion

According to the current standards on the used input and output, the modelling technique to be used should be able to use utilities, costs, transition probabilities, diagnostic performance of tests. Furthermore, the modelling technique should be able to use this input to generate output with regard to the QALYs, costs, SREs and survival. In order to translate the input into QALYs and survival, the modelling technique should include the time aspect into the model.

2.3.2. The desired situation

In order to obtain insights in what would be preferable characteristics of the modelling technique to be used, a literature study alone would not provide enough insights to be innovatory. Therefore, expert opinions will provide additional information about the researching community's wishes.

2.3.2.1. Literature

The literature study that has been performed aimed to obtain further insight in preferable output by assessing the used secondary and experimental endpoints in cost-effectiveness studies. As known, in cost-effectiveness studies the effectiveness is defined by clinical outcomes, which are supposed to provide measurable attributes. Clinical outcomes can be divided in primary endpoints and secondary endpoints. Primary endpoints are key in the final decision on cost-effectiveness while secondary endpoints support this decision or are experimental future primary endpoints.

The used search terms for the literature study where "Primary Endpoints" or "Primary Outcome" and "Castration Resistant Prostate Cancer". The included research fields are Life Sciences and Health Sciences. Other inclusion and exclusion criteria were: a maximum age of five years, the article should be about

the human species, the full text should be available and the article should be written in German, English or Dutch. This search strategy resulted in 163 articles on Scopus and 123 articles on PubMed. After deleting duplicates from the sample, 171 articles were left. This sample was reduced to 90 articles after reading the articles' titles and abstracts. No articles were added to this sample by cross-referencing and 3 articles were removed from the sample after reading them, so the final sample exists out of 87 articles, see Figure 10.

The used primary and secondary endpoints were extracted from the articles and combined into nine categories, which are: Survival Related, PSA Related, Progression Related, Treatment Related, Safety, Bone Related, Quality of Life, CTC and one category for additional endpoints. For example, the category "PSA Related" includes the following endpoints: PSA Decline > 30%, PSA Decline > 50%, PSA Slope, Time to PSA Progression and PSA Response Rate. Furthermore, the category "Survival Related" includes the Overall Survival and the 1-year Survival. The results for the nine categories and all separate endpoints are presented in Appendix A.

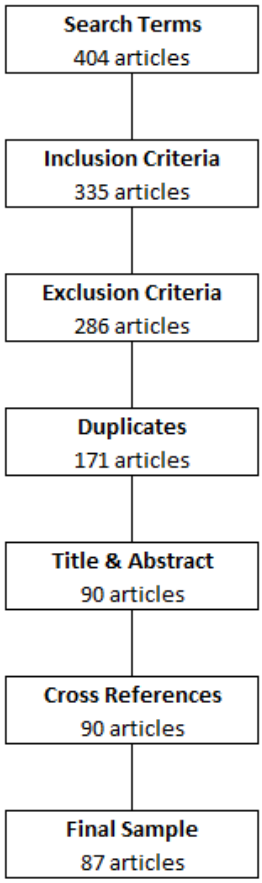


Figure 10. Number of articles during the search and select process.

The table shows that the most frequently used primary endpoints in the sample relate to the survival of the patients. The second most used primary endpoints relate to the PSA Related category, which is the most frequently used category for the secondary endpoints. Furthermore, the third most used primary endpoints relate to the progression of the disease and the fourth most frequently used primary endpoints are treatment related. While these four categories seem different on the first sight, in the end they are not that different at all. The PSA level correlates with overall survival and vice versa. Furthermore, when the disease does not progress it is more likely the patient survives for a longer period of time and when the patient responds to the treatment it can be assumed to be positive for the progression of the disease, the PSA level and the survival of the patient.

From this is can be concluded that, additional to the requirements listed in Section 2.3.1, it is preferable that a model should also be able to take into account several indicators like test values (PSA, Bone, CTC, etc.) and patient characteristics (progression, etc.).

2.3.2.2. Expert Opinion

The literature study provided some insight in requirements the modelling technique preferably should satisfy. However, what is reported on in literature does not necessarily represents the desires of the research community and the industry. So expert opinions are needed to further specify additional requirements to the capabilities of the modelling technique that is to be used.

The experts emphasized the importance of early treatment switching. Early treatment switching is so important, because it is expected to reduce the amount of overtreatment, increase survival and increase the effectiveness of second line treatment. Therefore, early treatment switching should be included in the model.

Furthermore and according to the experts, one of the most important current developments in the Health Technology Assessment research is about taking into account physician's behaviour in advising the patient based on different test results. Normally in cost-effectiveness studies, the assumption is made that a physician will always advise to the patient what is suggested by the tests. In practice this is not always the case and it is likely that a physician will doubt the results of a new test more than the results of a test he or she has been using for several years. Assuming the physician will always give the advice the test suggest will result in a non-realistic situation. Therefore, it is preferable to take into account physician's behaviour in advising the patient given several tests and test results.

2.3.2.3. Conclusion

In the end it can be concluded that, according to the experts and the literature, the modelling technique that will be chosen in the next section needs to be capable of including costs, transition probabilities, diagnostic performance, utilities, time, quality of life, survival, test outcomes, different patient's characteristics and physicians' behaviour in advising the patient. Only when the technique can include all these aspects it will satisfy today's requirements to Health Technology Assessment cost-effectiveness models. An overview of the requirements to the modelling technique is presented Table 4.

Requirement Category	Specification
Costs	- Treatment costs - Test costs - Follow Up costs - Physician consults costs
Effectiveness	- Survival of the patient - Utility or Quality of Life of the patient - Amount of Overtreatment - Amount of Under treatment
Diagnostics	- Sensitivity of the tests - Specificity of the tests - Specific test results
Time	- Different moments of treatment switching - Changes in survival over time - Changes in diagnostic performance over time
Other	- Physicians' behaviour - Transition probabilities - Patient characteristics

Table 4. Requirements to the modeling technique.

2.4. Modelling Techniques

Which modelling techniques can be used to model the treatment process of metastatic Castration Resistant Prostate Cancer to assess the Health Economic Impact and which method is the most appropriate to use?

This section focuses on which modelling technique should be used for modelling the treatment process described in Section 2.1. In the context of HTA, models are used to obtain information about cost-effectiveness of new medical technologies in a timely manner, by exploring the factors that influence the outcomes and costs (Halpern, Luce, Brown, & Geneste, 1998). In order to select a modelling technique, already used techniques are analysed and possible alternatives will be identified. In order to find alternatives to these modelling techniques it is difficult to perform a structured literature study, as search terms and inclusion and exclusion criteria are very likely to rule out some alternatives that not match them. Therefore, cross-referencing, general internet search and expert opinions will be used to identify different alternatives. Finally, a modelling technique will be chosen based on the process in Section 2.1, the requirements listed in Section 2.3 and the characteristics of the different techniques described in this section.

2.4.1. Currently used Techniques

As illustrated in the literature search on cost-effectiveness models in the previous section, the most used modelling techniques for Cost-Effectiveness or HTA Modelling are Decision Tree analysis Modelling and Markov Modelling with or without Monte-Carlo Simulation.

Decision Tree Analysis is a tool for decision making, which uses a tree-like graph or model of decisions and their possible consequences; most of the times it includes transition probabilities, costs and utility (Hunink et al., 2001). Decision Trees work well in analysing chance event with limited recursion and a limited time horizon.

Markov Models are mathematical models that contain a finite number of mutually exclusive and exhaustive states between which changes occur after a fixed time period, called a cycle, with a certain transition probability (Gold, 1998). This transition probability only depends on the current state, which is called the memoryless property, and is consistent over time in case of a stationary Markov Model. Markov Modelling is a form of simulation, as you can model a population over a certain time horizon, which is called a Cohort Markov Model. Markov Models are most useful when decision problems involve risk over time, when timing is important and events may happen more than ones (Hunink et al., 2001). A difficulty when using Markov Models is the choice of the cycle length, as it is very important and very difficult to determine (Stopeck et al., 2012). Furthermore, difficult processes and taking into account some sort of memory in determining transition probabilities will require a large amount of states and is likely to make the models very large and unclear (Karnon, 2003).

To take into account uncertainty regarding the input of the model, Markov Models are often combined with Monte-Carlo Simulation. Monte-Carlo

Simulation is a form of simulation and is closely related to Markov Modelling, since the basis for a Monte-Carlo Simulation is a Markov model. The difference is that in Monte-Carlo Simulation patients are not modelled as a cohort like in Markov Models, but each patient is modelled individually (Hunink et al., 2001). Monte-Carlo Simulation shows all possible outcomes and the distribution of them. So using Monte-Carlo Simulation would not only show what could happen, but also how likely that is to happen. This allows for better decision making under uncertainty compared to Markov Models on their own.

2.4.2. Alternatives

Besides currently used modelling techniques there are also alternative techniques that could be used, namely: Discrete Event Simulation, Continuous Simulation and Timed Automata.

Probably the most known alternative to Decision Tree Analysis and Markov Models is Discrete Event Simulation (DES), which is already used in the health care sector (Günal & Pidd, 2010). DES is a Stochastic Simulation Method, which means that it operates with variables that can change with certain probability. Where in Cohort Markov Models a population of objects moves to another state with a certain chance each cycle, DES simulates individual objects and their individual path through the model in which the model is triggered by an event and not by a fixed cycle length (Karnon, 2003). In DES the program keeps track of the state of the system, which is represented as a collection of state variables. A change in the state of the system only takes place instantaneously, which is referred to as an discrete event (Jacob, 2013). Furthermore, DES allows more complicated representations of the systems being modelled and more flexibility regarding the input of the model. However, this flexibility is outweighed by the increasing run and development time compared to Markov models for model that do not require the more complex model possibilities (Karnon, 2003). Therefore, it is only preferable to use DES when the model is expected to be so difficult that Markov Modelling does not provide a satisfying representation.

Continuous Simulation is another form of Stochastic Simulation and refers to a model that is continuously triggered as a function of time (Kwok, 1979). In other words, variables change in a continuous matter. So in a Continuous Simulation Model there are an infinite number of states, while in a Discrete Event Simulation Model there are a finite number of states. Continuous Simulation is interesting to use when the subjects (patients) can be considered as a continuous flow, not when you want to simulate the subjects individually (Law, 2007).

Another very innovative and promising modelling technique that could be used is the use of Timed Automata. Timed Automata (TA) relate to finite-state automata with real-valued clocks and communication channels (Alur & Dill, 1994). Finite-state automata is a technique in which the model can be in one of a finite number of states and is in only one state at a time, like a Markov Model. However, different compared to a Markov-Model that takes a certain transition based on a probability each cycle, a TA makes this transition when initiated by a triggering event or condition. The use of Timed Automata has already proved its capability of modelling in the biological context, by modelling Biological Pathway

Dynamics (Schivo et al., 2014). A TA model can exist out of several Automatons, i.e. a patient, a doctor, a treatment process or a test, which can communicate with each other and can work independently. Like stated before, each Automaton can be in different states and can transition to other states based on probabilities, conditions or triggered by other Automata. As far as known, TA is not yet used for modelling cost-effectiveness studies, but the expectations are that the technique is very suitable for it. Two Timed Automata experts are Rom Langerak and Stefano Schivo. According to these experts, expected benefits of using Timed Automata are the relatively simple construction of a model, the ease with which process can operate independently from each other, the possibility for statistical model checking and the optimization opportunities. The downside of TA is that, at this point, only the uniform and exponential statistical distributions are supported in the software tool UPPAAL.

2.4.3. Which technique should be used?

According to Section 2.3 the modelling technique should make it possible to include time, costs, quality of life, survival, test outcomes, patient's characteristics and physician's behaviour in advising the patient. This section will elaborate on which of these technologies will be used in this study and why this is the most appropriate technique.

Regarding the currently used modelling techniques, Decision Tree Analysis should not be used, as the case of metastatic Castration Resistant Prostate Cancer involves a relatively long time horizon and Decision Tree Analysis does not model time. It could be possible to divide the time horizon into cycles and represent cycles by branches in the decision tree. However, this would require an enormous amount of branches and is unlikely to work well. Furthermore, a combination of Markov-Modelling and Monte-Carlo Simulation probably could be used for modelling in this study. However, translating the process steps and all relevant historical data into a decent Markov-Model is likely to require such a large number of complex states that it would be (almost) impossible. Therefore, it is also not preferable to use a Markov-Model with Monte-Carlo Simulation.

Of the possible alternatives, the use of Continuous Simulation seems to be less preferable compared to Discrete Event Simulation. The reason for this is that the added value of continuous simulation, taking into account time in a continuous matter is not of added value for cost-effectiveness modelling, while it requires much more simulation resources. In cost-effectiveness modelling you only want to know when costs are made, not what happens in between these events, as costs arise instantaneously and mostly not continuous to time.

Both remaining modelling techniques are expected to be capable of modelling a treatment process like that of mCRPC. Discrete Event Simulation is selected as primary method, because it already has been successfully used for modelling cost-effectiveness in exploratory studies. Because the application of Timed Automata in this context has not been studied yet, Timed Automata is selected as secondary modelling method in order to study its usability. Assessing the usability of Timed Automata is an exploratory study in which M. IJzerman, E. Koffijberg, R. Langerak, S. Schivo and K. Degeling collaborate.

3. Modelling the metastatic Castration Resistant Prostate Cancer Treatment Process

With the literature research presented in Chapter 2, this chapter is about how all this obtained information is used for modelling the treatment process of metastatic Castration Resistant Prostate Cancer. First, the process that will be modelled will be described, as it is different from the process described in Section 2.1 at some points. Secondly, the input and output of the models are elaborated on, after which the two models are illustrated. Finally, the sensitivity analysis will be described.

3.1. Process

The first step in modelling the treatment process using different modelling techniques is to define a standard process for the control arm, the experimental arm and the hybrid arm of the experiment. This hybrid arm combines the control arm and the experimental arm. The reason why this hybrid arm is added to the experiment is that it is not yet known whether CTC Analysis would be used as only test or as additional test to treatment response. By adding the hybrid arm both scenarios are covered. The three arms will be identical except for the test that are used, the timing of the tests and the timing of the decision moments. The process will be described without providing exact numbers for the input parameters, as those will be presented in the next section on the input data and the outcome measures. To support the process description, a graphical representation of the general process is presented in Figure 11.

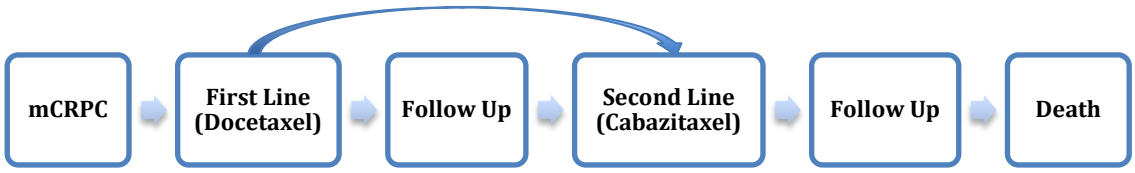


Figure 11. General treatment process of mCRPC.

The treatment process starts with all patients receiving first line treatment. For both the first line and the second line treatment, every treatment cycle exists of three or four events: performing tests, stopping treatment due to for example toxicity, receiving treatment and sometimes taking a decision on whether treatment should be continued or discontinued based on progression of the disease. This decision is based on the physicians' advice. The sequence of these events is as follows. First the tests are performed, after which treatment can be stopped due to reasons not related to progression of the disease or death. When a decision needs to be taken on continuation of the treatment, based on progression of the disease that is the third step in a treatment cycle. The last step is starting the treatment for that cycle. These steps are presented in Figure 12.

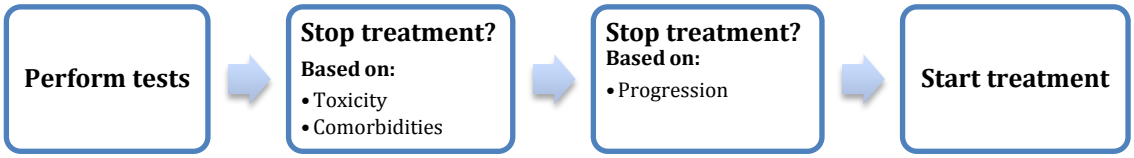


Figure 12. Graphical representation of the steps in a treatment cycle.

When first line treatment is completed, the patients will end up in the follow up phase until the disease progresses and second line treatment is started. Of the patients who do not go to the follow up (first line treatment is stopped) and do not depart this life, a certain amount will receive additional second line treatment. When second line treatment is completed, the patients will end up in the follow up phase until the patient departs this life.

Differences between the three arms of the experiment arise when the tests at the beginning of each cycle are further specified. In the control arm, the used tests are the PSA test and the bone scintigraphy or planar bone scan. One or both of these tests are performed at certain treatment cycles. The experimental arm only involves CTC Analysis. For the hybrid arm, the PSA test, bone scan and CTC Analysis are combined.

3.2. Input and Output

Models themselves are very important for obtaining usable outcomes. However, the input for these models is at least as important, as the input is what the models uses to generate the outcomes on which conclusions will be drawn in the end. This section elaborates on the input that is used, on the required output of the model and the difficulties with these both.

3.2.1. Input Data

Input data refers to data, probabilities and rules, which the models need in order to simulate the treatment process of mCRPC. The used input data can be divided into eight categories according to which this section is written and which are classified according to the different functions in the models. These categories are: treatments, guidelines, physician's behaviour, diagnostic performance, quality of life, survival, follow up, and direct medical costs.

3.2.1.1. Treatments

For the treatments four parameters are important: the effectiveness of the treatment, the probability of stopping treatment due to toxicity etc., the duration of the treatment and the costs of the treatment.

Regarding Docetaxel, the effectiveness is derived from the trial with which approval of the FDA was obtained as first line treatment drug in metastatic Castration Resistant Prostate Cancer (mCRPC). Tannock et al. (2004) report on the effectiveness in several ways: the progression of the disease, the pain response, a 50% PSA response, the tumour response and the Quality of Life response. The different values for the effectiveness were 62%, 35% (95% CI: 27-43), 45% (95% CI: 40-51), 12% (95% CI: 7-19) and 22% (95% CI: 17-27) respectively. Intuitively, the progression of the disease is the most likely to be used, but the article does not specify what is the definition of "progression of the disease". Therefore, the effectiveness according to the in that time and current used standard of progression, the PSA response, is used as a base-case.

For Cabazitaxel, the effectiveness is also derived from the trial with which approval of the FDA was obtained for Cabazitaxel as second line treatment after first line treatment with Docetaxel in mCRPC. de Bono et al. (2010) report on the effectiveness of Cabazitaxel in multiple ways: the progression of the disease, the tumour response, a 50% PSA response and the pain response rate. The different values for the effectiveness were 66.4%, 14.4% (95% CI: 9.6-19.3), 39.2% (95% CI: 33.9-44.5) and 9.2% (95% CI: 4.9-13.5) respectively. Due to the same reason as for Docetaxel, the 50% PSA response rate is used as base-case measure for the effectiveness of the treatment.

However, the expectation is that the patients in the experimental arm of the experiment and for who first line treatment is not effective, will switch to second line treatment earlier than the patients in the control arm. When ineffective treatment is stopped earlier, the disease had less time to progress and the second line treatment is expected to be more effective. Unfortunately, there is no data on such a difference in effectiveness of the treatment related to the moment it was started after progression under Docetaxel. Therefore, the assumption to

be made is that the effectiveness of Cabazitaxel is equal in both arms of the experiment, while the effectiveness is expected to be higher in the experimental arm. This assumption is expected to be disadvantageous for the QoL in the experimental arm of the experiment, which will be investigated in the sensitivity analysis.

Treatment can be stopped due to progression of the disease, the patient's death, completion of the treatment, and also due to other reasons like toxicity and comorbidities. According to Tannock et al. (2004) there was a chance of stopping Docetaxel treatment due to one of these additional reasons of 15%, for Cabazitaxel this chance was reported to be 17% (de Bono et al., 2010). However, to use these absolute probabilities in a model, they need to be translated into rates per time cycle. According to Sonnenberg and Beck (1993) a constant rate can be derived using the following formulas:

$$p = 1 - e^{-rt} \qquad \textbf{Equation 1}$$

$$r = \frac{-\ln(-p+1)}{t} \qquad \textbf{Equation 2}$$

In these formulas, p represents the probability of the event, t the number of time units and r the rate of the event per time unit. Knowing the probability of leaving the trial and the average time spent in the trial, the rate can be estimated.

Unfortunately, the average time spent in the trials are not reported on in the articles. However, the median and the range of the time spent in the trial are reported in the articles and according to Hozo, Djulbegovic, and Hozo (2005), the mean can be estimated by the median, the range and the sample size of a trial. Moreover, when the sample size is larger than seventy patients the mean can be directly estimated by the median. For the Docetaxel trial the sample size is 332, for Cabazitaxel the sample size is 378. So the mean number of received treatment cycles may be estimated directly by the median. Using these insights the rates of stopping treatment are calculated and presented in Table 5.

Treatment	Probability of stopping	Time period in treatment cycles	Stop rate per day
Docetaxel	0,15	9,5	0,00081…
Cabazitaxel	0,17	6	0,00147…

Table 5. Rates of stopping first or second line treatment due to reasons not related to death, completion of the treatment or progression of the disease.

The treatment duration for both lines of treatment are according to the before mentioned trials and the protocol for the CTC-Switch Trial (CTC-Switch, 2014). Namely, a maximum of ten cycles of three weeks per cycle. Furthermore, the assumption is made that all patient will receive both first and second line treatment. This will make the results comparable to the CTC-Switch Trial.

The costs of the treatments are according to the study on the Drug Costs Management in Canada by Dragomir et al. (2014). The costs per cycle are €428,- for Docetaxel and €4.170,- for Cabazitaxel[11], assuming vials cannot be used for multiple cycles and cannot be shared between patients.

3.2.1.2. Guidelines

In theory, physicians use guidelines to assist them in advising patients on the decisions these patients need to make. In practice, however, physicians do not always follow these guidelines. Data on the physicians' behaviour is presented in the next section, this section focusses on the guidelines only. The guidelines are very important, as they can compromise poor diagnostic performance of tests by building in some extra safety. This safety, however, is very likely to involve higher costs due to additional tests and overtreatment. The other way around, diagnostic performance can be underestimated with guidelines that involve more safety in the case of good performing, also involving higher costs.

Data on the guidelines is derived from the literature study presented in Section 2.1, the CTC-Switch trial (CTC-Switch, 2014) and from the experts. For the control arm of the experiment, a baseline PSA test and bone scan should be performed before treatment is started, followed by additional PSA test before the start of each following treatment cycle. After completing four treatment cycles, a second bone scan is performed together with the PSA test and a decision has to be made whether testing should be continued. For this decision, at least two of the latest three PSA tests or the latest bone scan should suggest progression in order to continue testing. Otherwise the treatment is suggested to be effective. When the test are to be continued, PSA tests again are taken before the start of every treatment cycle. After six cycles (2 additional cycles) a third bone scan is taken together with the PSA test and the last decision is made. For this decision, at least two of the latest three PSA tests and the latest bone scan should suggest progression in order to switch to second line treatment. When this is not the case, treatment is continued and completed without additional testing.

For the experimental arm, a baseline CTC count should also be performed before the start of the first treatment cycles, continued with additional CTC counts before the start of following treatment cycles. The decision moments are after two, three, four and five treatment cycles. When treatment is continued after the fifth cycle, no additional testing needs to be done and treatment is completed. Treatment is switched when the latest two CTC counts indicate progression.

For the hybrid arm, the test moments are the same as for the control strategy and the experimental strategy. The decision moments are the same as in the control strategy, but the decision rules are different. For the first decision, all three test methods need to indicate that there is no progression in order to continue treatment without additional testing. Regarding the second decision, two out of three test methods need to indicate progression to stop treatment.

[11] Costs were converted from Canadian Dollars in 2013 to Euros in 2015 using the inflation rate of 1.5% in 2013 and 0.5% in 2014 (Eurostat, 2015) and the currency rate of 0,7 Euro per Canadian Dollar in 2015 (XE, 2015a).

3.2.1.3. Physicians' Behaviour

You may assume that guidelines represent the best possible care for all patients and that physicians will act according these guidelines. However, there are several reasons why guidelines cannot be applied directly into practice, as guidelines cannot represent all possible scenarios. Therefore, in practice guidelines are more often used as reference point from which physicians compose their own practice. Assuming physicians will act completely to the modelled guidelines, therefore, is not realistic and it is preferable to include data on the behaviour of physicians in following the available guidelines.

Recently 121 physicians (100 oncologists, 17 urologists, 1 radiation oncologist and 3 other specialists) participated in a survey on their tendency in following the suggested advice on treatment effectiveness by PSA test, bone scans and CTC Analyses as suggested by the guidelines. Most of the information obtained from this survey is very specific and cannot be used for modelling, as not all scenarios in the model are covered in this survey. However, there are two general insights that were obtained from the study, which can be used. The survey indicated that approximately 15% of the physicians would not recognize progression by PSA, while there indeed is progression. Furthermore and surprisingly, 4.5% of the physicians indicated that they would not use CTC Analysis at all as only source for assessing the treatment effectiveness. An additional 61.8% indicates that this is unlikely to happen. Assuming that these additional 61.8% of the physician will not follow the suggestion of the CTC Analysis in 50% of the cases, indicates that in approximately 35% of the cases in which the CTC Analysis suggests progression of the disease in the experimental arm, the physicians will not follow the suggestion to switch. These two percentages, 15% for the control arm and 35% for the experimental arm, will be included to investigate the effect of physicians' behaviour on the cost-effectiveness of applying CTC Analysis. Due to the uncertainty around this input parameter sensitivity analysis is required.

3.2.1.4. Diagnostic Performance

Regarding the diagnostic performance, two things are important for all three tests: the diagnostic performance itself and possible changes in the diagnostic performance over time. As described in Section 2.2, the most important aspects for this study are the sensitivity and specificity. Regarding changes in the sensitivity and specificity as the patient's treatment time increases, the expectation is that the diagnostic performance of the PSA test will increase over time and that the benefit of using CTC Analysis becomes smaller. However, there is no data available about this expectation, so the assumption is made that the diagnostic performance of PSA test is stable over the treatment time.

Information on the diagnostic performance of these test is not hard to find. However, it is hard to find information on the diagnostic performance of these test specifically in their use for diagnosing whether there is progression or not in a patient suffering from metastatic Castration Resistant Prostate Cancer. As this is not comparable to other sorts of cancer, the information to be used on the diagnostic performance of the test is preferred to be specific for the disease and a somewhat different application, than a different disease and exactly the same application.

For the PSA test, there are some studies that report on the sensitivity and specificity in screening for Prostate Cancer. For example, Thompson et al. (2005) report on several cut-off point and the associated sensitivity and specificity of the PSA test in screening for Prostate Cancer in healthy men older than 50 years. However, no studies report on the diagnostic performance of the PSA test in the context of identifying the patient's response to treatment. Mistry and Cable (2003) performed a meta-analysis on the sensitivity and specificity of PSA in this screening context, which is considered as the best available evidence. The pooled sensitivity is 72,1% and the pooled specificity was 93,2%.

Regarding the bone scan, Even-Sapir et al. (2006) report on a sensitivity and specificity of 69% and 64% for the detection of bone metastases in patients with High-Risk Prostate Cancer. As the decision whether the disease is considered to be progressed based on a bone scan is made based on the number of metastases, this is the best available evidence to be used.

As presented in Section 2.2, Goodman et al. (2009) report on a diagnostic performance for the enumeration of CTC in patients with Castration Resistant Prostate Cancer with an exact threshold of 4 cells per 7,5 mL blood. In the article they report on a sensitivity of 61% and a specificity of 100%. This is the best available evidence on the diagnostic performance of CTC Analysis as test for progression, but the sensitivity is considerable lower compared to the PSA test. This is very suspicious, as CTC Analysis is expected to have a much better diagnostic performance. A comprehensive sensitivity analysis should be performed on these aspects.

3.2.1.5. Quality of Life

The differences in the Quality of Life (QoL) of patients are very important in cost-effectiveness studies as the QoL of patients is an important part of the effectiveness of a new technology in terms of Quality Adjusted Life Years (QALYs). For mCRPC patients not much is known about the differences in QoL during the different phases of the treatment process. The only usable information found is presented by Caffo et al. (2011).

This article is based on a prospective Phase II Trial in which patients were treated with Docetaxel and the QoL was assessed by the QLQ-C30 questionnaire. The QLQ-C30 questionnaire exists out of nine multi-item scales and indicates the QoL of the patient on a scale from zero to, and including, hundred (Aaronson et al., 1993). The results were that there is no significant change in the Global QoL during treatment with Docetaxel. However, the study does report on a difference in the baseline QoL with respect to responding and non-responding patients. At baseline, non-responders had an average Global QoL of 52.9 (95% CI: +/- 10.7) and responders had an average Global QoL of 70.5 (95% CI: +/- 6.5).

In order to use this information in the models, additional assumptions need to be made on the QoL of patient during other phases in the treatment process. The first assumption to be made, is that the QoL during second line treatment with Cabazitaxel is comparable to the QoL during treatment with Docetaxel. Secondly, the QoL of patients during follow up after completing first line treatment with

Docetaxel, has to be estimated. As receiving chemotherapy is considered to be have a quite negative impact on the QoL, and the difference between the QoL in effective and not-effective treatment is 17.6, the estimated QoL of patient in the first follow up is estimated to be 17.6 point higher than during first line treatment. The last assumption to be made regarding the QoL, is about the QoL during follow up after stopping second line treatment with Cabazitaxel. This assumption is the same as the assumption for the QoL during the first follow up.
By dividing the Global QoL scores by one hundred, utilities can be obtained on a scale of zero to and including one (0-1). An utility of zero indicates death, while an utility of one hundred indicates a patient in perfect health. The information presented in the (Caffo et al., 2011) article and these assumptions result in the different values for the utility of the patient in the different phases of the treatment process presented in Table 6.

Treatment Effectiveness (Docetaxel)	Treatment Effectiveness (Cabazitaxel)	Phase: Docetaxel	Phase: First Follow Up	Phase: Cabazitaxel	Phase: Second Follow Up
Effective	**Effective**	0.705	0.881	0.705	0.881
Effective	**Not-Effective**	0.705	0.881	0.529	0.705
Not-Effective	**Effective**	0.529	0.705	0.705	0.881
Not-Effective	**Not-Effective**	0.529	0.705	0.529	0.705

Table 6. The estimated utilities of patients during the different phases of the treatment process.

3.2.1.6. Survival

The survival time is very important in cost-effectiveness modelling, as it is responsible for the effectiveness outcome measure together with the utility of the patients. In this case the expectation is that not effective treatment is switched earlier in the experimental arm and that this will increase the survival of the patients. Obviously, this is very beneficial, but data confirming this expectation is missing.

Data that is available on the survival is the data presented in the articles about the trials that were performed for approval of Docetaxel and Cabazitaxel as first and second line treatment by the FDA. For Docetaxel, Tannock et al. (2004) report on a chance of 34% that a patient survived 25 months after the start of the treatment. For Cabazitaxel, de Bono et al. (2010) report on a chance of 27% that a patient survived 25 months after the start of the treatment. After these 25 months, no deaths were reported for three months, after which a steep trend downwards was visible on the survival curve. Following this trend, all patients would have died after 33 months after the start of the treatment. Using the same formula as in Section 3.2.1.1, this leads to survival rates presented in Table 7.

Phase	Probability of death	Time period in months	Death rate per day
Docetaxel	0,66	25	0,00143…
Cabazitaxel (<= 25 months)	0,73	25	0,00174…
Cabazitaxel (>25 months)	1	30	0,03837…

Table 7. Death rates during treatment with Docetaxel and Cabazitaxel.

The first assumption that needs to be made to use these numbers is that the rate of death is constant over time, while it is likely that the rate increases over time. The second assumption that has to be made is that patients in follow up after completing Docetaxel have the same survival rate as patients that are treated with Docetaxel. The third assumption made is that patients in follow up after treatments with Cabazitaxel have the same survival rate as patients that are treated with Cabazitaxel. The fourth assumption is that there is no difference between patients for whom treatment is effective and patients for whom treatment is not effective.

Besides these four assumptions, the most important assumption that is needed to be made is that the average survival time is equal in all three arms of the experiment. This assumption is necessary because otherwise unrealistic results are likely to occur, due to an expected lower survival in the experimental arm. Expectations are that the patients in the experimental arm will start second line treatment earlier on average compared to the patients in the control arm. Since in the models from that moment the survival curve for Cabazitaxel will be used to model the survival, the expected survival for patients treated with Cabazitaxel is also measured from that point. Therefore, the patients in the experimental arm are likely to die earlier on average than the patients in the control arm, while expectations are that the survival will improve when treatment is not effective treatment is stopped earlier.

Assuming the average survival to be equal still is disadvantageous for the experimental arm, but it is the best that can be done to obtain results that can be compared, given the time restrictions of this research. In order to take this assumption into account, the survival will first be modelled according to the presented data and assumptions. Afterwards, the average survival of the experimental arm and the hybrid arm will be set equal to the average survival in this control arm.

3.2.1.7. Follow Up

Regarding the follow up, two parameters are important: the expected time to progression after first line treatment and the costs during follow up.

de Bono et al. (2010) report a median time to progression after receiving the last Docetaxel cycle of 0.8 months or 24 days. Since the sample size of this observation is large enough (n=378) the mean can be also estimated at 0.8 months (Hozo et al., 2005).

The costs during follow up are estimated to be zero, because the patients do not receive chemotherapy during follow up and the assumption is made that no additional test will be performed during the follow up. In practice, progression of the disease during follow up will be indicated by tests, but there is too little information available to include this in the model. Furthermore, the mean period a patient spends in follow up is so short, e.g. 0.8 months, that this is not likely that many test will be performed in this period of time.

3.2.1.8. Direct Medical Costs

Several types of costs already have been mentioned in Subsections 3.2.1.1 up to 3.2.1.7. However, two additional direct medical cost types play a role in the models, namely: test costs and physician costs.

The costs for the tests are derived from several sources. The costs of a PSA test and bone scan are derived from the "Tarieventabel DBS 2015" by the NZA (The Dutch Healthcare Authority) and are €9,11 per PSA test and €285,36 per bone scan (NZA, 2015). The costs of a CTC Analysis are estimated at €475,- per analysis[12], based on prices between 450,- Dollar and 600,- Dollar in the United States of America (Stein, 2014).

The costs of a physician consult are also derived from the "Tarieventabel DBS 2015" by the NZA and are €65,17 per consult (NZA, 2015).

3.2.2. Outcome Measures

This second part of this Section 3.2 on input and output of the models, is about the outcome measures that are used. Both models need to be able to generate the primary outcomes, the secondary outcomes do not explicitly need to be generated by the models, because secondary outcomes are additional and not key in decision making.

The primary outcome measures that are used are those that are required to provide a cost-effectiveness estimate. This obviously includes the total costs and the effectiveness of treating the patients. Costs are expressed in Euros, as the input parameters are also expressed in Euros. Effectiveness should be valued in Quality Adjusted Life Years (QALYs), as this is the golden standard in Health Technology Assessment (Ryen & Svensson, 2014). QALYs exists out of two separate factors: the QoL or utility and the overall survival time.

Secondary outcome measures include the specific test result reported as progression or no progression, physicians' behaviour specified by the number of times the guidelines are not followed, the death cause of the patient, the amount of received treatment (specified in under treatment and overtreatment) and the reason for stopping the treatment.

[12] The price of a CTC Analysis was converted to US Dollars in 2014 to Euros in 2015 using the inflation rate of 0.5% in 2014 (Eurostat, 2015) and the currency rate of 0,9 Euro per US Dollar in the first quarter of 2015 (XE, 2015b).

3.3. Discrete Event Simulation Model

In this section the Discrete Event Simulation model is described. First the general thoughts behind the model will be stated, after which the elements and the way in which they interact are explained. Finally, several simulation parameters will be discussed. A snapshot of the model is presented in Figure 13.

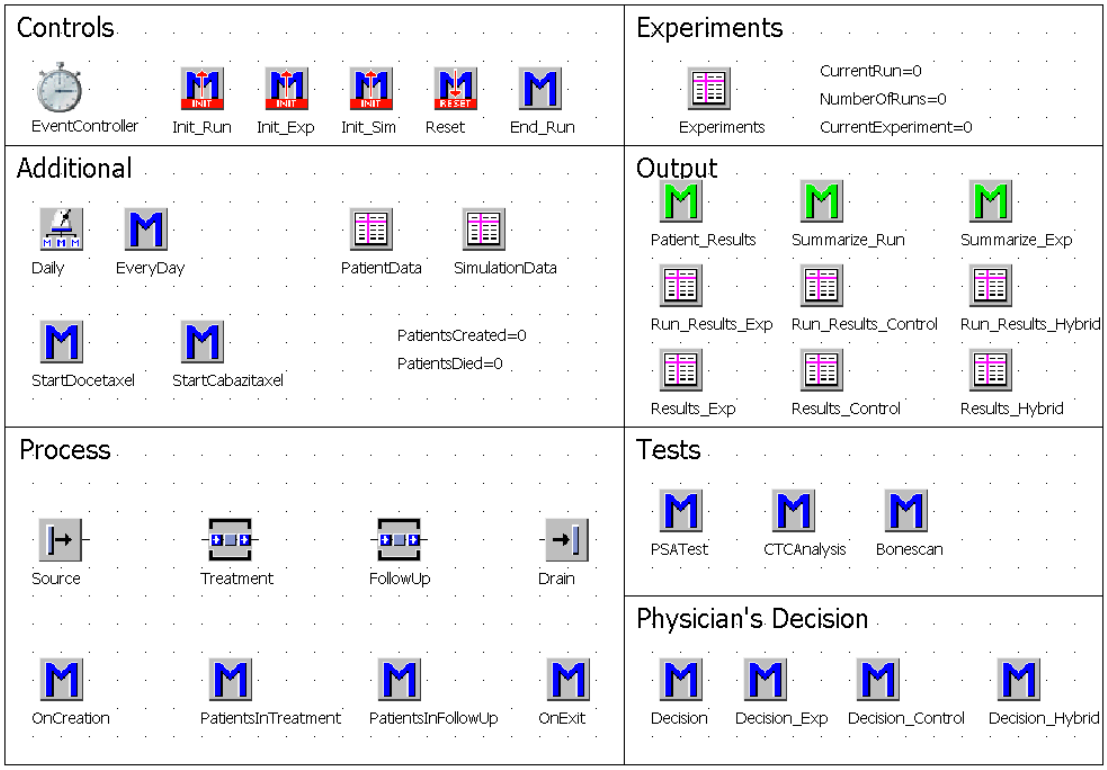


Figure 13. Snapshot of the Discrete Event Simulation model.

3.3.1. General model description

As visible in Figure 13 the actual process is very simplistic, as it exists out of only four objects: a source where the patients are created, a buffer called treatment where patients stay when they are treated, another buffer for patients that are in follow up and a drain where patients leave the model. Arrows do not connect these four objects, which implies all movements are triggered by methods programmed by code. The reason for this is that the process a patient goes through depends on the history of the patient in the model and to stochastic events. The software used, Tecnomatix Plant Simulation by Siemens, is designed for manufacturing processes and warehouses, which are more deterministic in nature. Therefore, the built-in features mostly cannot be used to model such a dynamic an stochastic process as the treatment process of metastatic Castration Resistant Prostate Cancer.

Roughly, the process the patient goes through in the model is as follows. When the patient is created in the "Source" the method "OnCreation" provides the patient it's characteristics, such as an ID and the arm of the experiment the patient belongs to. Next, the patient moves to the "Treatment" and the first line treatment with Docetaxel is started. Every week, the method "PatientsInTreatment" has a look at every patient that is in treatment and determines whether there is a chance that the patient stops the treatment due to

toxicity or other causes or whether the patient departs this life. When this is not the case, the method analyses whether one or multiple test need to be taken and whether the physician needs to give an advice on switching treatment or not. When a test needs to be performed, the associated method is called. That is: "PSATest", "CTCAnalysis" or "Bonescan", depending on the arm of the experiment and the treatment cycle the patient is in. When a physician's opinion is required on switching treatment, the "Decision" method is activated, which calls the right method according to the arm of the experiment the patient is in ("Decision_Exp", "Decision_Control" and "Decision_Hybrid" representing the associated guidelines) and determines how likely the physician is to advice according to the test results. In the model, patients will always follow the advice of the physician. When the advice is to switch treatment, the patient will start second line treatment with Cabazitaxel. When the patient completes all cycles of the first line treatment it goes to the follow up until the disease progresses and second line treatment is started. Progression of the disease while the patient is in follow up is determined using the daily-activated method "PatientsInFollowUp". For patient in the second line treatment the process is almost identical to the process for the first line treatment. The only difference is that stopping second line treatment will move the patient to the follow up, instead of the next line of treatment. When the patient is in the follow up after second line treatment, the method "PatientsInFollowUp" determines the survival of those patients each week.

3.3.2. Detailed model description

As stated in the introduction, now some more detailed information on the will be provided on important parts in the Discrete Event Simulation Model, starting with the patients themselves. The patients have several characteristics; some are written to the custom attributes of the patient in the model, others are (also) written to the table file "PatientData". The characteristics are written to the table file when they should be available for analysis later on. Custom Attributes can be assessed more directly by the model and encounter information as: the arm of the experiment the patient is in, the identification number of the patient, the phase the patient is in, whether tests are still taken, which test was taken last, the current treatment cycle and week of that cycle. Information about the patient that is stored in the "PatientData" table file is: the patient number, the arm of the experiment, the effectiveness of the treatments, the received treatment cycles, the reason for stopping treatment, the physician's behaviour, the death cause, the survival, the test results, the number of test, the number of follow up days, the number of physician visits and the costs. All these data enables detailed analysis of individual pathways of the patients later on.

Another important aspect of the model is the test section in which different methods are located that determine the test results. The test results are determined according to the patient's characteristics and the sensitivity and specificity of the test. For example, for a patient in the experimental arm of the experiment and for whom the treatment is initialized as not effective, the test should show that there is progression of the disease. However, the chance that the test indeed suggests there is progression equals the sensitivity of the test. So, a random number between zero and hundred is drawn from a uniform

distribution and compared to the sensitivity of the test to determine the result. When the drawn number is smaller or equal than the sensitivity, the test result is as it should be: “Progression”. All the test results are saved to the “PatientData” table file for analysis by the physician.

With regard to the advice of the physician on switching treatment or not, the model involves two steps: (1) forming a decision based on the test results and the guideline and (2) the determining whether the physician follows this suggestion in his advice. For the first step, the model analyses the number of positive tests of a predetermined number of latest tests. The number of positive tests should equal or exceed another predetermined number in order to provide the diagnosis of “Progression” according to that test. For the experimental arm, the model gives a diagnosis based on the CTC Analysis only. For the control arm the model used both the PSA Test and the Bone Scan to provide a diagnosis. For the patients in the hybrid arm all three tests are used. Regarding the second step, whether the physician follows the diagnosis in his advice, the model uses a percentage of the times the physician follows the advice or not.

By now quite some input for the model passed in review, all this input is provided to the model by the table file “SimulationData”. This table file contains information about: the number of simulation runs, the number of patients to be simulated in a run, the effectiveness of the treatments, the duration of the treatments, the chance of switching treatment due to toxicity etc., the moments of testing, the guidelines, the physician behaviour, the costs of the tests, the costs of the treatments, the costs of follow up, the costs of a physician consult, the survival of the patient, the time to progression of the disease in follow up and the diagnostic performance of the tests. The input related directly to the patients are assigned to the patient when they enter the model from the “Source” by the “OnCreation” method, other information is requested by the model when necessary. Performing experiments with different parameters can easily be done by initializing the “SimulationData” with other data at the start of a new experiment. Data for the different experiments is located in the “Experiments” table file.

As stated before, the “PatientData” table file contains all output data for each individual patient. This information is exported in a separate Microsoft Office Excel-file every time an experiment of multiple runs is finished for analysis of the outcomes and the distribution of the outcomes. However, the outcomes of different runs in the “PatientData” table file are also summarized into the table files ”Run_Results_Exp”, “Run_Results_Control” and “Run_Results_Hybrid”. These summarized run results are, at their turn, summarized into the average result for the different experiments. The table files “Results_Exp”, “Results_Control” and “Results_Hybrid” provide quick insights into the most important output measures of different experiments.

3.3.3. Simulation Parameters

A Discrete Event Simulation Model requires simulation parameters in order to obtain results that can be used for decision making. These parameters include the run length, the number of patients to be simulated and the number of runs per experiment.

Regarding the run length, simulations can be divided into two types: terminating simulations and nonterminating simulations (Law, 2007). Terminating simulations are simulations for which there is a "natural event" that specifies the length of each run or replication. This is often a point at which the system is "cleared out" or when no additional usable information is gathered. A nonterminating simulation is a type of simulation that does not have such a "natural event" to indicate the end of the simulation. In the case of a nonterminating simulation it is interesting to know the "steady-state performance" of the system.

The model in which the treatment process of mCRPC is simulated is a terminating simulation, as there is an obvious natural event that indicates the end of the simulation: the moment that all patients have died. This indicates that there is no fixed run length for the simulation, as there is no predetermined moment in time at which all patient will have died, so the simulation of a run will be stopped when all patients have left the model.

Since there is no distribution used for the arrival of patients and due to the stochastic character of the model, a certain amount of patients is needed to obtain a "steady-state" performance on the outcome measures. When the number of simulated patients is too low, outcome measure can be biased due to a sample size that is too small. To estimate the number of patients that need to be simulated, the general idea behind the method for determining the warm-up period, proposed by Law (2007), is used. This general idea is that you are looking for a value for the parameter that is considered for which the outcomes stabilize, which is called "flattening of the curve".

The estimation of the required number of simulated patients per run shows that 15.000 patients need to be simulated in order to obtain sufficient stabilized results. The determination of this number can be found in Appendix B. Using this number of patients that will be simulated in each run, the required number of runs per experiment can be calculated. Law (2007) argues that when the precision of the confidence interval is not that overwhelming important, for example in exploratory studies, one should use the fixed-sample-size procedure and should at least make three to five runs. However, as this study is more than just an exploratory study the absolute error β or the relative error γ should be used to determine the required number of runs.

Calculation of the required number of runs per experiment, using both the relative error and absolute error, resulted in a required amount of 13 runs per experiment. These calculations can be found in Appendix F. Combining this number with the 15.000 patients that will be simulated each run, each experiment will require the simulation of 195.000 patients.

3.4. Timed Automata Model

After the primary model was introduced in the previous section, this section introduces the Timed Automata model. First, the model will be explained in general. Secondly, a more detailed description is provided. No simulation parameters are discussed, as the software that is used, UPPAAL[13], does not require those parameters. Based on a value for alpha (Type I Error), the software automatically calculates the number of simulations that are needed. In the Timed Automata Model the hybrid arm of the experiment is not taken into account. To provide some visual feedback during the model description, the template for the Doctor is added in Figure 16.

3.4.1. General Model Description

The Timed Automata (TA) model exists out of several Automata, which are defined by templates. These templates are built for the different actors and parts in the model. In this model, templates have been built for the patient, the doctor, the tests and the guidelines. The Automata can operate independently of each other, but they can also communicate and interact with each other.

The patient is the main Automaton and follows the same process as in the DES model. This means the patient can be in the following states: receiving first line treatment, in first follow up, receiving second line treatment, in second follow up or the patient can be in the death-state. Transitions between these states can occur and can depend on variables, interaction with other Automata or probabilities. Variables can change due to transitions that the automata make or due to clocks. Clocks are counters that can run continuously or when triggered by an Automaton in a certain state. For example, a clock to track the received amount of first line treatment of a patient is activated while the patient is in the "first line treatment" state. After the simulation is finished, the value of that clock shows the amount of time the patient was in first line treatment. Furthermore, not only the patient can make transitions between states and influence variables and clocks, all Automata can.

To gather the outcomes, queries need to be used (see Figure 14). By using these queries, questions can be asked that will be answered by UPPAAL. Some examples of these questions are: "what is the chance that a patient survives for two years?", "is it possible to finish second line treatment, with costs lower than 10.000,- Euros?" and "how long are patient in first line treatment on average?". UPPAAL can also show the distribution of the distribution of a variable (see Figure 15). This statistical model checking feature can also help to validate the model. For example by asking whether it is possible that a patient will survive forever.

[13] http://www.uppaal.org/

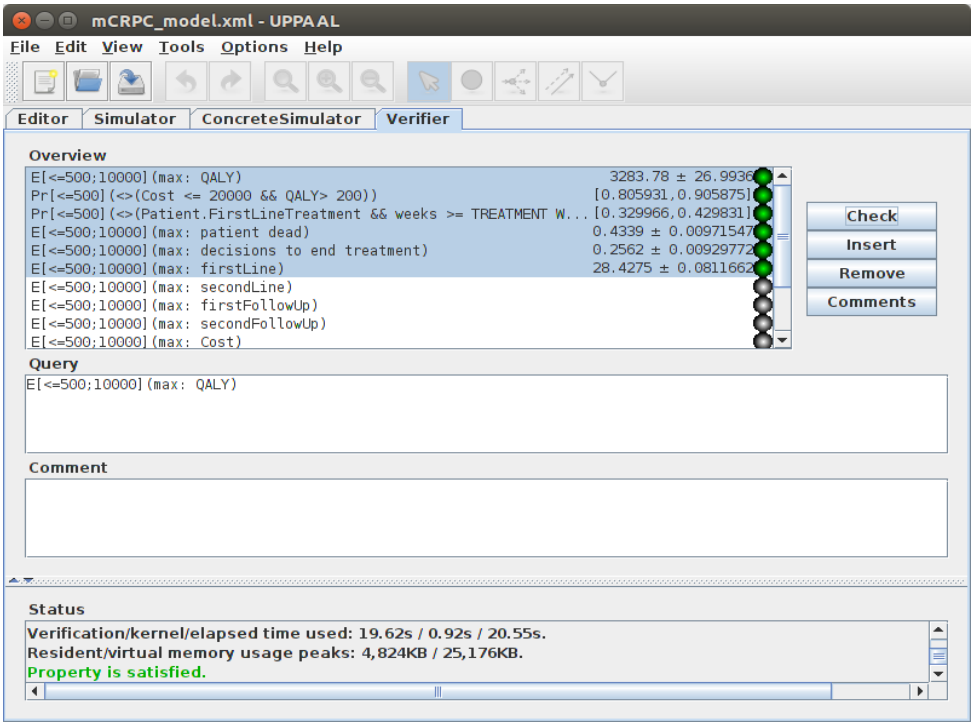


Figure 14. Snapshot of some of the queries used in UPPAAL.

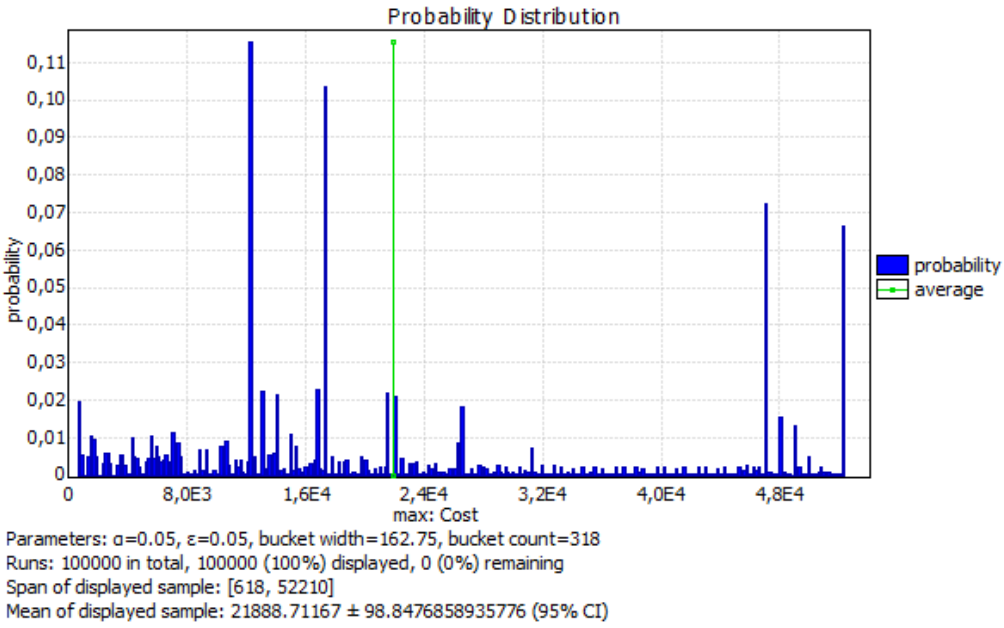


Figure 15. Snapshot of a graph showing the distribution of an outcome measure UPPAAL.

3.4.2. Detailed Model Description

To illustrate the model in more detail, the template for the doctor presented in Figure 16 will be used. This template will be walked through step by step.

The doctor gets involved when the first line of treatment for the patient is started at "begin treatment!" at the left of the Automata. When this transition takes place the number of CTC tests that are taken are reset and the variable "line_of_treatment" is set to one. Then the doctor comes in the state "WaitingForTests" and there are four possible transitions to the states: WaitingForTest via OneMoreTest, PatientDead, NoMoreTreatment and return to WaitingForTests after starting second line treatment. The transitions towards "NoMoreTreatment" and "PatientDead" have no possible additional transitions, so the doctor is finished. When the transition is made to return to "WaitingForTests" by starting second line treatment, the doctor returns in the same state, but then while the patient receives second line treatment.

However, things get a little more interesting when the transition towards "OneMoreTest" is taken. Then there are two additional transition possibilities. When the number of CTC tests that are taken is sufficient to provide an advice to the patient, the doctor takes the transition towards "TakeDecision". When the number of CTC tests is insufficient for providing an advice to the patient, the doctor returns to the state "WaitingForTests". When the doctor is going to prepare an advice for the patient, the model first computes what the decision should be according to the test results and guidelines (other Automata). Next the model used the likelihood of following these guidelines in order to advice the patient to make one of the following decisions: continue treatment with additional testing, continue treatment without additional testing or to stop treatment. All Automata work this way, but with different states and transitions.

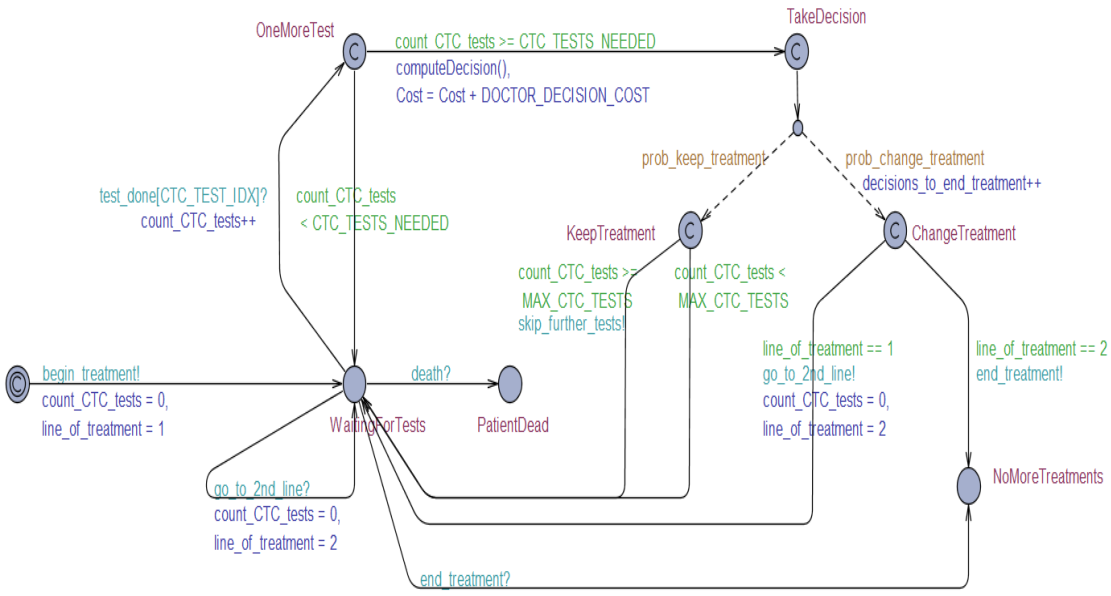


Figure 16. The template for the Doctor automata in the experimental arm of the experiment.

3.5. Sensitivity Analysis

Since there is a lot of uncertainty around the input data for the models, it is important to perform a sensitivity analysis on the most important and uncertain input parameters. In this section, a well-founded set of input parameters is selected and appropriate values for the sensitivity analysis are identified in order to perform a valuable and manageable sensitivity analysis.

3.5.1. Diagnostic Performance

Very important input parameters in the models are those regarding the sensitivity and specificity of the tests. For the bone scan, a good estimation of the diagnostic performance was found in literature, so there is no need for a sensitivity analysis on this parameter. However, regarding the PSA test and the CTC Analysis there is a need for sensitivity analysis.

The meta-analysis on the PSA test that was used reported on a pooled (combined) sensitivity of 72.1% and a pooled specificity of 93.2%, which will be used as base-case (Mistry & Cable, 2003). Using additional information from this article, a worst-case and best-case scenario will be added. The worst-case reported is a sensitivity 66.67% and a specificity of 18%. However, sensitivity and specificity are inversely proportional, meaning that as the sensitivity increases the specificity should decrease (Parikh, Mathai, Parikh, Sekhar, & Thomas, 2008). Therefore, the specificity of the PSA test is assumed to be 100% in the worst-case scenario with this sensitivity of 66.67%. The best-case scenario found in the article is a sensitivity 92.3% of and a specificity of 63.1%.

The best available evidence on the diagnostic performance of CTC Analysis, a sensitivity of 61% and a specificity of 100% (Goodman et al., 2009), is considered to be a worst-case scenario, as it relates to counting an exact amount of CTC. In order to assess a patient's response to treatment a change in the amount of CTC needs to be observed, which is considered easier than observing an exact amount of CTC. Nagrath et al. (2007) report on a best-case scenario of a sensitivity of 99.1% and a specificity of 100%. The base-case scenario is estimated to be in between the worst-case and best-case scenario with a sensitivity of 80% and a specificity of 100%.

3.5.2. Treatment Effectiveness

An overestimation of the treatment effectiveness is expected to be beneficial for the control arm, as it is less likely that overtreatment will occur. The worst-case scenario for the treatment effectiveness includes a very low effectiveness for both Docetaxel and Cabazitaxel, 12% according to tumour response for Docetaxel (Tannock et al., 2004) and 14,4% according to tumour response for Cabazitaxel (de Bono et al., 2010). The best-case scenario is a treatment response 62% for Docetaxel according to progression of the disease (Tannock et al., 2004) and 66.4% according to progression of the disease for Cabazitaxel (de Bono et al., 2010). The base-case scenario is according to the data presented in Section 3.2.1.1 and includes more realistic numbers of an effectiveness of 45% for Docetaxel according to a 50% PSA Response (Tannock et al., 2004) and 39.2 for Cabazitaxel according to a 50% PSA Response (de Bono et al., 2010).

3.5.3. Quality of Life

Also regarding the QoL it is desirable to perform a sensitivity analysis, as there were quite some assumptions made in order to include these numbers in the models. Again three scenarios are interesting to observe to begin with: one using the data as presented in Section 3.2.1.5, one with a smaller difference between responders and non-responders and one scenario with a larger difference between responders and non-responders. The difference in Global QoL according to the QLQ-C30 between responders and non-responders was 17.6 as presented by Caffo et al. (2011). For the two additional scenarios this number will be decreased or increased with 50%. The input data generated using the smaller difference of 8.8 for scenario two and the larger difference of 26.4 for the third scenario are presented in Table 11 and Table 12 in Appendix G.

3.5.4. Guideline for the Experimental Arm

An important benefit of using CTC Analysis is that the decision to switch treatment can be taken earlier. A sensitivity analysis is desirable on the timing of the first decision moment, as in practice it might happen that decisions are made earlier or later on in the process. Again three scenarios are investigated: the guideline as presented in Section 3.2.1.2, a scenario with the first decision moment one cycle earlier in the treatment process and a scenario with the first decision moment one cycle later in the treatment process.

3.5.5. Physicians' Behaviour

The last input parameter that needs to be taken into account in the sensitivity analysis is the parameter on the behaviour of the physicians. There are two reasons why sensitivity analysis is preferable regarding this topic. The first reason is that the data that is available on this topic is limited. The second reason is that the use of this parameter is quite experimental. When it turns out that the results of the experiments in which the behaviour of the physicians is taken into account are not usable, it should be possible to fall back on the more conservative experiments that do not include the physicians' behaviour.

The data from the survey presented in Section 3.2.1.3 showed expectations about what physicians are likely to do. This data will be used in one of the two scenarios taken into account in the sensitivity analysis. The other scenario involves "totally obediently" physicians, meaning that the physicians will always follow perfectly follow the guidelines. This ensures that the experimental input parameter is taken into account in the model, but also that conventional results are obtained to fall back on. Of course it is also interesting to compare the results of both scenarios to assess the added value of taking into account the physicians' behaviour.

3.5.6. Set of Experiments

When all the scenarios for the sensitivity analysis are combined, a total of 486 experiments need to be carried out. Hereby all combinations of the two times three scenarios for the diagnostic performance, the three scenarios the treatment effectiveness, the QoL and the guidelines with the two scenarios for the physicians' behaviour are combined and simulated. As each experiment consists out of 13 runs of 15.000 patients per run (see Section 3.3.3), in total the treatments of 99.8 million patients need to be simulated in the Discrete Event Simulation Model to perform all these experiments. All the different values for the input parameters are summarized in Table 8.

Input Parameter	Worst-Case	Base-Case	Best-Case
PSA Performance	Sensitivity: 66.67% Specificity: 100%	Sensitivity: 72.1% Specificity: 93.2%	Sensitivity: 92.3% Specificity: 63.1%
CTC Performance	Sensitivity: 61% Specificity: 100%	Sensitivity: 80% Specificity: 100%	Sensitivity: 99.1% Specificity: 100%
Treatment Effect.	Docetaxel: 12% Cabazitaxel: 14.4%	Docetaxel: 45% Cabazitaxel: 39.2%	Docetaxel: 62% Cabazitaxel: 66.4%
Guideline Exp. Arm	First Decision After 1 Treatment Cycle	First Decision After 2 Treatment Cycles	First Decision After 3 Treatment Cycles
Quality of Life	Difference between Responding and Not-Responding = 8.8	Difference between Responding and Not-Responding = 17.6	Difference between Responding and Not-Responding = 26.4
Physicians' Obedience	Exp. Arm: 65% Control Arm: 85%	Exp. Arm: 100% Control Arm: 100%	-

Table 8. Overview of the input parameters that are varied in the sensitivity analysis in the values over which these input parameters are varied.

4. Results

What is the Health Economic Impact of using CTC Analysis in the treatment process of metastatic Castration Resistant Prostate Cancer?

In this chapter the result of the models are presented and analysed. In the first section of this chapter the results of the Discrete Event Simulation Model are treated. The second section is about the comparison of the results of the Timed Automata Model with the results of the Discrete Event Simulation Model.

4.1. Discrete Event Simulation Model

The results of the Discrete Event Simulation Model are presented in four steps according to which this section is written. First, the results on the base-case scenario will be presented. Next, a one-parameter sensitivity analysis is done, after which an additional threshold analysis is performed. The last step is to summarize and thereby answer the sub-research question this section is about.

4.1.1. Base-Case Scenario

In Figure 17 the results for the base-case scenario experiment are presented in an ICER Plot (see Section 2.3.1.2). In this graph each dot represents the average outcome of one of the thirteen simulation runs on the base-case scenario. The results show that the experimental arm of the experiment dominates the control arm of the experiment by decreasing costs with €2.618,61 on average and increasing effectiveness with 0.04 QALY on average. This indicates that applying CTC Analysis as only test for response to treatment can be considered cost-effective according to the base-case scenario in this study. The results also show that the outcomes for the hybrid arm are above the Willingness to Pay (WTP). This indicates that applying CTC Analysis as additional test can be considered cost-ineffective according to the base-case scenario in this study.

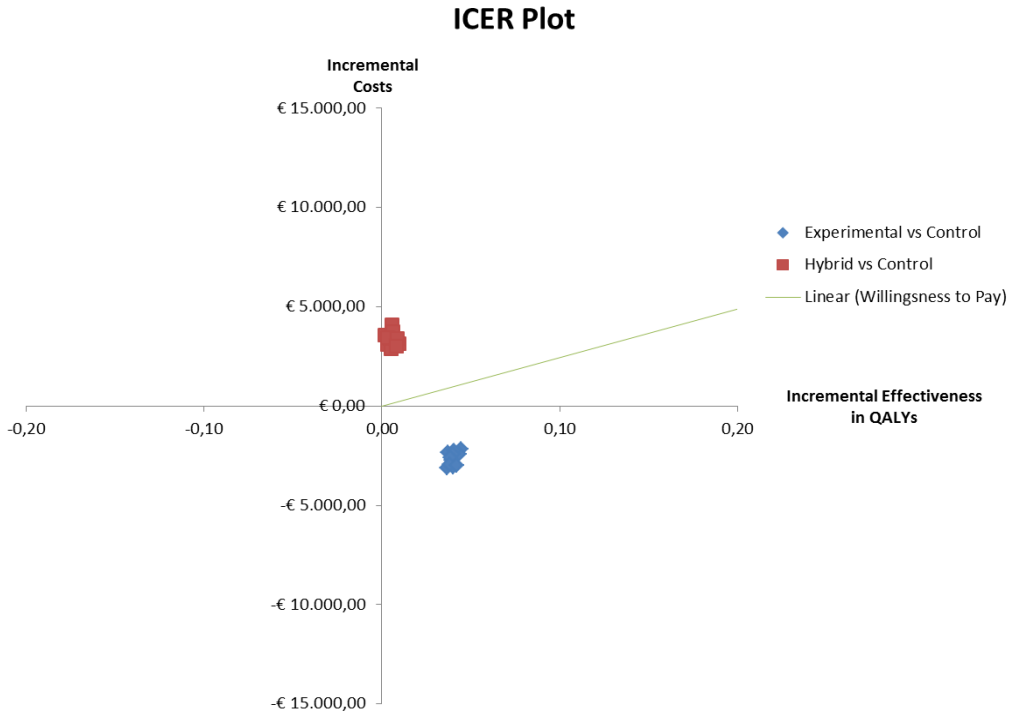


Figure 17. ICER Plot showing the Run Averages of the Base-Case Scenario Experiment.

In Figure 18 and Figure 19 the performance of the three arms of the experiment for the base-case scenario are presented separately. Figure 18 shows the average costs per patient and the average utility of the patients and Figure 19 shows the amount of treatment the patients received specified in effective and not effective treatment. The results regarding the survival are not presented, because the assumption is made that the survival is equal in all arms of the experiments. The average survival of the patients in the model was 67 weeks and 1 day.

According to the ICER Plot in Figure 17, Figure 18 shows a decrease in average cost per patient for the experimental arm and an increase of the average costs per patient for the hybrid arm, both compared to the control arm. The average costs per patient are € 20.075,54 in the experimental arm, € 22.694,15 in the control arm and the average costs are € 26.048,23 in the hybrid arm.

Figure 18 also shows that the average utilities are according to the effectiveness in the ICER Plot. The average utility per patient in the experimental arm equals 0.648, 0.617 in the control arm and 0.621 in the hybrid arm. So, the experimental treatment strategy improves the average of the utility of the patients and reduces the average costs per patient compared to the control strategy. The hybrid strategy improves the average utility a little, but also increase the average costs per patient compared to the control arm.

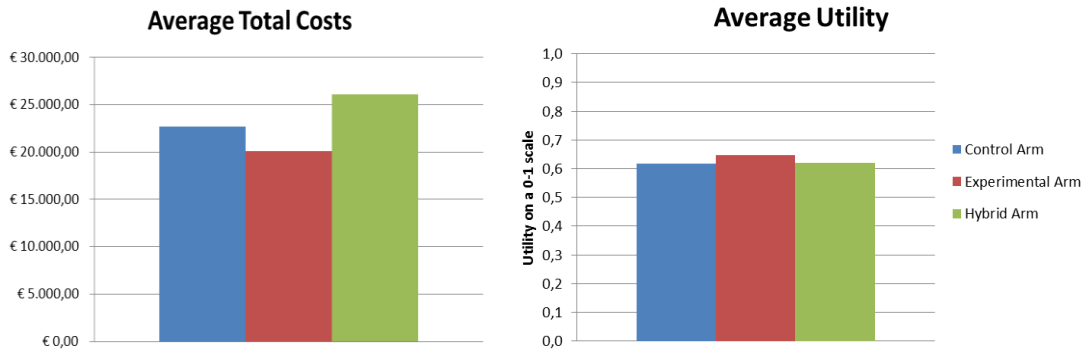


Figure 18. The Average Costs and the Average Utility for the Base-Case Scenario.

Regarding the average amount of received treatment, Figure 19 shows that the average amount of received first line treatment cycles of Docetaxel are 6.8, 4.9 and 6.5 for the experimental arm, control arm and hybrid arm, respectively. These treatment cycles exist out of effective treatment and not effective treatment (overtreatment). The average number of received effective treatment cycles is 3.4 per patient and is equal for all treatment strategies. However, the average number of undesirable overtreatment cycles are 3.4, 1.5 and 3.1 for the experimental arm, control arm and hybrid arm, respectively. For second line treatment with Cabazitaxel the average number of received cycles per patient are 4.4, 3.4 and 4.3 for the experimental arm, control arm and hybrid arm, respectively. The average number of effective treatment cycles are 1.9, 2.2 and 2.0, the average number overtreatment cycles are 2.5, 1.3 and 2.4, for the experimental arm, control arm and hybrid arm, respectively. From these numbers it can be concluded that both alternative strategies, experimental and hybrid, are improvements regarding the amount of received overtreatment compared to the control strategy. However, the improvements of the experimental arm are more significant than the improvements of the hybrid arm.

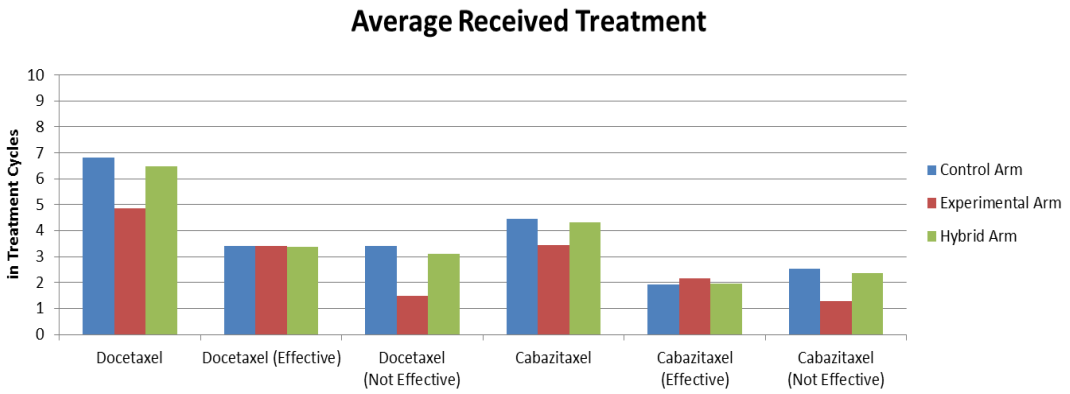


Figure 19. The results for the Base-Case Scenario on the Received Amount of Treatment.

The results regarding the base-case scenario indicate that CTC Analysis as only test to treatment response improves the average utility of the patients, reduces the amount of overtreatment and increases the amount of effective second line treatment, while lowering costs. Therefore, this experimental alternative treatment strategy is considered cost-effective compared to the control treatment strategy. The hybrid treatment strategy improves the average utility of the patient, reduces the amount of overtreatment and increase the amount of effective treatment compared to the control arm. However, these improvements are small and the average costs per patients increase a lot. Therefore, the hybrid treatment strategy is considered to be cost-ineffective.

4.1.2. One-Parameter Sensitivity Analysis

While the base-case scenario shows promising results, it is unlikely that this scenario indeed represents the situation in practice. Therefore, it is interesting to know how the outcomes are influenced by changes in the input parameters. To assess this sensitivity a total of 486 experiments are performed, in which all possible scenarios of input parameter combinations, as introduced in Section 3.5 on the sensitivity analysis, are combined. The results are presented in Figure 20.

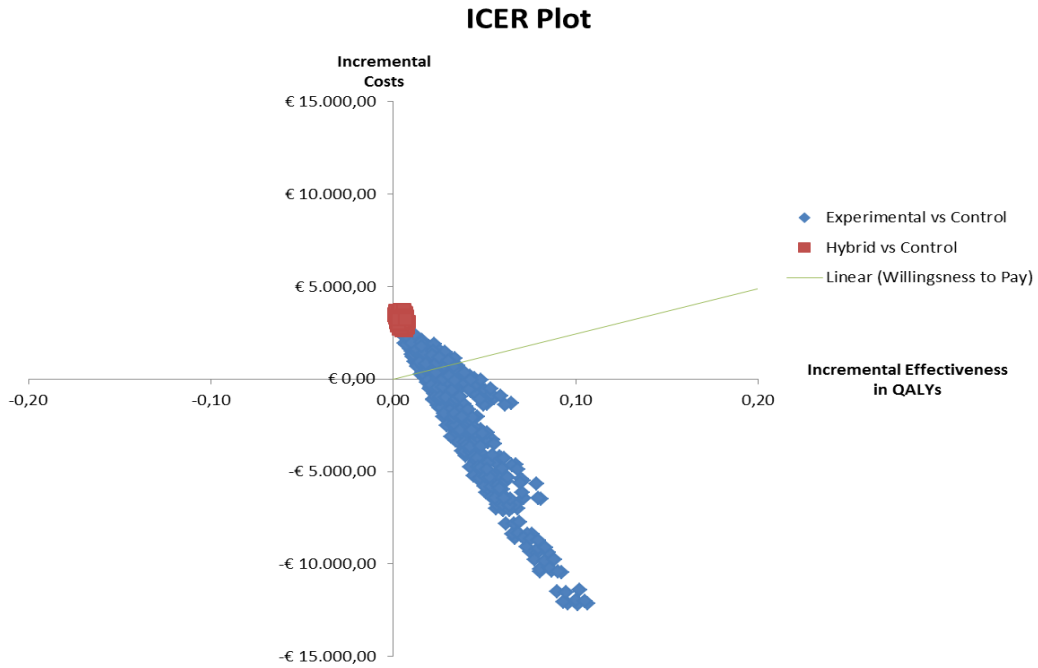


Figure 20. ICER Plot showing the Experiment Averages of all 486 Scenarios.

Figure 20 shows that the hybrid arm of the experiment is not cost-effective compared to the control arm in any of the experiments, because all the results are above the "Willingness to Pay" line. Therefore, it can be concluded that CTC Analysis as additional test is not of added value to the current treatment process. Therefore, the results for the hybrid arm will not be further analysed.

One-parameter sensitivity analysis is used to investigate the sensitivity of the outcomes to changes in one of the input parameter. This is done using Tornado Diagrams, which provide direct insight into the effect of a change in an input parameter on the outcome measure that is considered. The Tornado Diagram for the ICER is presented in Figure 21.

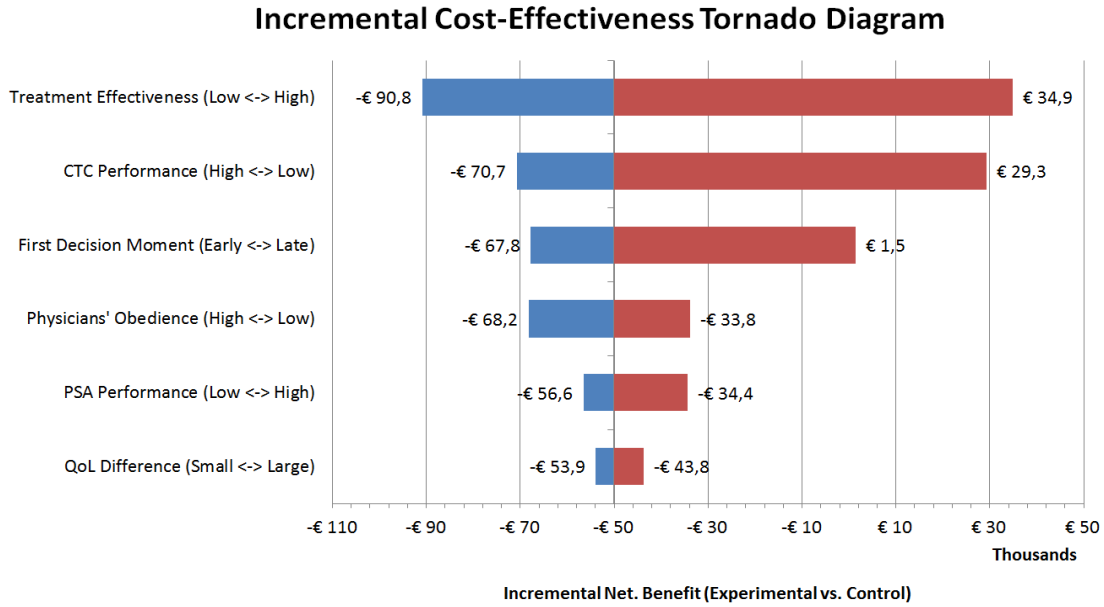


Figure 21. Input parameters' effect on the ICER (Lower = Better, for CTC Analysis).

Figure 21 shows that, according to the input values of this sensitivity analysis, the effectiveness of the treatments has the largest influence on the cost-effectiveness of CTC Analysis as only test to treatment response. When the treatment effectiveness increases the cost-effectiveness decreases. This can be explained by the fact that an increase in treatment effectiveness involves less possible overtreatment, which is beneficial for the underperforming PSA test.

The performance of the CTC Analysis and the first allowed decision moment in the experimental arm also have a large impact on the outcomes. A better diagnostic performance is beneficial for the CTC Analysis, as this leads to more accurate diagnoses. An earlier allowed decision moment for treatment switching is also beneficial for the CTC Analysis, because this advances the benefit of stopping not effective treatment in an earlier stage compared to the control arm.

Interesting to see is that the behaviour of the physician also influences the cost-effectiveness and that this indicates that it indeed is important to take this behaviour into account. The results show that the more obedient the physicians are according to the guideline, the more the cost-effectiveness of CTC Analysis improves. These results are also according to the expectations, because the physicians are more likely to distrust the CTC Analysis according to the data.

Regarding the PSA test, an increase in diagnostic performance of the PSA test will lead to more accurate diagnoses in the control arm, which is considered disadvantageous for the cost-effectiveness of the CTC Analysis. However, the results also show that the diagnostic performance of the PSA test does not has a large influence on the cost-effectiveness of the CTC Analysis.

Strikingly is that the input parameter regarding the difference in Quality of Life (QoL) ranks last in the list of input parameters. Because of the assumed equal survival, this parameter was expected to have a large influence on the effectiveness outcome, but this expectation turns out to be wrong. Moreover, the relation between the difference in QoL and the outcomes is also not as one would expect. A larger difference in QoL is expected to be beneficial for the CTC Analysis due to the decrease in overtreatment, but Figure 21 shows the opposite. The unexpected relation could be caused by the fact that the ICER is calculated by dividing the incremental costs by the incremental effectiveness. This division makes it possible that when the both the incremental costs and the incremental effectiveness worsen, the ICER improves.

In order to confirm the found relations between the input parameters and the ICER, the same analysis is performed separately on the two components of this outcome measure: the incremental costs and the incremental effectiveness.

The results on the incremental effectiveness are presented in Figure 22. This figure shows a different ranking order of the input parameters, but the relations are almost the same as in Figure 21. The only differences are the relation between the outcomes and the difference in QoL and between the outcomes and the performance of the PSA test. The latter difference is negligible due to the small difference between the actual values. The results on the difference in QoL are as one would expect; an increase in the difference in QoL is beneficial for the CTC Analysis. Worth mentioning is the fact that the experimental arm performs better than the control arm of the experiment in all scenarios.

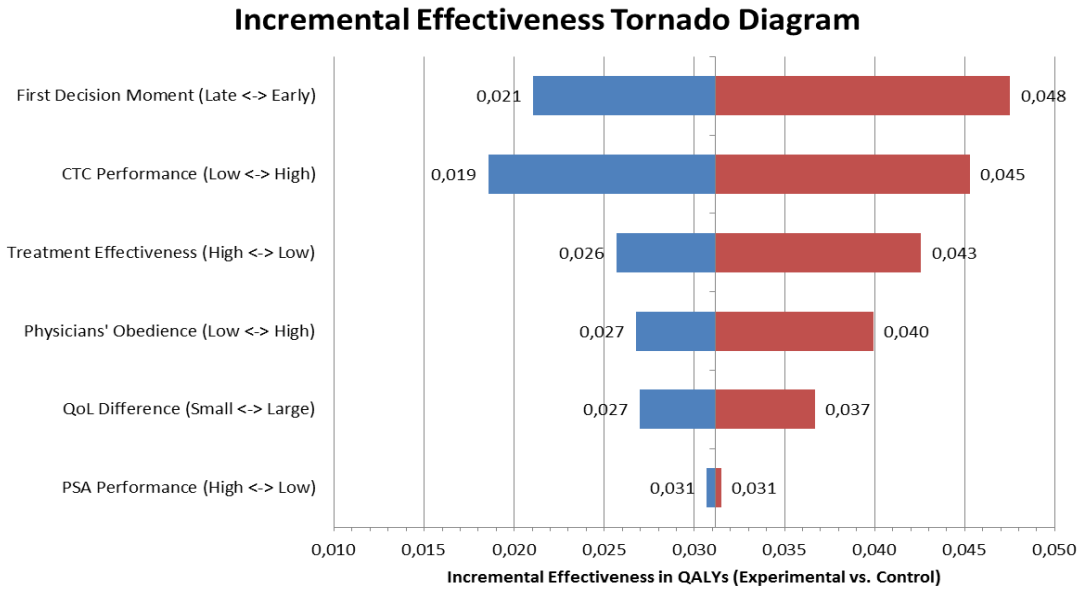


Figure 22. Input parameters' effect on the Incr. QALYs (Higher = Better, for CTC Analysis).

The results on the incremental costs are presented in Figure 23. These results are almost completely in accordance with the result on the ICER. The only difference between the two is the relation between the difference in QoL and the outcome measure. This relation is according to what one would expect; an increase in the difference in QoL is beneficial for the CTC Analysis.

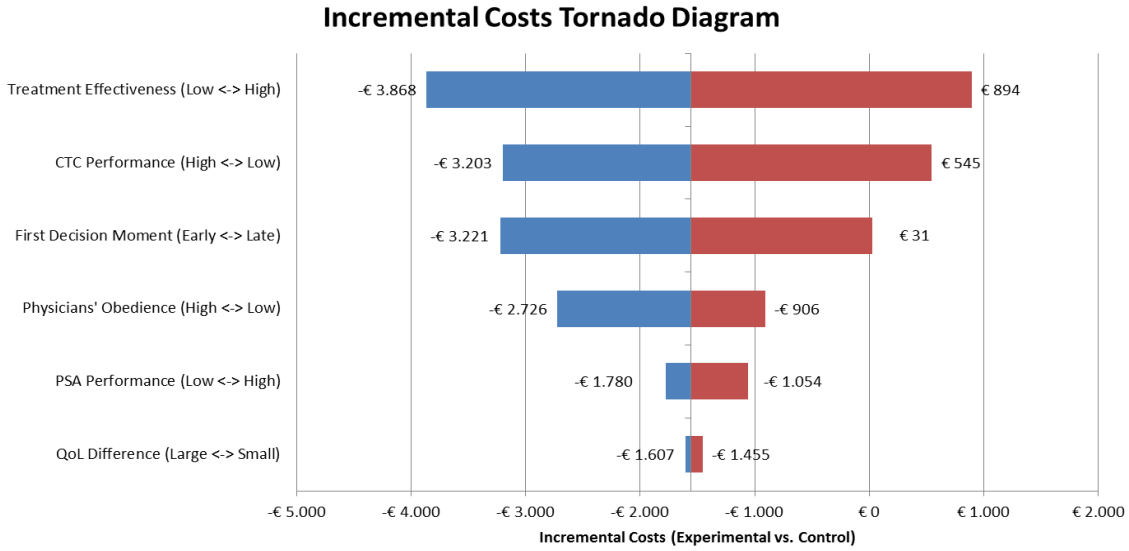


Figure 23. Input parameters' effect on the Incr. Costs (Lower = Better, for CTC Analysis).

The base-case scenario showed that the amount of overtreatment received by the patients also was an interesting outcome measure. Therefore, this secondary outcome measure is also included in this sensitivity analysis and the results are presented in Figure 24. The results, except for relation with the difference QoL, are completely according to the results for the ICER. The results for the relation with the difference in QoL are according to the incremental effectiveness and the incremental costs. Also for this outcome measure the experimental arm performs better than the control arm of the experiment in all scenarios.

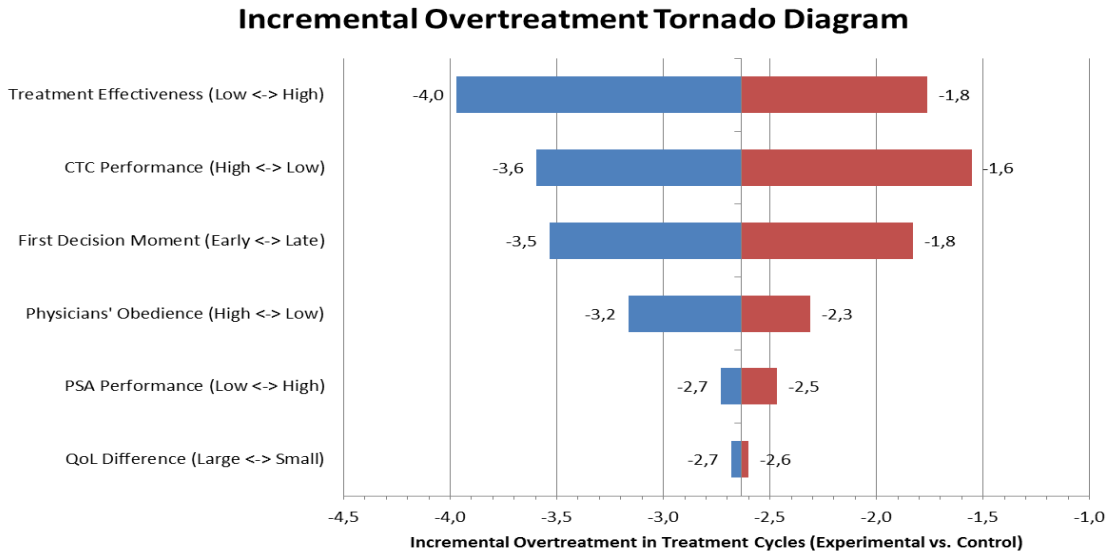


Figure 24. Input parameters' effect on the Incr. Overtreatment (Lower = Better, for CTC Analysis).

From this one-parameter sensitivity analysis it can be concluded that the several outcome measures are sensitive to changes in the input parameters. Especially the changes in the treatment effectiveness, diagnostic performance of the CTC Analysis and the first allowed decision moment have a large impact on the outcome measures. Increases in the diagnostic performance of the CTC Analysis, the physicians' obedience and in the difference in QoL between responders and non-responders turn out to be beneficial for the cost-effectiveness of the CTC Analysis. Furthermore, CTC Analysis also benefits by decreases in treatment effectiveness, the first decision moment and the diagnostic performance of the PSA test.

4.1.3. Threshold Analysis

Now that the relations between input parameters and outcome measures are explored, it is interesting to determine if the performed experiments can provide insight into the minimum requirements to the set of input parameter values in order to result in a cost-effective alternative treatment strategy involving the application of CTC Analysis. In order to identify the thresholds for the cost-effectiveness of using CTC Analysis, the results of all experiments are analysed using the insight obtained in the previous two sections.

The analysis on the Incremental Cost Effectiveness shows that three combinations of input parameters will lead to the application of CTC Analysis as a cost-ineffective alternative and that one combination of input parameters results in a doubtful cost-effectiveness of CTC Analysis. The ICER Plot in Figure 25 shows for which experiments the use of CTC as response marker are considered cost-effective, doubtful or cost-ineffective according to a WTP of €24.500,- as introduced in Section 2.3.1.2. These scenarios will now be further analysed to indicate cost-effectiveness threshold values for the input parameters.

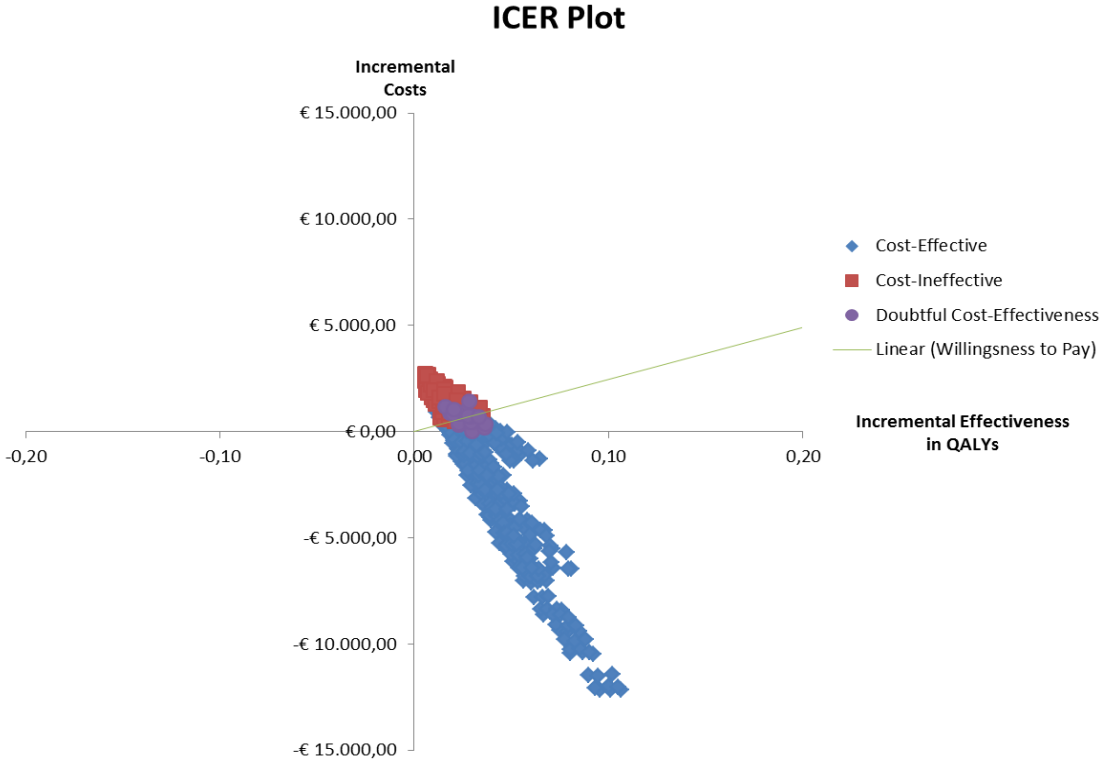


Figure 25. ICER Plot showing the results of the Threshold Analysis.

The first scenario in which the alternative treatment strategy is considered cost-ineffective, Scenario 1, is when the treatment effectiveness is high and the diagnostic performance of the CTC Analysis is low. The exact values for these input parameters are presented in Table 9.

Scenario 2, as presented in Table 9, also shows cost-ineffective results for the use of CTC Analysis. This scenario involves a high treatment effectiveness, performance of the CTC Analysis as in the base-case and a postponed earliest decision moment.

The last scenario in which the alternative treatment strategy is considered cost-ineffective is Scenario 3. In this scenario the treatment effectiveness is as in the base-case, the performance of the CTC Analysis is low and the earliest decision moment is postponed.

The cost-effectiveness of CTC Analysis is considered doubtful when the treatment effectiveness is high and the performance of the CTC Analysis and the earliest decision moment are as in the base-case. This scenario is presented in Table 9 as Scenario 4.

An additional threshold analysis on the average amount of received overtreatment showed that the use of CTC Analysis reduces the average amount of overtreatment in all experiments and no thresholds could and needed to be identified. The average decrease in first and second line overtreatement over all 486 experiments is 2.9 cycles per patient. The smallest improvement was a decrease of 0.4 treatment cycles per patient. The largest improvement in the average amount of overtreatment was a decrease of 7.6 treatment cycles per patient. This indicates that the use of CTC as response marker indeed is very effective in reducing the amount of overtreatment.

Scenario	Treatment Effectiveness	CTC Analysis Performance	First Decision Moment
Scenario 1	Docetaxel: 62% Cabazitaxel: 66%	Sensitivity < 61%	-
Scenario 2	Docetaxel: 62% Cabazitaxel: 66%	Sensitivity < 80%	After 3 Cycles
Scenario 3	Docetaxel: 45% Cabazitaxel: 39%	Sensitivity < 61%	After 3 Cycles
Scenario4 (Doubtful)	Docetaxel: 62% Cabazitaxel: 66%	Sensitivity < 80%	After 2 Cycles

Table 9. Scenarios for which the use of the experimental strategy is cost-ineffective or doubtful.

4.1.4. Summarizing the results

After extensive analysis of the results it can be concluded that Discrete Event Simulation is a usable modelling technique for modelling personalized treatment processes. Most of the results are as expected and for the results that were not as one would expect an explanaition could be found. Furthermore, building the final model was done in a couple of days and running an exeriment of 13 runs of 15000 patients only took between 1 and 1.5 minutes.

The results regarding the cost-effectiveness of CTC Analysis as test to treatment response are both discouraging and encouraging. From the results of the model it can be concluded that the application of CTC Analysis as additional test is not cost-effective. This hybrid treatment strategy did not result in a cost-effective performance in any of the performed experiments. On the other hand, the results regarding CTC Analysis as only test to treatment response are very promising.

Especially when keeping in mind the limitations regarding the input data and the assumptions that were needed to be made, the results for the experimental treatment strategy are very encouraging. In the base-case scenario the experimental arm of the experiment dominates the control arm of the experiment by lowering costs with €2.618,61 (12%) and improving the effectiveness with 0.04 QALY (5%). Furthermore, the experimental arm reduces the average number of not effective first line treatment cycles per patient from 3.4 in the control arm to 1.5 cycles per patient in the experimental arm. The average number not effective second line treatment cycles is reduced from 2.5 to 1.3 cycles per patient.

Sensitivity analysis shows that changes in the treatment effectiveness, diagnostic performance of the CTC Analysis and in the first allowed decision moment have a large impact on the outcome measures. Increases in the diagnostic performance of the CTC Analysis, the physicians' obedience and in the difference in QoL between responders and non-responders turn out to be beneficial for the cost-effectiveness of CTC Analysis. CTC Analysis also benefits from decreases in the treatment effectiveness, the first decision moment and from decreases in the diagnostic performance of the PSA test. Furthermore, the use of CTC as response marker resulted in a decrease in overtreatment and an increase in effectiveness no matter which input parameter was changed.

A threshold analysis shows that the application of CTC Analysis as only test to treatment response is cost-effective, except for four scenarios. Three of those scenarios result in CTC Analysis being a cost-ineffective alternative and one scenario results in doubtful outcomes. Additional analysis showed that the use of CTC as response marker always resulted in a decrease in overtreatment.

Finally and regarding the Health Economic Impact, it can be concluded that the use of CTC Analysis as only test to treatment response can be considered a cost-effective alternative treatment strategy. The use of CTC Analysis is expected to be beneficial for the effectiveness outcomes, while lowering costs.

4.2. Comparison: Discrete Event Simulation vs. Timed Automata

This section is about the comparison of the Timed Automata Model and the Discrete Event Simulation Model. First, the modelling itself will be treated, after which the results of both models will be compared.

4.2.1. Modelling mCRPC using Timed Automata

As the fact that the Timed Automata (TA) Model was already introduced in Section 3.4 suggest, it was possible to model the treatment process of metastatic Castration Resistant Prostate Cancer (mCRPC) using this modelling technique in combination with the software tool UPPAAL. Besides that the modelling was successful, it was also considered quite easy, as the model could be built in several days just like the Discrete Event Simulation (DES) Model.

Modelling the treatment process itself was considered easier using TA than using DES. The reason for this is that TA allows you to model the patient, physician, treatment, tests and guideline as independent Automata with their own level of abstraction. It was also very helpful that the Automata can act independent of each other, while being capable of communicating with each other and being capable of triggering each other, when needed.

A little less easy was running different experiments in UPPAAL, this was far more easy using the DES Model. In UPPAAL all input data needs to be adjusted by hand, while the DES Model used tables with different values for the input parameters. Also the outcomes could be gathered easier in the DES Model using reports and tables, which is not possible in UPPAAL. Of course, future software developments may solve these issues, but at this time, these are large drawbacks on the use of Timed Automata.

The expected benefits of modelling the mCRPC process with TA were: easy modelling, the statistical model checking function and the optimization possibilities. That TA offered relative easy modelling is already confirmed. The statistical model checking function also was really helpful in validating the model, as it enables the developer to ask the model, for example, “is it possible that a patient receives second line treatment without getting first line treatment?”. Furthermore, by asking these type of questions using queries, the statistical model checking function shows results, as outcome distributions, which would require external data analysis afterwards when using DES. The optimization opportunities could not be exploited, since the built-in optimization possibilities only work for deterministic processes and not for stochastic processes as that of mCRPC.

4.2.2. Comparison of the results

In order to further analyse the two modelling techniques, the results of the TA Model and the results of the DES Model are analysed on a worst-case, base-case and best-case scenario. The outcomes are compared on the Incremental Costs Effectiveness Ratio and the decrease in the received amount of treatment.

Figure 26 shows the ICER values for the worst-case, base-case and best-case scenario for the TA Model and the DES Model. For the worst-case scenario the results are comparable. The results for the base-case and best-case scenario are a bit different for the TA Model compared to the DES Model. However, the conclusions about the cost-effectiveness that are drawn from these outcomes are the same. In the worst-case scenario the use of CTC Analysis is considered to be cost-ineffective. For the base-case and best-case scenario the use of CTC Analysis is considered to be cost-effective.

Due to time restrictions, the reasons for the differences in the outcomes are not yet studied. A possible reason could be that both modelling techniques use data in different ways. For example, in the DES Model the survival is simulated as a rate of all patients in the model, in the TA Model the survival is modelled as an individual probability. Further research is required to confirm this expectation and to identify possible other reasons for the differences in the outcomes.

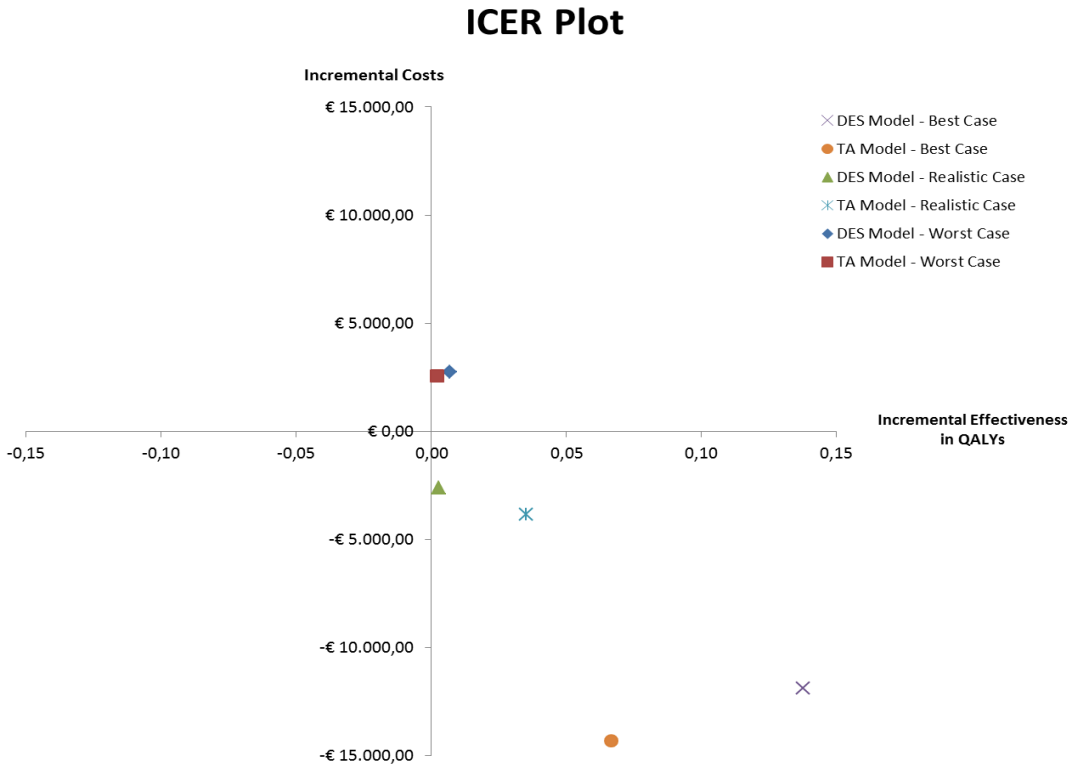


Figure 26. ICER Plot showing the different scenario for both modelling methods.

Because the reduction in overtreatment and under treatment turned out to be a very interesting alternative outcome measure while analysing the result of the DES Model, the treatment reduction is also investigated for the comparison of the TA Model and DES Model.

The reduction in treatment weeks relatively to the average amount of received treatment is presented in Figure 27. The reduction is not measured in treatment cycles like in the DES Model, because the TA Model reports on this outcome measure in weeks. Again comparable results with small differences are visible. The largest difference is the received amount of second line treatment with Cabazitaxel in the best-case scenario. This difference is relatively small, as it equals 1.6 weeks, which is approximately half a treatment cycle.

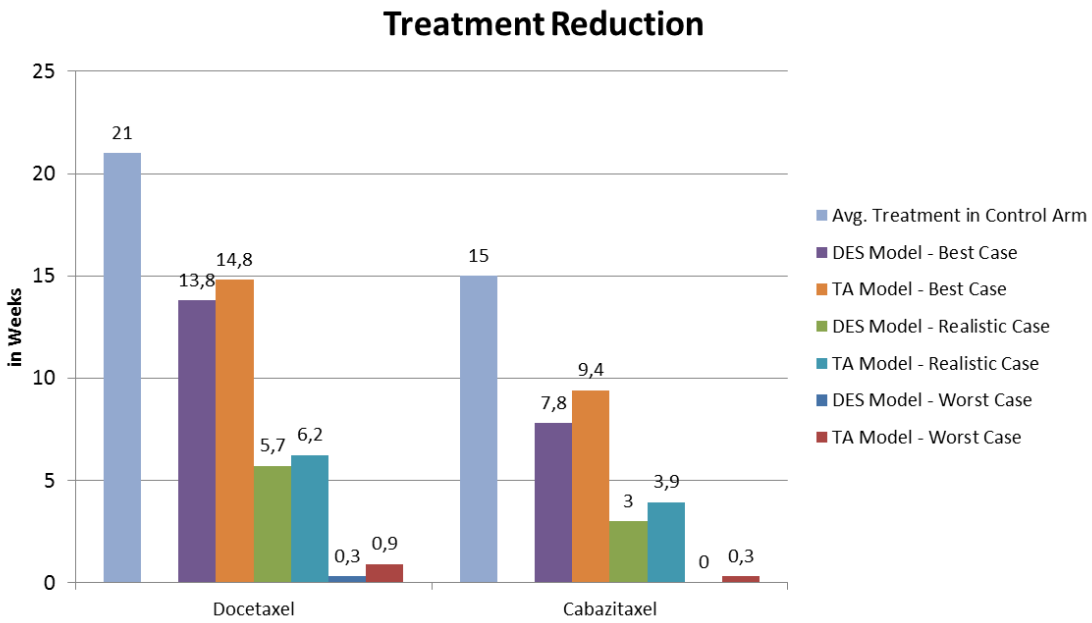


Figure 27. The results of the two models on the amount of treatment reduction in weeks for the different scenarios.

4.2.3. Conclusion

Based on the experience and the results of modelling the treatment process of metastatic Castration Resistant Prostate Cancer with Timed Automata in UPPAAL, it can be concluded that Timed Automata is a promising modelling technique for Health Economic Modelling. Especially when it is taken into account that this is the first known experiment with an application of this modelling technique in the field of Medical Decision Making, the results are very close to that of the Discrete Event Simulation Model. Modelling was considered a little more easier and the statistical model checking function is consider very helpful. Nevertheless, there are some issues that need to be solved before Timed Automata Modelling in UPPAAL can be used as primary modelling technique for these cost-effectiveness studies. Performing multiple experiments and analysing the results are very labour intensive at this moment and the optimization features are not usable for probabilistic processes.

These findings on the comparison of Timed Automata with Discrete Event Simulation in the case of metastatic Castration Resistant Prostate Cancer are presented during the MIRA Event 2015[14]. The poster used for this presentation is included in Appendix H, please send an e-mail to the author if you would like to receive the PDF-file of the poster. Additional, two abstract have been submitted to the Society for Medical Decision Making Congress[15] and to the International Society for Pharmacoeconomics and Outcomes Research Congress[16]. One abstract is about Timed Automata itself as a modelling technique (Appendix J), the other abstract is about the comparison of Timed Automata with Discrete Event Simulation (Appendix I).

[14] University of Twente's Research Centre for Biomedical Technology and Technical Medicine: http://www.utwente.nl/mira/
[15] http://smdm.org/
[16] http://www.ispor.org/

5. Conclusion

'What is the Health Economic Impact of using CTC as a response marker for mCRPC treatment, compared to the current used standard?'

The treatment process of metastatic Castration Resistant Prostate Cancer is a highly personalized treatment process involving costly treatments with low response rates and several decision moments on switching from first line to second line treatment. The results of the Discrete Event Simulation Model are used to support decision making on the Health Economic Impact of using CTC Analysis in the treatment process of metastatic Castration Resistant Prostate Cancer.

The use of CTC Analysis as additional test to the currently used tests turns out to be a cost-ineffective alternative strategy, as the cost-effectiveness outcomes of all studied scenarios were above the Willingness to Pay.

On the other hand, the results for the use of CTC as only response marker are very promising. In the base-case scenario the use of CTC as only response marker dominates the control arm of the experiment by lowering costs with €2.618,61 (12%) and improving the effectiveness with 0.04 QALY (5%). Furthermore, this strategy reduces the average number of not effective first line treatment cycles per patient from 3.4 in the control arm to 1.5 cycles in the experimental arm and the average number of not effective second line treatment cycles from 2.5 to 1.3 cycles per patient.

Sensitivity analysis shows that the cost-effectiveness of CTC Analysis benefits from increases in the diagnostic performance of the CTC Analysis, the physicians' obedience and in the difference in QoL between responders and non-responders. Increases in the treatment effectiveness, the first allowed decision moment and in the diagnostic performance of the PSA test are disadvantageous for the cost-effectiveness of the CTC Analysis. The sensitivity analysis also shows that the outcome measures are most sensitive to changes in the treatment effectiveness, diagnostic performance of the CTC Analysis and the first allowed decision moment. Furthermore, the use of CTC Analysis as only response marker always results in a decrease in overtreatment and in an increase in effectiveness according to the experiments that are performed in this study.

Concluding, the Health Economic Impact of CTC Analysis to assess patients' response to treatment, compared to the currently applied PSA test and bone scan, is that CTC as only response marker are expected to decrease the average costs and the average amount of overtreatment, while the average effectiveness increases. Therefore, the use of CTC Analysis as only test to treatment response can be considered as an cost-effective alternative and should be the new golden standard for testing metastatic Castration Resistant Prostate Cancer patients' response to treatment.

6. Limitations and Further Research

The last chapter of this report is about the limitations of this research and the possibilities for further research.

6.1. Limitations

There are several limitations to this research regarding the availability of the full text of scientific articles, data limitations and regarding the simulation.

During the literature study, the full text of some articles that did meet all other inclusion criteria was not available. Therefore, these articles could not be included in the final sample of the literature study. This has led to a possible loss of important information that could have been included when the full text of the articles would have been available.

There are also quite some limitations regarding the input data. The only input parameters for which reliable and complete data could be found are the treatment effectiveness, the maximum amount of treatment cycles, the length of a treatment cycle, the diagnostic performance of the bone scan and the costs. For the other input parameters assumptions were made.

Regarding the survival, the assumption needed to be made was that the average survival times are equal for all arm of the experiments. This assumption is considered disadvantageous for the experimental arm of the experiment, because it reduces the expected effect of early treatment switching.

Another expected benefit of early treatment switching that is not taking into account is an increase in second line treatment effectiveness. The assumption on this input parameter is that the effectiveness is equal for all patients, which is beneficial for the CTC Analysis, as sensitivity analysis shows that an increase in effectiveness has a large and disadvantageous effect on its cost-effectiveness.

The results also show that the physicians' behaviour indeed has an effect on the cost-effectiveness of the alternative treatment strategy. However, the data on this input parameter was limited and it cannot be said whether the assumptions are advantageous or disadvantageous for the CTC Analysis.

Assumptions are also made regarding the patients' Quality of Life and the changes in diagnostic performance of the PSA test over time. Nevertheless the sensitivity analysis shows that the influence of these parameters on the cost-effectiveness and the amount of overtreatment is small.

Another point worth discussing, is the number of runs that are performed per experiment. According to the outcomes on the incremental effectiveness, the required number of runs per experiments should exceed one thousand. This would require an unworkable amount of simulation time and the number of runs was determined based on the incremental costs instead.

The last limitation to this research also relates to the simulation, namely the validity of the simulation model. The model only is validated by extensive

analysis of the programming code by the developer of the model and by extensively analysing the behaviour and results of the model. Validation of the model by others will require knowledge of both the metastatic Castration Resistant Prostate Cancer treatment process and about Discrete Event Simulation and will require a lot of time. However, such additional validation would be very contributory to the credibility of the model.

6.2. Further Research

During this research many opportunities for further research were identified. These opportunities do not only relate to the specific case of applying CTC Analysis in the treatment process of metastatic Castration Resistant Prostate Cancer, but also to the use of Discrete Event Simulation for cost-effectiveness studies in general, other applications of Discrete Event Simulation and to the use of Timed Automata in Health Economic Modelling.

Regarding the modelling of the treatment process of metastatic Castration Resistant Prostate Cancer there are three interesting possibilities for further research. The data on this specific treatment process is very limited and additional and stronger evidence is required to further support decision making. Especially information on the effect of early treatment switching and the effect of ineffective or effective treatment on the survival is missing. Also the effect of early treatment switching on the effectiveness of second line treatment is not yet studied. Furthermore, additional research should be done on the treatment processes that are applied in practice. Actual practice is suspected to differ from the guidelines presented by the several world-wide health care organizations. It also is very interesting to study an alternative way of defining diagnostic performance, as not much is known about the diagnostic performance of tests for diagnosing treatment response in the case of metastatic Castration Resistant Prostate Cancer.

There are also some research opportunities for the application of Discrete Event Simulation in general in the field of Health Economic Modelling. This study shows that a lot of specified data is needed in order to use the full potential of Discrete Event Simulation. It is interesting to study these data requirements and the availability of this type of data in (health care) databases. Furthermore, it would be interesting to investigate whether a Tumour Growth Model could be simulated to further increase the dynamical character of the patients characteristics and further approach reality. Another interesting application of this modelling technique would be to optimize guidelines when trials have gathered all the required evidence.

The last topic for further research is the use of Timed Automata in Health Economic Modelling. There are several interesting points to start with. First of all the reasons for the differences between the Timed Automata and the Discrete Event Simulation Model need to be studied. Furthermore, the use of several additional input distributions could be studied, just like the reachability of the expected benefits of using Timed Automata. Additional, more experiments could be performed and the possibilities for carrying out a larger number of experiments more easily could be identified.

7. References

Aaronson, N. K., Ahmedzai, S., Bergman, B., Bullinger, M., Cull, A., Duez, N. J., . . . Takeda, F. (1993). The European Organization for Research and Treatment of Cancer QLQ-C30: A Quality-of-Life Instrument for Use in International Clinical Trials in Oncology. *Journal of the National Cancer Institure, 85*(5), 365-376.

ACS. (2014). Guide to Cancer Drugs Retrieved 11-02-2012, 2015, from http://www.cancer.org/treatment/treatmentsandsideeffects/guidetocancerdrugs/index

Allard, W. J., Matera, J., Miller, M. C., Repollet, M., Connelly, M. C., Rao, C., . . . Terstappen, L. W. M. M. (2004). Tumor Cells Circulate in the Peripheral Blood of All Major Carcinomas but not in Healthy Subjects or Patients With Nonmalignant Diseases. *Clinical Cancer Research, 10*, 6897-6904.

Allard, W. J., Miller, M. C., Connelly, M. C., Tibbe, A. G. J., Matera, J., Repollet, M., . . . Terstappen, L. W. M. M. (2004). Tumor Cells Circulate in the Peripheral Blood of All Major Carcinomas but not in Healthy Subjects or Patients With Nonmalignant Diseases. *Clinical Cancer Research, 10*, 6897-6904.

Alur, R., & Dill, D. L. (1994). A theory of timed automata. *Theoretical Computer Science, 126*, 183-235.

Ang, J. E., Olmos, D., & de Bono, J. S. (2009). CYP17 blockade by abiraterone: further evidence for frequent continued hormone-dependence in castration-resistant prostate cancer. *Br J Cancer, 100*(5), 671-675. doi: 10.1038/sj.bjc.6604904

Antonarakis, E. S., Heath, E. I., Posadas, E. M., Yu, E. Y., Harrison, M. R., Bruce, J. Y., . . . Carducci, M. A. (2013). A phase 2 study of KX2-391, an oral inhibitor of Src kinase and tubulin polymerization, in men with bone-metastatic castration-resistant prostate cancer. *Cancer Chemother Pharmacol, 71*(4), 883-892. doi: 10.1007/s00280-013-2079-z

Antonarakis, E. S., Heath, E. I., Smith, D. C., Rathkopf, D., Blackford, A. L., Danila, D. C., . . . Carducci, M. A. (2013). Repurposing itraconazole as a treatment for advanced prostate cancer: a noncomparative randomized phase II trial in men with metastatic castration-resistant prostate cancer. *Oncologist, 18*(2), 163-173. doi: 10.1634/theoncologist.2012-314

Antonarakis, E. S., Lu, C., Wang, H., Luber, B., Nakazawa, M., Roeser, J. C., . . . Luo, J. (2014). AR-V7 and resistance to enzalutamide and abiraterone in prostate cancer. *N Engl J Med, 371*(11), 1028-1038. doi: 10.1056/NEJMoa1315815

Armstrong, A. J., & Febbo, P. G. (2009). Using Surrogate Biomarkers to Predict Clinical Benefit in Men with Castration-Resistant Prostate Cancer: An Update and Review of the Literature. *Oncologist, 147*, 816. doi: 10.1634/

Armstrong, A. J., Garrett-Mayer, E., Ou Yang, Y. C., Carducci, M. A., Tannock, I., de Wit, R., & Eisenberger, M. (2007). Prostate-specific antigen and pain surrogacy analysis in metastatic hormone-refractory prostate cancer. *J Clin Oncol, 25*(25), 3965-3970. doi: 10.1200/JCO.2007.11.4769

Armstrong, A. J., Shen, T., Halabi, S., Kemeny, G., Bitting, R. L., Kartcheske, P., . . . George, D. J. (2013). A phase II trial of temsirolimus in men with castration-resistant metastatic prostate cancer. *Clin Genitourin Cancer, 11*(4), 397-406. doi: 10.1016/j.clgc.2013.05.007

Aslam, S., & Emmanuel, P. (2010). Formulating a researchable question: A critical step for facilitating good clinical research. *Indian Journal of Sexually Transmitted Diseases and AIDS, 31*(1), 47-50.

Attard, G., Reid, A. H., A'Hern, R., Parker, C., Oommen, N. B., Folkerd, E., . . . de Bono, J. S. (2009). Selective inhibition of CYP17 with abiraterone acetate is highly active in the treatment of castration-resistant prostate cancer. *J Clin Oncol, 27*(23), 3742-3748. doi: 10.1200/JCO.2008.20.0642

Bahl, A., Bellmunt, J., & Oudard, S. (2012). Practical aspects of metastatic castrationresistant prostate cancer management: patient case studies. *BJU International, 100*(2), 14-19.

Basch, E., Loblaw, D. A., Oliver, T. K., Carducci, M., Chen, R. C., Frame, J. N., . . . Virgo, K. S. (2014). Systemic therapy in men with metastatic castration-resistant prostate cancer:American Society of Clinical Oncology and Cancer Care Ontario clinical practice guideline. *J Clin Oncol, 32*(30), 3436-3448. doi: 10.1200/JCO.2013.54.8404

Beveridge, R. (2007). Circulating tumor cells in the management of metastatic breast cancer patients. *Community Oncology, 4*(2), 79-82.

Bianchini, D., Omlin, A., Pezaro, C., Lorente, D., Ferraldeschi, R., Mukherji, D., . . . Danila, D. C. (2013). First-in-human Phase I study of EZN-4176, a locked nucleic acid antisense oligonucleotide to exon 4 of the androgen receptor mRNA in patients with castration-resistant prostate cancer. *Br J Cancer, 109*(10), 2579-2586. doi: 10.1038/bjc.2013.619

Bidard, F. C., Hajage, D., Bachelot, T., Delaloge, S., Brain, E., Campone, M., . . . Pierga, J. Y. (2012). Assessment of circulating tumor cells and serum markers for progression-free survival prediction in metastatic breast cancer: a prospective observational study. *Breast Cancer Res, 14*(1), R29. doi: 10.1186/bcr3114

Bidard, F. C., Mathiot, C., Delaloge, S., Brain, E., Giachetti, S., de Cremoux, P., . . . Pierga, J. Y. (2010). Single circulating tumor cell detection and overall survival in nonmetastatic breast cancer. *Ann Oncol, 21*(4), 729-733. doi: 10.1093/annonc/mdp391

Bobinac, A., Van Exel, N. J., Rutten, F. F., & Brouwer, W. B. (2010). Willingness to pay for a quality-adjusted life-year: the individual perspective. *Value Health, 13*(8), 1046-1055. doi: 10.1111/j.1524-4733.2010.00781.x

Bouter, L. M., van Dongen, M. C. J. M., & Zielhuis, G. A. (2005). *Epidemiologisch onderzoek. Opzet en interpretatie*. Houten: Bohn Stafleu van Lohum.

Caffo, O., Sava, T., Comploj, E., Fariello, A., Zustovich, F., Segati, R., . . . Galligioni, E. (2011). Impact of docetaxel-based chemotherapy on quality of life of patients with castration-resistant prostate cancer: results from a prospective phase II randomized trial. *BJU Int, 108*(11), 1825-1832. doi: 10.1111/j.1464-410X.2011.10277.x

Caro, J. J., Moller, J., & Getsios, D. (2010). Discrete event simulation: the preferred technique for health economic evaluations? *Value Health, 13*(8), 1056-1060. doi: 10.1111/j.1524-4733.2010.00775.x

Carter, H. E., Martin, A., Schofield, D., Duchesne, G., Haworth, A., Hornby, C., . . . Jackson, M. (2014). A decision model to estimate the cost-effectiveness of intensity modulated radiation therapy (IMRT) compared to three dimensional conformal radiation therapy (3DCRT) in patients receiving radiotherapy to the prostate bed. *Radiother Oncol, 112*(2), 187-193. doi: 10.1016/j.radonc.2014.03.020

Cassinello, J., Climent, M. A., Gonzalez del Alba, A., Mellado, B., & Virizuela, J. A. (2014). SEOM clinical guidelines for the treatment of metastatic prostate cancer. *Clin Transl Oncol, 16*(12), 1060-1066. doi: 10.1007/s12094-014-1225-3

Climent, M. A., Piulats, J. M., Sánchez-Hernández, A., Arranz, J. A., Cassinello, J., García-Donas, J., . . . Pérez-Valderrama, B. (2012). Recommendations from the Spanish Oncology Genitourinary Group for the treatment of patients with metastatic castration-resistant prostate cancer. *Critical Reviews in Oncology/Hematology, 83*, 341–352.

Cohen, S. J., Punt, C. J., Iannotti, N., Saidman, B. H., Sabbath, K. D., Gabrail, N. Y., . . . Meropol, N. J. (2008). Relationship of circulating tumor cells to tumor response, progression-free survival, and overall survival in patients with metastatic colorectal cancer. *J Clin Oncol, 26*(19), 3213-3221. doi: 10.1200/JCO.2007.15.8923

Cristofanilli, M., Hayes, D. F., Budd, G. T., Ellis, M. J., Stopeck, A., Reuben, J. M., . . . Terstappen, L. W. (2005). Circulating tumor cells: a novel prognostic factor for newly diagnosed metastatic breast cancer. *J Clin Oncol, 23*(7), 1420-1430. doi: 10.1200/JCO.2005.08.140

CTC-Switch. (2014). Outline of the CTC-Switch Trial.

Danila, D. C., Fleisher, M., & Scher, H. I. (2011). Circulating tumor cells as biomarkers in prostate cancer. *Clin Cancer Res, 17*(12), 3903-3912. doi: 10.1158/1078-0432.CCR-10-2650

Danila, D. C., Morris, M. J., de Bono, J. S., Ryan, C. J., Denmeade, S. R., Smith, M. R., . . . Scher, H. I. (2010). Phase II multicenter study of abiraterone acetate plus prednisone therapy in patients with docetaxel-treated

castration-resistant prostate cancer. *J Clin Oncol, 28*(9), 1496-1501. doi: 10.1200/JCO.2009.25.9259

Das, M., Riess, J. W., Frankel, P., Schwartz, E., Bennis, R., Hsieh, H. B., . . . Bruce, R. H. (2012). ERCC1 expression in circulating tumor cells (CTC) using a novel detection platform correlates with progression-free survival (PFS) in patients with metastatic non-small-cell lung cancer (NSCLC) receiving platinum chemotherapy. *Lung Cancer, 77*(2), 421-426. doi: 10.1016/j.lungcan.2012.04.005

de Bono, J. S., Oudard, S., Ozguroglu, M., Hansen, S., Machiels, J. P., Kocak, I., . . . Sartor, A. O. (2010). Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. *Lancet, 37*(6), 1147-1154.

de Bono, J. S., Scher, H. I., Montgomery, R. B., Parker, C., Miller, M. C., Tissing, H., . . . Raghavan, D. (2008). Circulating tumor cells predict survival benefit from treatment in metastatic castration-resistant prostate cancer. *Clin Cancer Res, 14*(19), 6302-6309. doi: 10.1158/1078-0432.CCR-08-0872

de Rooij, M., Crienen, S., Witjes, J. A., Barentsz, J. O., Rovers, M. M., & Grutters, J. P. (2014). Cost-effectiveness of magnetic resonance (MR) imaging and MR-guided targeted biopsy versus systematic transrectal ultrasound-guided biopsy in diagnosing prostate cancer: a modelling study from a health care perspective. *Eur Urol, 66*(3), 430-436. doi: 10.1016/j.eururo.2013.12.012

Dragomir, A., D., D., Vanhuyse, M., Cury, F. L., & Aprikian, A. G. (2014). Drug costs in the management of metastatic

castration-resistant prostate cancer in Canada. *BMC Health Services Research, 14*(252), 1-14.

Dreicer, R., MacLean, D., Suri, A., Stadler, W. M., Shevrin, D., Hart, L., . . . Agus, D. B. (2014). Phase I/II trial of orteronel (TAK-700)--an investigational 17,20-lyase inhibitor--in patients with metastatic castration-resistant prostate cancer. *Clin Cancer Res, 20*(5), 1335-1344. doi: 10.1158/1078-0432.CCR-13-2436

Economos, C., Morrissey, C., & Vessella, R. L. (2012). Circulating tumor cells as a marker of response: implications for determining treatment efficacy and evaluating new agents. *Curr Opin Urol, 22*(3), 190-196. doi: 10.1097/MOU.0b013e3283519b58

El-Amm, J., & Aragon-Ching, J. B. (2013). The changing landscape in the treatment of metastatic castration-resistant prostate cancer. *Therapeutic Advances in Medical Oncology, 5*(1), 25-60. doi: 10.1177/

Eurostat. (2015). Euro Area Inflation Rate. Retrieved 06-05-2015, 2015, from http://www.tradingeconomics.com/euro-area/inflation-cpi

Even-Sapir, E., Metser, U., Mishani, E., Lievshitz, G., Lerman, H., & Leibovitch, I. (2006). The Detection of Bone Metastases in Patients with High-Risk Prostate Cancer: 99mTc-MDP Planar Bone Scintigraphy, Single- and Multi-Field-of-View SPECT, 18F-Fluoride PET, and 18F-Fluoride PET/CT. *Journal of Nuclear Medicine, 287-297*(47).

FDA. (2004). CellSearch™ Epithelial Cell Kit / CellSpotter™ Analyzer *U.S. Food and Drug Administration: Protecting and Promoting Your Health.* Retrieved 13-02-2015, 2015, from http://www.fda.gov/medicaldevices/productsandmedicalprocedures/deviceapprovalsandclearances/recently-approveddevices/ucm081239.htm

Ferlay, J., Soerjomataram, I., Ervik, M., Dikshit, R., Eser, S., Mathers, C., . . . Bray, F. (2013). GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. *International Agency for Research on Cancer*.

Freedland, S. J., Richhariya, A., Wang, H., Chung, K., & Shore, N. D. (2012). Treatment patterns in patients with prostate cancer and bone metastasis among US community-based urology group practices. *Urology, 80*(2), 293-298. doi: 10.1016/j.urology.2012.04.007

Gazzaniga, P., Naso, G., Gradilone, A., Cortesi, E., Gandini, O., Gianni, W., . . . Cristofanilli, M. (2010). Chemosensitivity profile assay of circulating cancer cells: prognostic and predictive value in epithelial tumors. *Int J Cancer, 126*(10), 2437-2447. doi: 10.1002/ijc.24953

Gold, M. R. (1998). Standardizing Cost-Effectiveness Analyses: The Panel on Cost-Effectiveness in Health and Medicine. *Academic Radiology, 5*(Supplement 2), 351-354.

Gold, M. R., Siegel, J. E., Russell, L. B., & Weinstein, M. C. (1996). *Cost-Effectiveness in Health and Medicine*: Oxford University Press.

Goodman, O. B., Jr., Fink, L. M., Symanowski, J. T., Wong, B., Grobaski, B., Pomerantz, D., . . . Vogelzang, N. J. (2009). Circulating tumor cells in patients with castration-resistant prostate cancer baseline values and correlation with prognostic factors. *Cancer Epidemiol Biomarkers Prev, 18*(6), 1904-1913. doi: 10.1158/1055-9965.EPI-08-1173

Goodman, O. B., Jr., Symanowski, J. T., Loudyi, A., Fink, L. M., Ward, D. C., & Vogelzang, N. J. (2011). Circulating tumor cells as a predictive biomarker in patients with hormone-sensitive prostate cancer. *Clin Genitourin Cancer, 9*(1), 31-38. doi: 10.1016/j.clgc.2011.04.001

Günal, M. M., & Pidd, M. (2010). Discrete event simulation for performance modelling in health care: a review of the literature. *Journal of Simulation, 4*(1), 42-51. doi: 10.1057/jos.2009.25

Guzzo, T. J., McNeil, B. K., Bivalacqua, T. J., Elliott, D. J., Sokoll, L. J., & Schoenberg, M. P. (2012). The presence of circulating tumor cells does not predict extravesical disease in bladder cancer patients prior to

radical cystectomy. *Urol Oncol, 30*(1), 44-48. doi: 10.1016/j.urolonc.2009.10.008

Halpern, M. T., Luce, B. R., Brown, R. E., & Geneste, B. (1998). Health and Economic Outcomes Modeling Practices: A Suggested Framework. *Value in Health, 1*(2), 131-147.

Hayes, D. F., Cristofanilli, M., Budd, G. T., Ellis, M. J., Stopeck, A., Miller, M. C., . . . Terstappen, L. W. (2006). Circulating tumor cells at each follow-up time point during therapy of metastatic breast cancer patients predict progression-free and overall survival. *Clin Cancer Res, 12*(14 Pt 1), 4218-4224. doi: 10.1158/1078-0432.CCR-05-2821

Heidenreich, A., Bastian, P. J., Bellmunt, J., Bolla, M., Joniau, S., van der Kwast, T., . . . European Association of, U. (2014). EAU guidelines on prostate cancer. Part II: Treatment of advanced, relapsing, and castration-resistant prostate cancer. *Eur Urol, 65*(2), 467-479. doi: 10.1016/j.eururo.2013.11.002

Hiltermann, T. J., Pore, M. M., van den Berg, A., Timens, W., Boezen, H. M., Liesker, J. J., . . . Groen, H. J. (2012). Circulating tumor cells in small-cell lung cancer: a predictive and prognostic factor. *Ann Oncol, 23*(11), 2937-2942. doi: 10.1093/annonc/mds138

Horwich, A., Parker, C., de Reijke, T., Kataja, V., & Group, E. G. W. (2013). Prostate cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol, 24 Suppl 6*, vi106-114. doi: 10.1093/annonc/mdt208

How does the CELLSEARCH® System work? (2014). *CellSearch: Circulating Tumor Cell Test.* Retrieved 13-02-2015, 2015, from https://www.cellsearchctc.com/about-cellsearch/how-cellsearch-ctc-test-works

Hozo, S. P., Djulbegovic, B., & Hozo, I. (2005). Estimating the mean and variance from the median, range, and the size of a sample. *BMC Med Res Methodol, 5*, 13. doi: 10.1186/1471-2288-5-13

Hunink, M., Glasziou, P., Siegel, J., Weeks, J., Pliskin, J., Elstein, A., & Weinstein, M. (2001). *Decision making in health and medicine*. Cambridge: Cambridge University Press.

Jacob, M. (2013). Discrete event simulation. *Resonance, 18*(1), 78-86. doi: 10.1007/s12045-013-0010-x

Jiang, Z. F., Cristofanilli, M., Shao, Z. M., Tong, Z. S., Song, E. W., Wang, X. J., . . . Zhang, M. (2013). Circulating tumor cells predict progression-free and overall survival in Chinese patients with metastatic breast cancer, HER2-positive or triple-negative (CBCSG004): a multicenter, double-blind, prospective trial. *Ann Oncol, 24*(11), 2766-2772. doi: 10.1093/annonc/mdt246

Karnon, J. (2003). Alternative decision modelling techniques for the evaluation of health care technologies: Markov processes versus discrete event simulation. *Health Econ, 12*(10), 837-848. doi: 10.1002/hec.770

Klinac, D., Gray, E. S., Freeman, J. B., Reid, A., Bowyer, S., Millward, M., & Ziman, M. (2014). Monitoring changes in circulating tumour cells as a prognostic indicator of overall survival and treatment response in patients with metastatic melanoma. *BMC Cancer, 14*, 423. doi: 10.1186/1471-2407-14-423

Koerber, F., Waidelich, R., Stollenwerk, B., & Rogowski, W. (2014). The cost-utility of open prostatectomy compared with active surveillance in early localised prostate cancer. *BMC Health Serv Res, 14*, 163. doi: 10.1186/1472-6963-14-163

Kvale, R., Auvinen, A., Adami, H. O., Klint, A., Hernes, E., Moller, B., . . . Bray, F. (2007). Interpreting trends in prostate cancer incidence and mortality in the five Nordic countries. *J Natl Cancer Inst, 99*(24), 1881-1887. doi: 10.1093/jnci/djm249

Kwok, B. P.-c. (1979). Continuous simulation. *SIGSIM Simul. Dig., 11*(2), 55-57. doi: 10.1145/1102838.1102847

Law, A. M. (2007). *Simulation Modelling and Analysis* (Vol. Fourth Edition). Tuscon: McGraw-Hill.

Lee, R. J., Saylor, P. J., Michaelson, M. D., Rothenberg, S. M., Smas, M. E., Miyamoto, D. T., . . . Smith, M. R. (2013). A dose-ranging study of cabozantinib in men with castration-resistant prostate cancer and bone metastases. *Clin Cancer Res, 19*(11), 3088-3094. doi: 10.1158/1078-0432.CCR-13-0319

Lord, J., Willis, S., Eatock, J., Tappenden, P., Trapero-Bertran, M., Miners, A., . . . Ruiz, F. (2013). Economic modelling of diagnostic and treatment pathways in National Institute for Health and Care Excellence clinical guidelines: the Modelling Algorithm Pathways in Guidelines (MAPGuide) project. *Health Technol Assess, 17*(58), v-vi, 1-192. doi: 10.3310/hta17580

Malik, Z., Payne, H., Ansari, J., Chowdhury, S., Butt, M., Birtle, A., . . . Bahl, A. (2013). Evolution of the treatment paradigm for patients with metastatic castration-resistant prostate cancer. *Adv Ther, 30*(12), 1041-1066. doi: 10.1007/s12325-013-0070-z

Mistry, K., & Cable, G. (2003). Meta-Analysis of Prostate-Specific Antigen and Digital Rectal Examination as Screening Tests for Prostate Carcinoma. *The Journal of the American Board of Family Medicine, 16*, 95-101.

Miyamoto, D. T., Sequist, L. V., & Lee, R. J. (2014). Circulating tumour cells-monitoring treatment response in prostate cancer. *Nat Rev Clin Oncol, 11*(7), 401-412. doi: 10.1038/nrclinonc.2014.82

Morris, M. J., Eisenberger, M. A., Pili, R., Denmeade, S. R., Rathkopf, D., Slovin, S. F., . . . Carducci, M. A. (2012). A phase I/IIA study of AGS-PSCA for

castration-resistant prostate cancer. *Ann Oncol, 23*(10), 2714-2719. doi: 10.1093/annonc/mds078

Nagrath, S., Sequist, L. V., Maheswaran, S., Bell, D. W., Irimia, D., Ulkus, L., . . . Toner, M. (2007). Isolation of rare circulating tumour cells in cancer patients by microchip technology. *Nature, 450*(7173), 1235-1239. doi: 10.1038/nature06385

Naoe, M., Ogawa, Y., Morita, J., Omori, K., Takeshita, K., Shichijyo, T., . . . Yoshida, H. (2007). Detection of circulating urothelial cancer cells in the blood using the CellSearch System. *Cancer, 109*(7), 1439-1445. doi: 10.1002/cncr.22543

NZA. (2015). Tarieventabel DBC zorgproducten en overige producten. *Tarieven en prestaties DBC/DOT.* Retrieved 06-05-2015, 2015, from http://www.nza.nl/regelgeving/tarieven/ziekenhuiszorg/tarievenDBCDOT/tarieven-prestaties-DBC-DOT/

Olmos, D., Arkenau, H. T., Ang, J. E., Ledaki, I., Attard, G., Carden, C. P., . . . de Bono, J. S. (2009). Circulating tumour cell (CTC) counts as intermediate end points in castration-resistant prostate cancer (CRPC): a single-centre experience. *Ann Oncol, 20*(1), 27-33. doi: 10.1093/annonc/mdn544

Parikh, R., Mathai, A., Parikh, S., Sekhar, G. C., & Thomas, R. (2008). Understanding and using sensitivity, specificity and predictive values. *Indian Journal of Ophthalmology, 56*(1), 45-50.

Parker, C., Muston, D., Melia, J., Moss, S., & Dearnaley, D. (2006). A model of the natural history of screen-detected prostate cancer, and the effect of radical treatment on overall survival. *Br J Cancer, 94*(10), 1361-1368. doi: 10.1038/sj.bjc.6603105

Pataky, R., Gulati, R., Etzioni, R., Black, P., Chi, K. N., Coldman, A. J., . . . Peacock, S. (2014). Is prostate cancer screening cost-effective? A microsimulation model of prostate-specific antigen-based screening for British Columbia, Canada. *Int J Cancer, 135*(4), 939-947. doi: 10.1002/ijc.28732

Poveda, A., Kaye, S. B., McCormack, R., Wang, S., Parekh, T., Ricci, D., . . . Monk, B. J. (2011). Circulating tumor cells predict progression free survival and overall survival in patients with relapsed/recurrent advanced ovarian cancer. *Gynecol Oncol, 122*(3), 567-572. doi: 10.1016/j.ygyno.2011.05.028

Prostate cancer survival statistics. (2014). *Let's beat cancer sooner.* 2014, from http://www.cancerresearchuk.org/cancer-info/cancerstats/types/prostate/survival/prostate-cancer-survival-statistics#source1

Ramsey, S., Willke, R., Briggs, A. B., R., Buxton, M., Chawla, A., Cook, J., . . . Reed, S. (2005). Good Research Practices for Cost-Effectiveness

Analysis Alongside Clinical Trials: The ISPOR RCT-CEA Task Force Report. *Value in Health, 8*(5), 521-533.

Reed, S. D., Stewart, S. B., Scales, C. D., Jr., & Moul, J. W. (2014). A framework to evaluate the cost-effectiveness of the NADiA ProsVue slope to guide adjuvant radiotherapy among men with high-risk characteristics following prostatectomy for prostate cancer. *Value Health, 17*(5), 545-554. doi: 10.1016/j.jval.2014.04.010

Reid, A. H., Attard, G., Danila, D. C., Oommen, N. B., Olmos, D., Fong, P. C., . . . de Bono, J. S. (2010). Significant and sustained antitumor activity in post-docetaxel, castration-resistant prostate cancer with the CYP17 inhibitor abiraterone acetate. *J Clin Oncol, 28*(9), 1489-1495. doi: 10.1200/JCO.2009.24.6819

Riva, J. J., Malik, K. M. P., Burnie, S. J., Endicott, A. R., & Busse, J. W. (2012). What is your research question? An introduction to the PICOT format for clinicians. *The Journal of the Canadian Chiropractic Association, 56*(3), 167-171.

Ryen, L., & Svensson, M. (2014). The Willingness to Pay for a Quality Adjusted Life Year: A Review of the Empirical Literature. *Health Econ*. doi: 10.1002/hec.3085

Saad, F., Hotte, S., Catton, C., Drachenberg, D., Finelli, A., Fleshner, N., . . . Chi, K. N. (2013). CUA-CUOG guidelines for the management of castration-resistant prostate cancer (CRPC): 2013 update. *Can Urol Assoc J, 7*(7-8), 231-237. doi: 10.5489/cuaj.1542

Scher, H. I., Jia, X., de Bono, J. S., Fleisher, M., Pienta, K. J., Raghavan, D., & Heller, g. (2009). Circulating tumour cells as prognostic markers in progressive, castration-resistant prostate cancer: a reanalysis of IMMC38 trial data. *Lancet Oncology, 10*, 233-239. doi: 10.1016/S14702045(08)70340-1

Schivo, S., Scholma, J., Wanders, B., Uriquidi Camacho, R. A., Van der Vet, P. E., Karperien, M., . . . Post, J. N. (2014). Modeling Biological Pathway Dynamics With Timed Automata. *IEEE Journal of Biomedical and Health Informatics, 18*(3), 832-839.

Schulze, K., Gasch, C., Staufer, K., Nashan, B., Lohse, A. W., Pantel, K., . . . Wege, H. (2013). Presence of EpCAM-positive circulating tumor cells as biomarker for systemic disease strongly correlates to survival in patients with hepatocellular carcinoma. *Int J Cancer, 133*(9), 2165-2171. doi: 10.1002/ijc.28230

Shaffer, D. R., Leversha, M. A., Danila, D. C., Lin, O., Gonzalez-Espinoza, R., Gu, B., . . . Scher, H. I. (2007). Circulating tumor cell analysis in patients with progressive castration-resistant prostate cancer. *Clin Cancer Res, 13*(7), 2023-2029. doi: 10.1158/1078-0432.CCR-06-2701

Shamash, J., Jacob, J., Agrawal, S., Powles, T., Mutsvangwa, K., Wilson, P., & Stebbing, J. (2012). Whole blood stem cell reinfusion and escalated

dose melphalan in castration-resistant prostate cancer: a phase 1 study. *Clin Cancer Res, 18*(8), 2352-2359. doi: 10.1158/1078-0432.CCR-11-3293

Sher, D. J., Parikh, R. B., Mays-Jackson, S., & Punglia, R. S. (2014). Cost-effectiveness analysis of SBRT versus IMRT for low-risk prostate cancer. *Am J Clin Oncol, 37*(3), 215-221. doi: 10.1097/COC.0b013e31827a7d2a

Shiota, M., Bishop, J. L., Nip, K. M., Zardan, A., Takeuchi, A., Cordonnier, T., . . . Zoubeidi, A. (2013). Hsp27 regulates epithelial mesenchymal transition, metastasis, and circulating tumor cells in prostate cancer. *Cancer Res, 73*(10), 3109-3119. doi: 10.1158/0008-5472.CAN-12-3979

Snedecor, S. J., Carter, J. A., Kaura, S., & Botteman, M. F. (2013). Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a cost-effectiveness analysis. *J Med Econ, 16*(1), 19-29. doi: 10.3111/13696998.2012.719054

Sonnenberg, F. A., & Beck, J. R. (1993). Markov Models in Medical Decision Making: A Practical Guide. *Medical Decision Making, 13*(4), 322-338. doi: 10.1177/0272989x9301300409

Stattin, P., Holmberg, E., Johansson, J. E., Holmberg, L., Adolfsson, J., Hugosson, J., & National Prostate Cancer Register of, S. (2010). Outcomes in localized prostate cancer: National Prostate Cancer Register of Sweden follow-up study. *J Natl Cancer Inst, 102*(13), 950-958. doi: 10.1093/jnci/djq154

Stein, J. (2014). Upcoming Medicare decision threatens coverage of cancer test *Modern Medicine Network.* Retrieved 06-05-2015, 2015, from http://managedhealthcareexecutive.modernmedicine.com/managed-healthcare-executive/content/tags/cancer/upcoming-medicare-decision-threatens-coverage-cance?page=full

Stopeck, A., Rader, M., Henry, D., Danese, M., Halperin, M., Cong, Z., . . . Chung, K. (2012). Cost-effectiveness of denosumab vs zoledronic acid for prevention of skeletal-related events in patients with solid tumors and bone metastases in the United States. *J Med Econ, 15*(4), 712-723. doi: 10.3111/13696998.2012.675380

Tannock, I. F., de Wit, R., Berry, W. R., Horti, J., Pluzanska, A., Chi, K. N., . . . Eisenberger, M. A. (2004). Docetaxel plus Prednisone or Mitoxantrone plus Prednisone for Advanced Prostate Cancer. *The new england journal of medicine, 153*(15), 1502-1512.

Thompson, I. M., Pauler Ankerst, D., Chi, C., Scott Lucia, M., Goodman, P. J., Crowley, J. J., . . . Coltman, C. A. (2005). Operating Characteristics of Prostate-Specific Antigen in Men With an Initial PSA Level of 3.0 ng/mL or Lower. *American Medical Association, 294*(1), 66-71.

Wallwiener, M., Riethdorf, S., Hartkopf, A. D., Modugno, C., Nees, J., Madhavan, D., . . . Schneeweiss, A. (2014). Serial enumeration of circulating tumor cells predicts treatment response and prognosis in

metastatic breast cancer: a prospective study in 393 patients. *BMC Cancer, 14*(512), 1-12.

Wilson, L., Tang, J., Zhong, L., Balani, G., Gipson, G., Xiang, P., . . . Srinivas, S. (2014). New therapeutic options in metastatic castration-resistant prostate cancer: Can cost-effectiveness analysis help in treatment decisions? *J Oncol Pharm Pract, 20*(6), 417-425. doi: 10.1177/1078155213509505

Wolff, J. M., & Mason, M. (2012). Drivers for change in the management of prostate cancer – Guidelines and new treatment techniques. *BJU International, 109*(6), 33-41.

Wolfswinkel, J. F., Furtmueller, E., & Wilderom, C. P. M. (2011). Using grounded theory as a method for rigorously reviewing literature. *European Journal of Information Systems, 22*(1), 45-55. doi: 10.1057/ejis.2011.51

XE. (2015a). XE Currency Charts (CAD/EUR). *XE - The World's Trusted Currency Authority.* Retrieved 06-05-2015, 2015, from http://www.xe.com/currencycharts/?from=CAD&to=EUR&view=1Y

XE. (2015b). XE Currency Charts (USD/EUR). *XE - The World's Trusted Currency Authority.* Retrieved 06-05-2015, 2015, from http://www.xe.com/currencycharts/?from=CAD&to=EUR&view=1Y

Zhong, L., Pon, V., Srinivas, S., Nguyen, N., Frear, M., Kwon, S., . . . Wilson, L. (2013). Therapeutic options in docetaxel-refractory metastatic castration-resistant prostate cancer: a cost-effectiveness analysis. *PLoS One, 8*(5), e64275. doi: 10.1371/journal.pone.0064275

8. Appendix

8.1. Appendix A: Endpoints Literature Research Results

Endpoint Category	Primary Endpoints	Secondary Endpoints
Survival Related	30	26
PSA Related	28	55
Progression Related	19	41
Treatment Related	9	35
Safety	4	27
Bone Related	3	9
QoL	0	12
CTC	0	6
Additional	2	7

Primary and Secondary Endpoints Literature Research Results.

Endpoint	Explanation	Primary	Secondary
PSA Decline > 50%		10	11
PSA Decline > 30%		1	6
PFS	Progression Free Survival	15	26
Time to PSA Progression		0	16
TTP	Time to Progression	3	12
OS	Overall Survival	30	25
Tumour Response Rate		0	9
PSA Response Rate		11	15
Gene Expression		0	1
PK	Pharmacokinetics	1	2
Immunogenicity		0	2
Clinical Activity		0	1
Response to Treatment		6	10
TFSRE	Time to First Skeletal-Related Event	3	9
CTC	Circulating Tumour Cells	0	6
CECs	Circulating Endothelial Cells	0	1
Pain reduction > 30%		0	1
1-Year Survival		0	1
Treatment Related Toxicity		2	13
Safety		4	27
PSA Slope		6	7
TTF	Time to Treatment Failure	1	2
Stable Disease > 6 months		1	3
QoL	Quality of Life	0	11
# Adverse Events		1	1

Primary and Secondary Endpoints Literature Research Results.

8.2. Appendix B: Required number of Simulated Patients per Run

In order obtain insights in the number of patients that need to be simulated the results of the base-case scenario are analysed based on the most important outcome measures and different numbers of simulated patients. Starting with the average total costs per patient, the average survival per patient and the average utility per patient, which are presented in Figure 28.Figure 28, Figure 29 and Figure 30, respectively. The figures show the minimum, maximum and average outcomes for the three different arm of the experiment on the vertical axis related to the number of patients that are simulated on the horizontal axis. Larger versions of these figures are added in Appendix C, Appendix D and Appendix E, respectively.

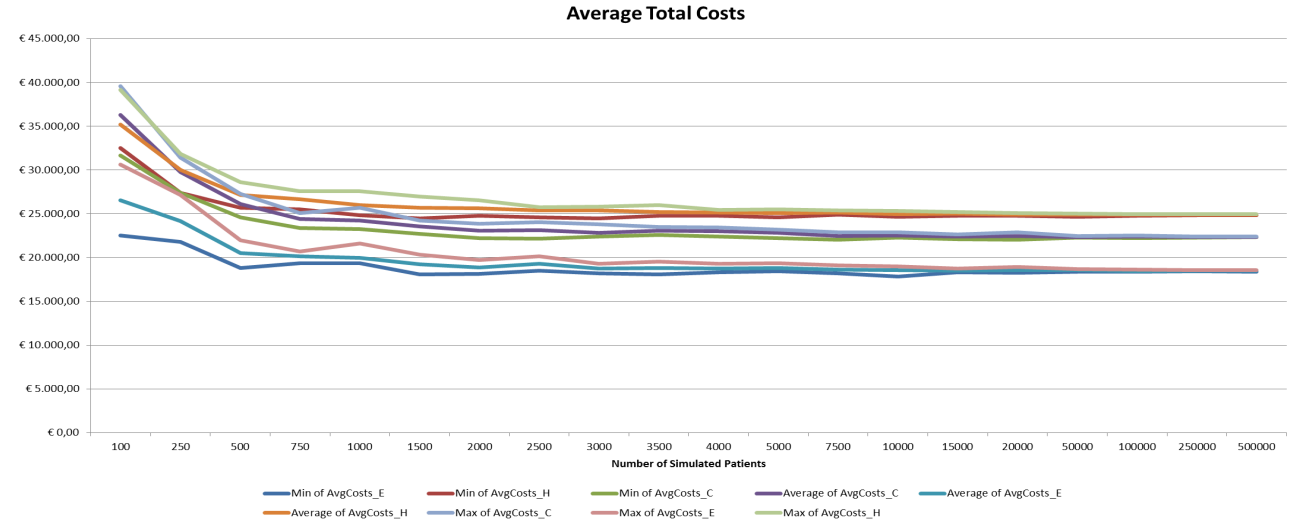


Figure 28. The average total costs per patient plotted against the number of simulated patients.

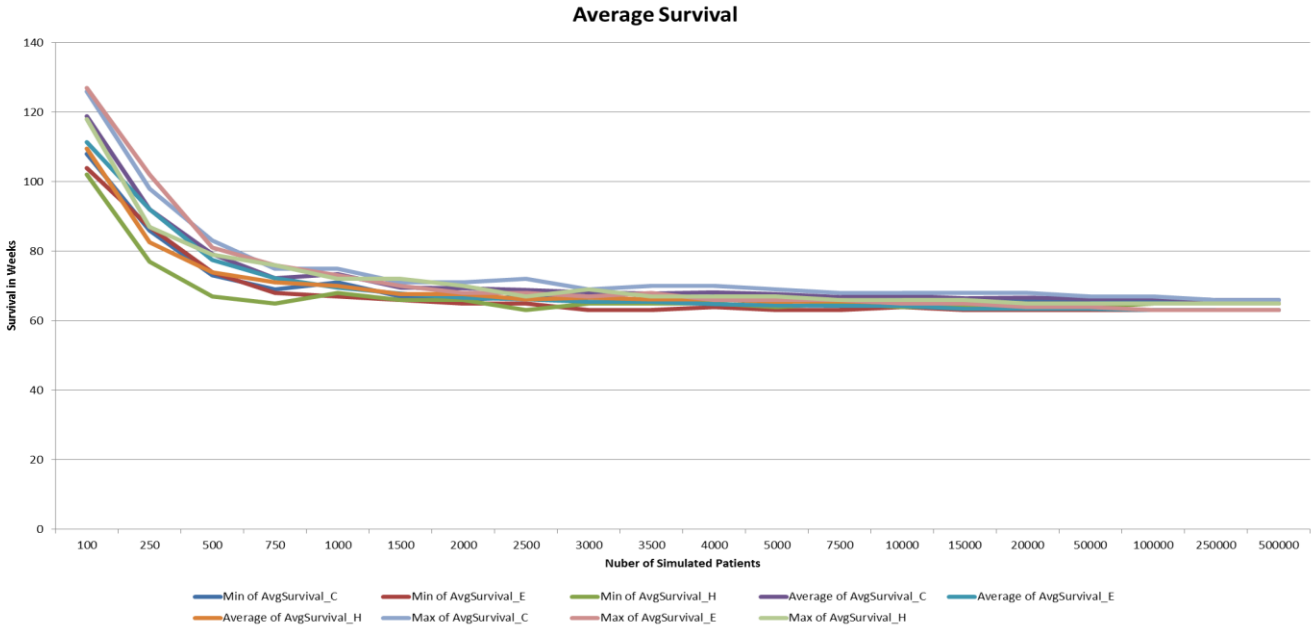


Figure 29. The average survival per patient plotted against the number of simulated patients.

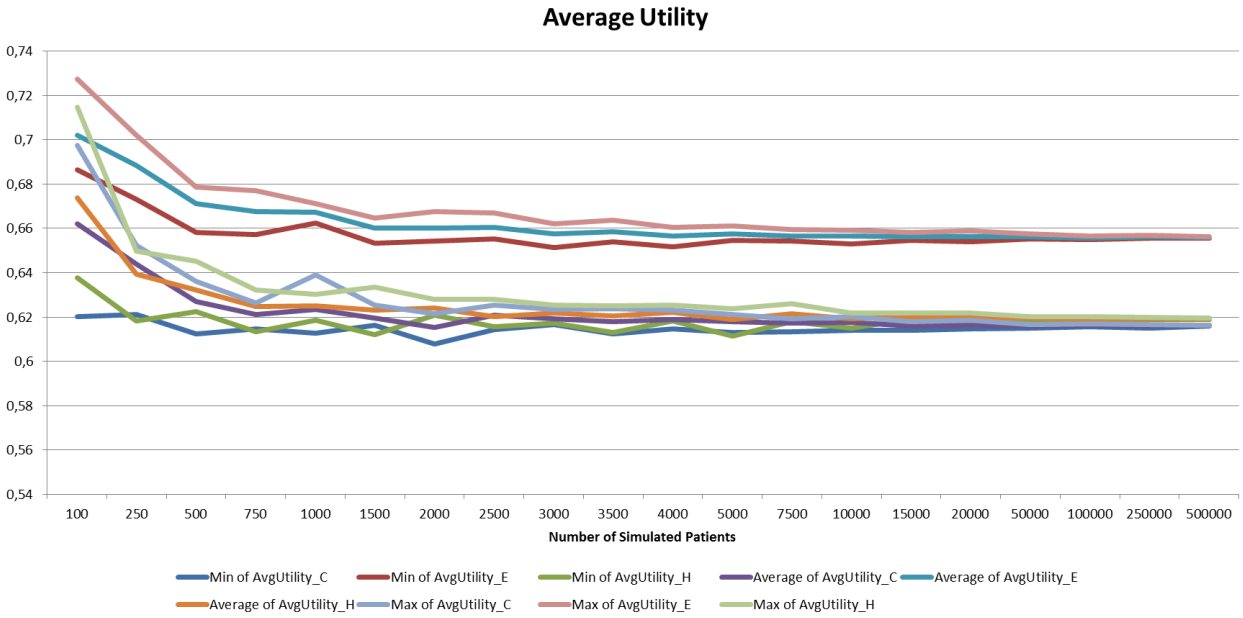


Figure 30. The average utility per patient plotted against the number of simulated patients.

The figures show that, as expected, the results on the different outcome measures are different for a small amount of simulated patients compared to a larger amount of simulated patients. The figures also show that the outcomes stabilize as the number of simulated patients increases. Moreover, the difference between the minimum and maximum values on the outcome measures decreases when the number of simulated patients increases. The average outcomes approximately reach their assumed final value when around 4.000 to 5.000 patients are simulated. When 10.000 to 15.000 patients are simulated, the differences between the minimum and maximum values get negligible. According to the figures, the outcomes become almost completely stable when more than 100.000 patients are simulated.

The combination of the different arms in the experiment and the three outcome measures lead to the Incremental Cost Effectiveness Ratio (ICER), which is very important in Medical Decision Making. This final outcome measure includes a lot of uncertainty, because it is composed out of all these separate outcome measures. Therefore, it is likely that the results for the ICER are not as stable as the results of the before mentioned outcome measures. The incremental cost and incremental effectiveness are presented in Figure 31 and Figure 32, respectively.

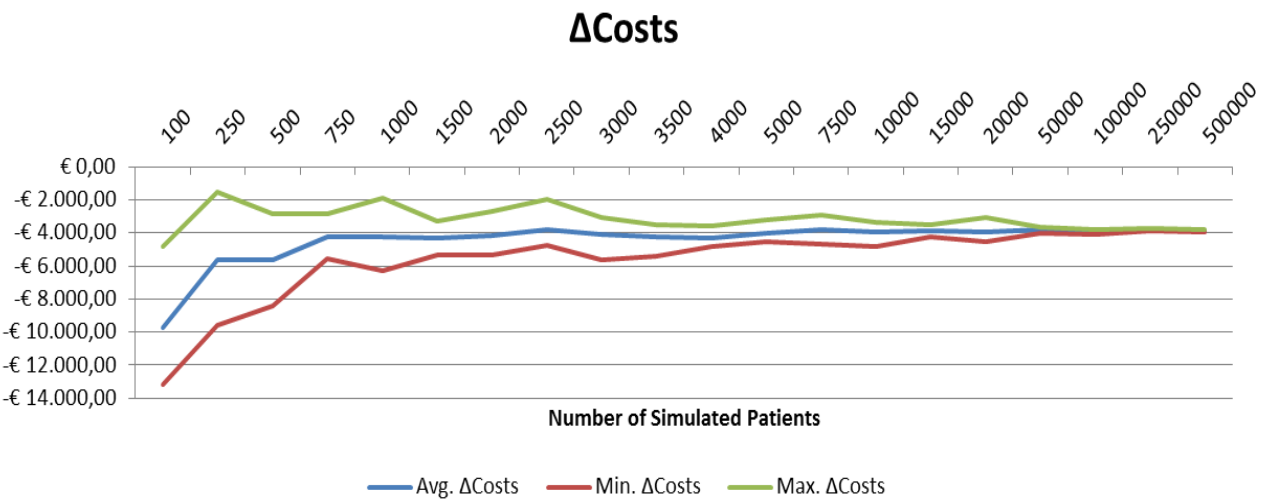


Figure 31. The incremental costs plotted against the number of simulated patients.

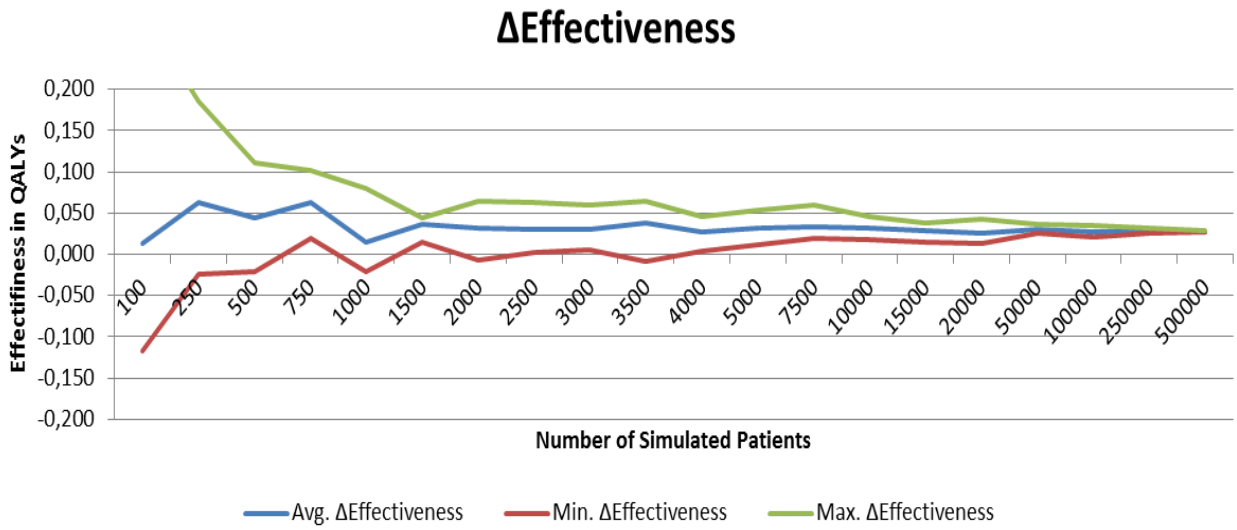
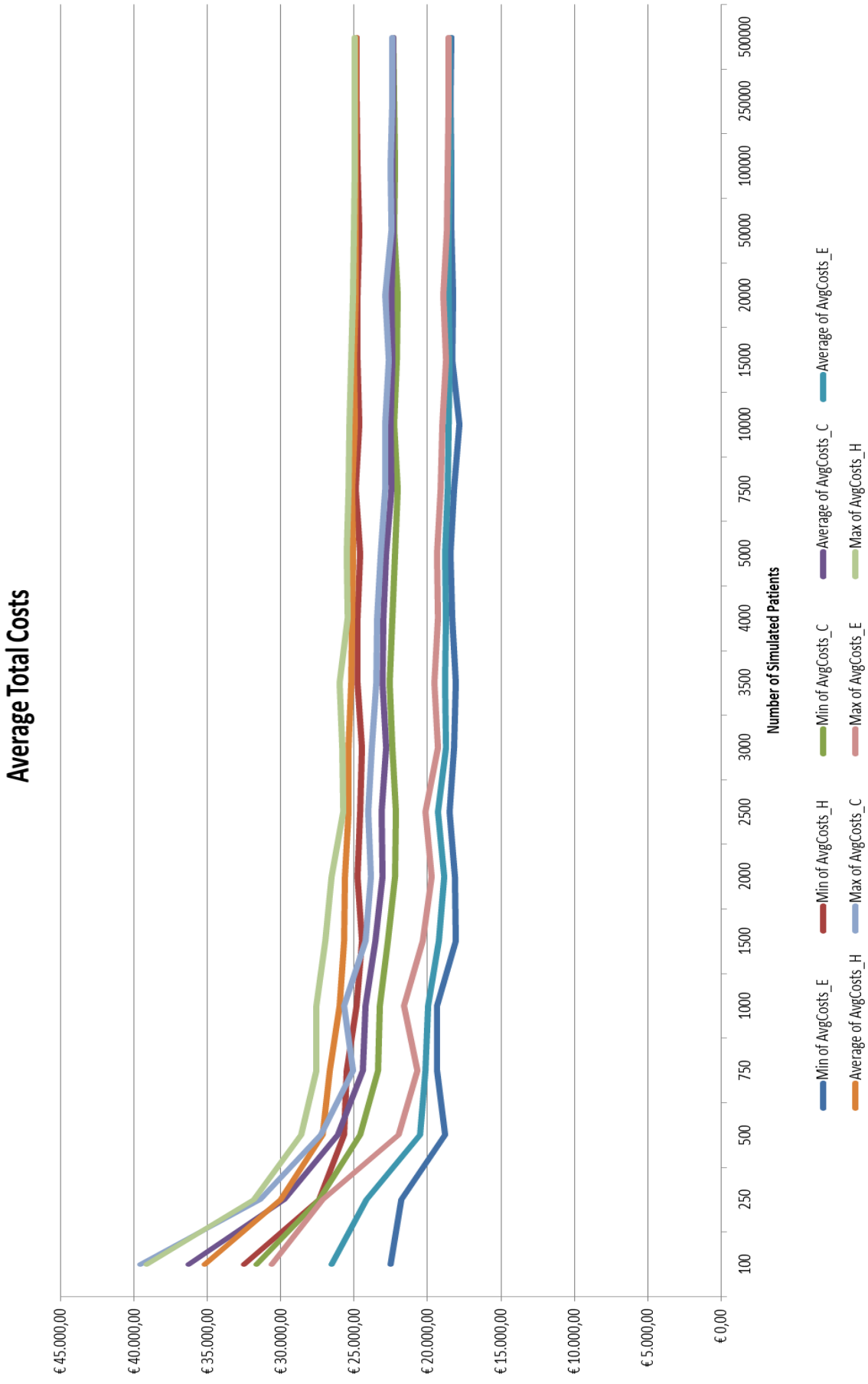


Figure 32. The incremental effectiveness in QALYs plotted against the number of simulated patients.

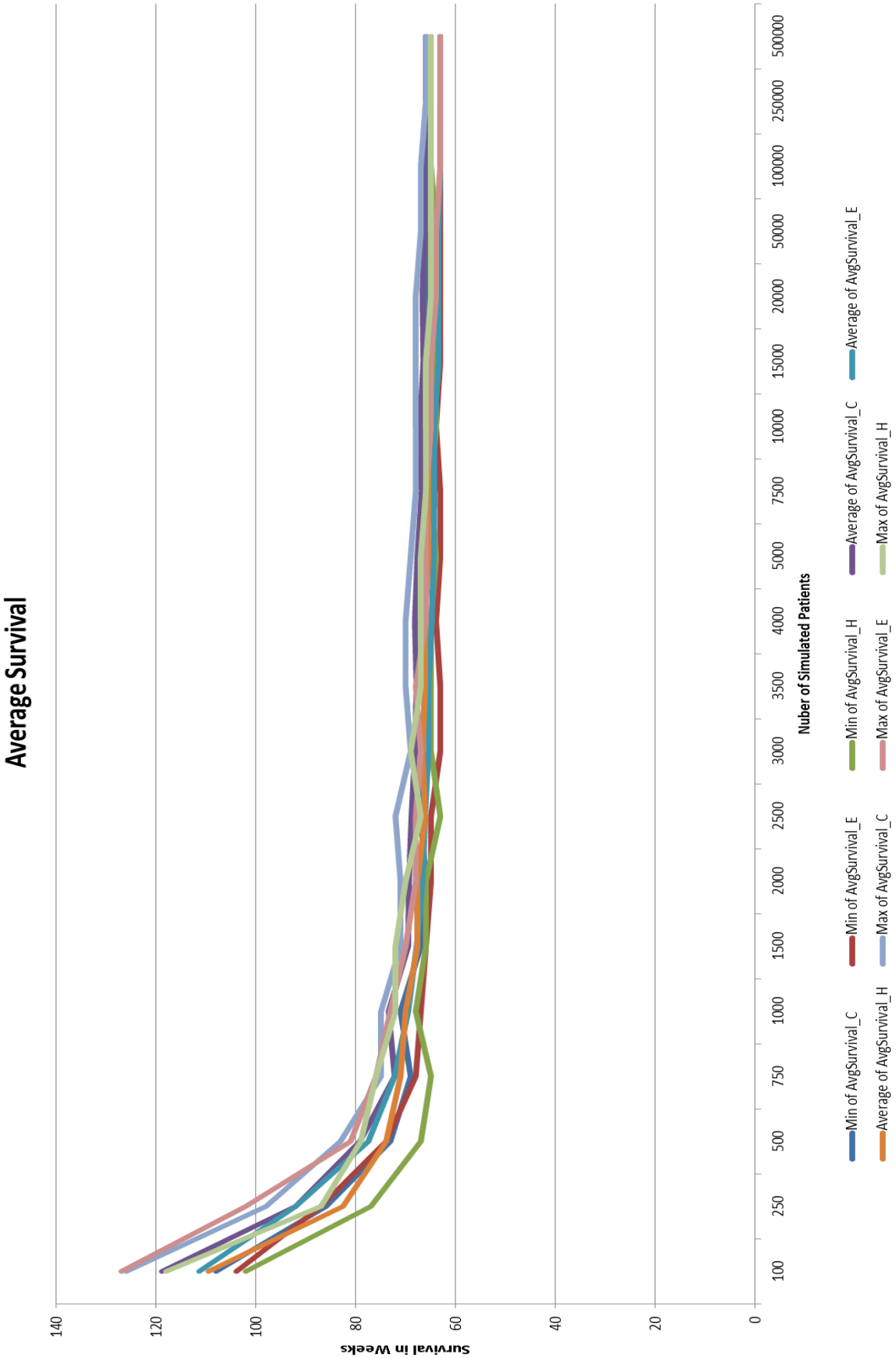
Both figures again show that the average values on the outcome measures reach the estimated final values when around 4.000 to 5.000 patients are simulated. However, at that point there is quite a large difference between the average and the minimum and maximum values. This difference becomes a lot smaller when 10.000 to 15.000 patients are simulated and negligible when more than 100.000 patients are simulated.

Since simulating more patients also means that the time of the simulation increases a trade-off needs to be made between the required simulation time and the variation in the results on the outcome measures. Simulating one run with 100.000 patients requires approximately 45 seconds, while simulating 15.000 patients requires less than 5 seconds. For this case, the number of patients that will be simulated is chosen to be 15.000, because of the stability of the average value, the small difference between the maximum and minimum values at that point and the large number of patients that need to be simulated extra to obtain more consistent results.

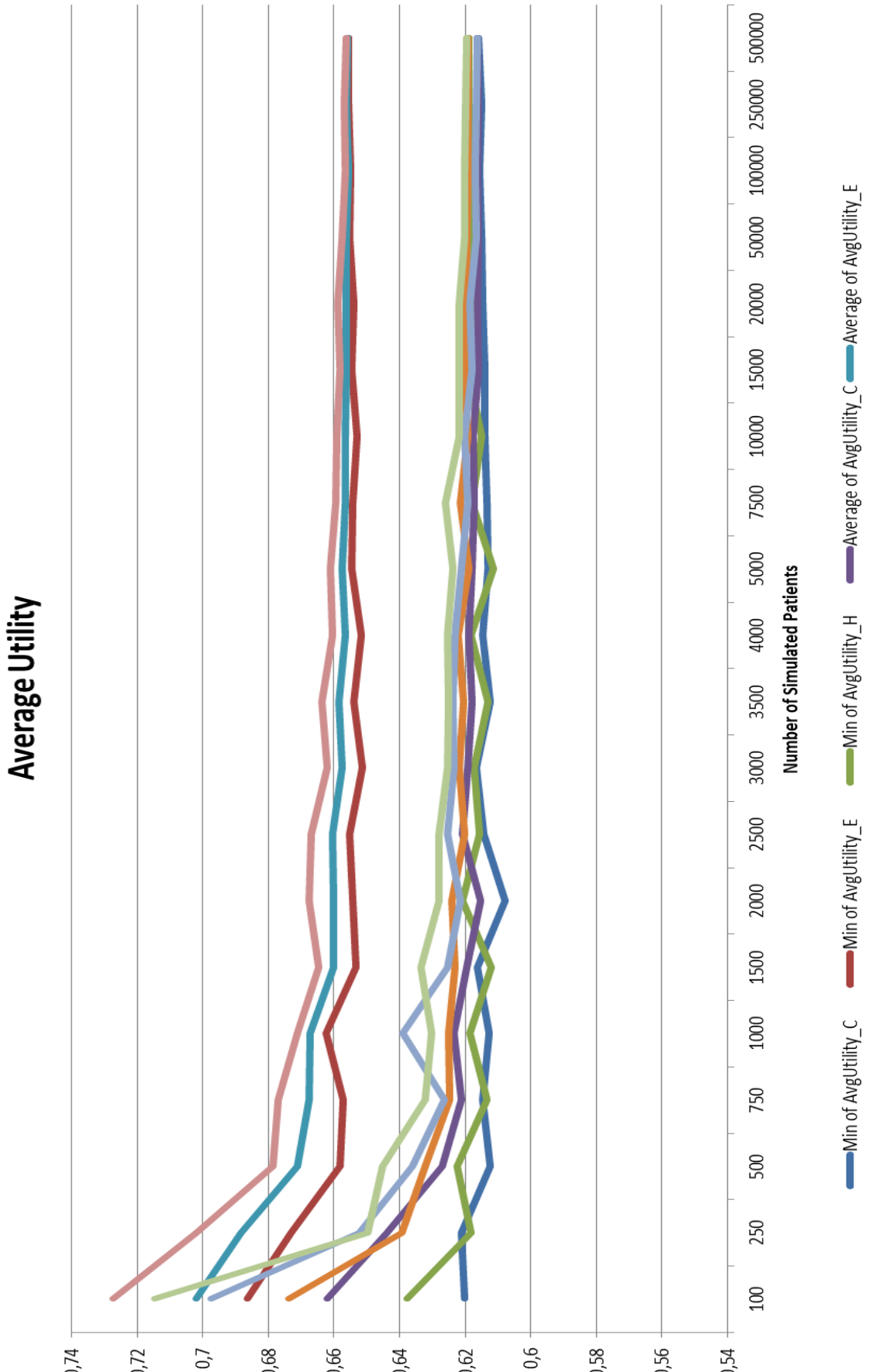
8.3. Appendix C: Average Total Costs vs. Number of Simulated Patients



8.4. Appendix D: Average Survival vs. Number of Simulated Patients



8.5. Appendix E: Average Utility vs. Number of Simulation Patients



8.6. Appendix F: Required number of Runs per Experiment

The data on the outcome measures that is used are obtained from 1.000 runs of 15.000 patients in the base-case scenario. These outcome measures include: the average costs, the average utility, the average survival, the incremental costs and the incremental QALYs. The assumption underlying these calculations is that the point estimate and confidence interval for the mean X_j's of these outcome measures are Independent and Identically Distributed (IID). This assumption applies to this case, as the runs are not influenced by each other and are identically distributed due to the same input parameters and distributions..

To determine the desired amount of runs according to the absolute error β, we first define β by the formula presented in Equation 3, in which $\bar{X}$ is the average of all runs and μ is the real average. Then one should make the number of runs so that the half-length of the confidence interval (Equation 4 and 5) of $\bar{X}$ is less or equal to β and β > 0. So, a way for determining the desired amount of runs is increasing I in Equation 6, until the half-length of the confidence interval is smaller than the absolute error β. The assumption made is that S^2 does not depends on the number of runs made.

$$\boldsymbol{\beta} = |\bar{\boldsymbol{X}} - \boldsymbol{\mu}| \qquad \textbf{Equation 3}$$

$$\boldsymbol{t_{n-1,1-\alpha/2}\sqrt{\frac{S^2(n)}{n}}} \qquad \textbf{Equation 4}$$

$$\boldsymbol{S^2(n) = \frac{\sum_{i=1}^{n}[X_i - \bar{X}(n)]^2}{n-1}} \qquad \textbf{Equation 5}$$

$$\boldsymbol{n_a^*(\beta) = \min\left\{ i \geq n : t_{n-1,1-\frac{\alpha}{2}}\sqrt{\frac{S^2(n)}{i}} \leq \beta \right\}} \qquad \textbf{Equation 6}$$

Another way for determining the desired amount of runs is using the relative error γ defined in Equation 7. Under the assumption that the population mean and population variance will not change as the number of replication increase, we can use Equation 8 to determine the number of required runs so that an actual relative error of γ is obtained.

$$\boldsymbol{\gamma = \frac{|\bar{X} - \mu|}{|\mu|}} \qquad \textbf{Equation 7}$$

$$\boldsymbol{n_r^*(\gamma) = \min\left\{ i \geq n : \frac{t_{n-1,1-\frac{\alpha}{2}}\sqrt{S^2(n)/i}}{|\bar{X}(n)|} \leq \dot{\gamma} \right\}} \qquad \textbf{Equation 8}$$

First the standard error α is set to 0.05. Secondly, alpha is used to determine the values for β and γ. B is estimated by multiplying the standard error α with the average outcome of all 1.000 experiments. The relative error γ is set equal to α. Using these errors and the methods explained above the required number of runs are calculated on the five outcome measures. The results are presented in Table 10.

The table shows that according to the outcomes on the average costs, the average utility and the average survival and according both the absolute error and the relative error, three runs per experiment would be sufficient. However, with regard to the incremental costs the number of runs should be twelve according to the absolute error and thirteen according to the relative error. According to the incremental effectiveness in QALYs the number of runs per experiment should be more than a thousand. This is caused by the very small value for β due to the small values for the incremental effectiveness, which are probably caused by the way the survival is simulated in the model, which confirms the need to assume the survival is equal for all arms of the experiment.

Under the assumption that the results on the survival of the patients are biased, the number of runs that will be performed for each experiment is chosen to be thirteen.

Outcome Measure	β	$n_a^*(\beta)$	γ	$n_r^*(\gamma)$
Average Costs	€ 1.123,31	3	0,05	3
Average Utility	0,0308	3	0,05	3
Average Survival	3,3	3	0,05	3
Incremental costs	€ 195,46	12	0,05	13
Incremental QALYs	0,0006	1001	0,05	1001

Table 10. The required number of runs per experiment for different outcome measures.

1.1. Appendix G: QoL Sensitivity Analysis Values

Treatment Effectiveness (Docetaxel)	Treatment Effectiveness (Cabazitaxel)	Phase: Docetaxel	Phase: First Follow Up	Phase: Cabazitaxel	Phase: Second Follow Up
Effective	**Effective**	0.661	0.837	0.661	0.837
Effective	**Not-Effective**	0.661	0.837	0.573	0.749
Not-Effective	**Effective**	0.573	0.749	0.661	0.837
Not-Effective	**Not-Effective**	0.573	0.749	0.573	0.749

Table 11. Utilities for the scenario with a small difference between responders and non-responders.

Treatment Effectiveness (Docetaxel)	Treatment Effectiveness (Cabazitaxel)	Phase: Docetaxel	Phase: First Follow Up	Phase: Cabazitaxel	Phase: Second Follow Up
Effective	**Effective**	0.749	0.925	0.749	0.925
Effective	**Not-Effective**	0.749	0.925	0.485	0.661
Not-Effective	**Effective**	0.485	0.661	0.749	0.925
Not-Effective	**Not-Effective**	0.485	0.661	0.485	0.661

Table 12. Utilities for the scenario with a large difference between responders and non-responders.

1.2. Appendix H: Timed Automata vs. Discrete Event Simulation Poster

Please find the poster on the next page.

Modeling Personalized Treatment Decisions: Comparison of Timed Automata with Discrete Event Simulation

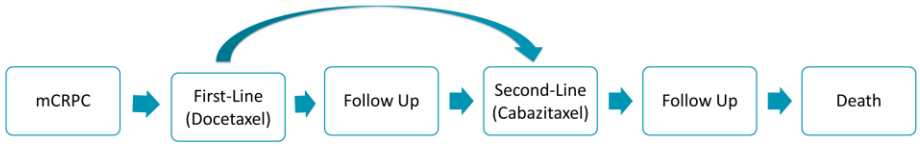
Koen Degeling[1], Hendrik Koffijberg[1], Stefano Schivo[2], Rom Langerak[2] and Maarten IJzerman[1],
[1]Health Technology and Services Research, MIRA University of Twente
[2]Formal Methods and Tools, CTIT University of Twente

Introduction

The aim of this study is to compare the usefulness of two promising modeling techniques, Timed Automata (TA) originating from informatics, and Discrete Event Simulation (DES) known in operations research, for modeling complex and personalized treatment decisions involving multiple interacting processes and decisions over time.

Methods

The usefulness of both modeling techniques was assessed in a case study on the use of Circulating Tumor Cells to decide when to switch from first-line to second-line treatment of metastatic Castration Resistant Prostate Cancer (mCRPC). The use of this marker for early therapy switching was modeled using TA in UPPAAL and DES in Tecnomatix Plant Simulation.



Model Parameters and Comparison

Input
- Costs
- Prognosis
- Treatment Effectiveness
- Diagnostic Performance
- Physician's Behavior

Output
- Costs
- Survival
- Effectiveness

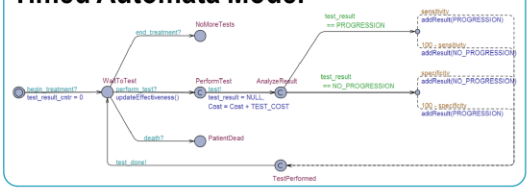
Comparison
- Input Requirements
- Input Possibilities
- Model Checking
- Outcome values

Results

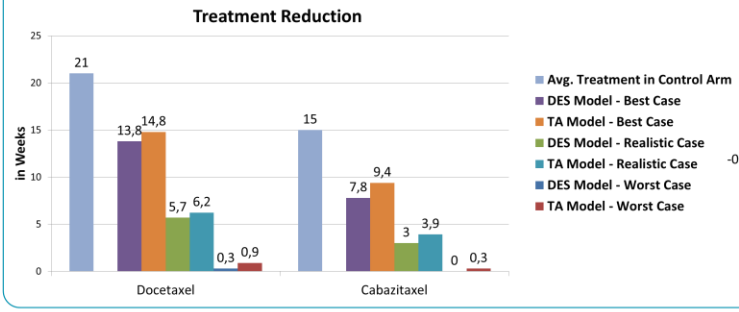
Both modeling approaches yield comparable results. While comparing the methods, it appeared that translating the process into a model was easier using TA, as this method allows independent modeling of the components comprising the treatment process such as patients, physicians, tests and treatments, whose mutual interaction and communication could be modeled easier and more extensively. Furthermore, the model checking feature of UPPAAL was found to be a powerful tool for internal validation of the model.

Discrete Event Simulation Model

Timed Automata Model



Outcomes



Conclusion

Timed Automata is a new and interesting modeling technique, moving beyond standard health economic modeling methods, and allowing explicit separation of model components and statistical model checking to validate models. Both Timed Automata and Discrete Event Simulation seem to be suitable for modeling complex and personalized treatment processes like that of metastatic Castration Resistant Prostate Cancer.

1.3. Appendix I: Timed Automata vs Discrete Event Simulation Abstract

COMPARISON OF TIMED AUTOMATA WITH DISCRETE EVENT SIMULATION FOR MODELING PERSONALIZED TREATMENT DECISIONS: THE CASE OF METASTATIC CASTRATION RESISTANT PROSTATE CANCER

Koen Degeling, BSc, Hendrik Koffijberg, PhD, Stefano Schivo, PhD, Rom Langerak, PhD and Maarten J. IJzerman, PhD, University of Twente, Enschede, Netherlands

Purpose: Traditional Markov Models are often inadequate to accurately represent complex and personalized treatment decisions over time. The aim of this study is to compare the usefulness of two promising alternative modeling techniques, Timed Automata (TA) originating from informatics, and Discrete Event Simulation (DES) known in operations research, for modeling these healthcare delivery processes involving multiple interactions and decision gates.

Method: The usefulness of both modeling techniques was assessed in a case study on the treatment of metastatic Castration Resistant Prostate Cancer (mCRPC). Circulating Tumor Cells (CTC) or cell-free tumor DNA may be used as a response marker for switching first (Docetaxel) to second line (Cabazitaxel) drug treatment. The use of these markers for early therapy switching was modeled using TA in UPPAAL and DES in Tecnomatix Plant Simulation. Techniques were compared on user-friendliness, input requirements and input possibilities, model checking facilities, and on actual outcomes for the case study. Input parameters were the same in both models and consisted of costs, QoL, treatment effectiveness, diagnostic performance, physicians' behavior and survival. Primary outcome measures were costs, effectiveness expressed in QALYs and survival.

Result: Model building took several days for both techniques. Both modeling approaches yield comparable results. For TA, CTC reduced treatment with Docetaxel and Cabazitaxel by, on average, 108.9 and 107.6 days, respectively. For DES, treatment was reduced by 83.6 and 85.0 days. CTC therefore reduced healthcare costs by €28,998 and €21,992 according to TA and DES respectively.

While comparing the methods, it appeared that translating the process into a model was easier using TA, as this method allows independent modeling of the components comprising the treatment process such as patients, physicians, tests and treatments, whose mutual interaction and communication could be modeled easier and more extensive. Furthermore, the model checking feature of UPPAAL was found to be a powerful tool for validation of the model.

Conclusion: Timed Automata is a new and interesting alternative modeling technique, as it allows explicit separation of model components and supports statistical model checking to validate models. Both Timed Automata and Discrete Event Simulation seem to be suitable for modeling complex and personalized treatment processes like that of metastatic Castration Resistant Prostate Cancer.

1.4. Appendix J: Timed Automata Abstract

TIMED AUTOMATA MODELING OF THE PERSONALIZED TREATMENT DECISIONS IN METASTATIC CASTRATION RESISTANT PROSTATE CANCER

Stefano Schivo, PhD, Koen Degeling, BSc, Hendrik Koffijberg, PhD, Maarten J. IJzerman, PhD and Rom Langerak, PhD, University of Twente, Enschede, Netherlands

Purpose: The Timed Automata modeling paradigm has emerged from Computer Science as a mature tool for the functional analysis and performance evaluation of timed distributed systems. It has been applied successfully to a large variety of systems, like communication networks, manufacturing plants, and signaling pathways in human stem cells. This study is a first exploration of the suitability of Timed Automata in evaluating the potential benefits of a personalized treatment process of metastatic Castration Resistant Prostate Cancer (mCRPC).

Method: The treatment process has been modeled by creating several independent timed automata, where an automaton represents a patient, a physician, a test, or a treatment/testing guideline schedule. The automata interact with each other via message passing. Messages can be passed, asynchronously, from one automaton to one or more other automata, at any point in time, thereby triggering events and decisions in the treatment process. The automata are fully parameterized in order to deal with quantitative information.

In the automata time is continuous, and both QALYs and costs can be incorporated using (assignable) local clocks. Uncertainty can be modeled using probabilities and timing intervals that can be uniformly or exponentially distributed.

The modeling and analysis has been performed using the state-of-the-art tool UPPAAL. Behaviour like reachability of states can be checked in order to validate the functional correctness of the model. Once sufficient confidence in the correctness of model has been obtained, performance can be evaluated by using the statistical model checking facility of UPPAAL where properties are checked on repeated simulations.

Result: In a relatively short time (several days) a model has been produced that is compositional (consisting of smaller building blocks), easy to understand (also because of the visual UPPAAL interface) and easy to update. The performance of the model has been assessed using the UPAAL SMC tool. The comparison of the results of this analysis with the results of a discrete event simulation is the topic of a separate study.

Conclusion: The Timed Automata paradigm can be successfully applied to evaluate the potential benefits of a personalized treatment process of mCRPC. The compositional nature of the resulting model provides a good separation of all relevant components. This leads to models that are easy to formulate, validate, understand, maintain and update.