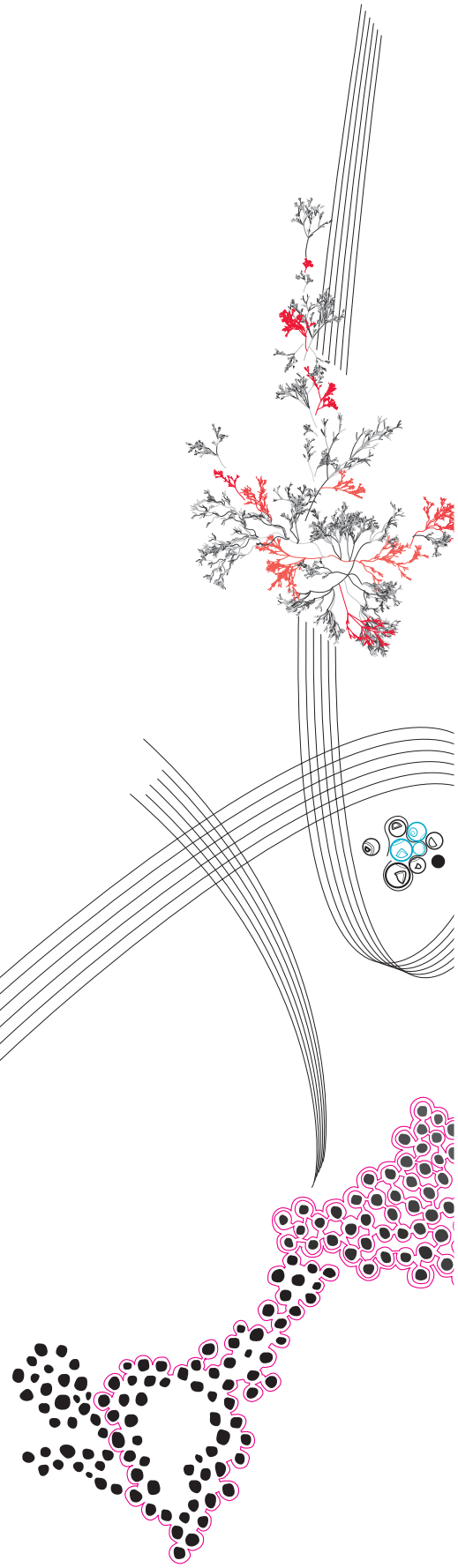

MSc Thesis Technical Computer Science

Modelling OSA Diagnosis and Treatment using UPPAAL

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A year and a half ago, I contacted Rom Langerak with the question of whether he had ideas for a master thesis project. He enthusiastically explained that he had a project about modelling Obstructive Sleep Apnea. Although I had barely heard of OSA, Rom quickly managed to convince and enthuse me for this project. Throughout the thesis project, Rom provided guidance, support and pushed me to create good work. I consider myself blessed to have worked with such a supervisor.

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Modelling OSA Diagnosis and Treatment using UPPAAL

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Abstract

Obstructive Sleep Apnea (OSA) is a highly prevalent medical disorder, linked to severe consequences. Diagnosis of OSA presently has long waiting times and has high costs.

This thesis introduces a tool-chain for analysing diagnosis strategies. This tool-chain is used for assessing the traditional Dutch OSA diagnosis strategy, as well as multiple alternative strategies for OSA diagnosis. This analysis showed that alternative diagnosis strategies can lower costs and waiting times, while maintaining diagnosis precision.

Keywords: Sleep Apnea, OSA, UPPAAL

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Contents

1 Introduction

Obstructive Sleep Apnea (OSA) is a medical condition, characterised by interrupted breathing during the patient's sleep. This is caused by a collapse of the airway [11]. These interruptions in breathing typically occur only when the patient is asleep, and therefore the patient may be totally unaware of this occurring. As a direct consequence, the patient may wake up for short durations, multiple times each night. The patient is likely to have no memory of this. These frequent arousals can prevent the patient from reaching deep sleep, which is an important sleep phase.

There are indications that a large number of people suffering from OSA go untreated, while (untreated) OSA is linked to increased blood pressure, hypertension, stroke, depression and more [42]. Getting good sleep is essential for anyone, and OSA disturbs sleep in a lot of patients.

Treatment is available for OSA; the most common treatment option in the Netherlands is Continuous Positive Airway Pressure. This treatment involves the patient wearing a plastic face mask while sleeping. Attached to this mask is a machine that ensures the pressure of the air they breathe is always higher than the air pressure of the air in the room they are in. This prevents the airway from collapsing. When used effectively, treatment can have a large, and near-immediate effect on the lives of OSA patients, with quality of life-improving significantly [3] [10].

OSA is a highly prevalent medical issue. Estimates of prevalence numbers vary wildly, but a realistic lower bound of OSA prevalence in adults is 5 to 10% [34]. Increased prevalence is reported for patients who are male, obese and of increased age. However, also outside these groups the prevalence of OSA is not low.

For this research, the Dutch healthcare system is taken as the basis of all models. This means that any patient starts at the General Practitioner, as per Dutch health care standards. Among patients for which the General Practitioner suspects OSA, the incidence of OSA is estimated to be 57 %.

The current practice for diagnosing OSA depends on complicated tests that are taken by sleep laboratories. These tests are expensive and have long waiting lists. Less expensive diagnosis strategies for OSA exist, but are rarely used in practice. Some alternative diagnosis strategies have been tested in trials [13] [18] [27], but this has not yet led to a change in medical procedure.

This research analyses a multitude of diagnosis strategies for OSA, and revolves around the following problem statement:

How to use UPPAAL to analyse diagnosis alternatives for OSA

In this research multiple alternative diagnosis strategies are evaluated, using computer modelling in UPPAAL, a modelling framework based on Timed Automata. Although the main problem statement is primarily medical, this research centers around computer scientific work, by adding a domain specific language for analysing diagnosis strategies. This enables the simulation of much larger input sets than conventionally feasible in UPPAAL.

This research was done in collaboration with Drs. Miranda Wetselaar-Glas, dentist with specialisation in dental sleep medicine, and Drs. Piet-Heijn van Mechelen, chairman of

the Dutch Apnea Association from 2002 to 2018. They provided information about Obstructive Sleep Apnea, and lent their expertise when required.

This thesis starts with research questions and related work. This is followed by giving the theoretical background of diagnosis modelling. After this, the medical background is provided, with a chapter on background information on OSA. In the following chapters, a modelling infrastructure is defined, and instantiated for diagnosing OSA. After this, two sections of results and analysis are written. The report ends on discussions and suggestions for future study.

2 Research Questions

This thesis sets out to use UPPAAL to obtain insights in diagnosis strategies for OSA. This research is based on two pillars; a medical pillar and a computer science pillar. These two pillars give rise to two main research questions.

2.1 Can UPPAAL modelling be used to explore and compare diagnosis strategies for OSA?

This is the central medical question of this thesis, and the reason for the computer science question to be asked in the first place.

OSA can be diagnosed using different diagnosis strategies, and these strategies should be compared, to gain insight on their properties.

2.1.1 What is OSA?

To answer questions about modelling OSA diagnosis strategies, first OSA itself must be explored. This is required to obtain the required parameters for models of diagnosis strategies. This question is answered in chapter 5: About OSA.

2.1.2 What improvements can be made to OSA diagnosis strategies?

A specific sub-question that has to be answered is what alterations can be made to the contemporary diagnosis strategy. This question is answered in two parts: a description of the contemporary diagnosis strategy for OSA, as well as a description of what can be improved. This question is answered in section 5.6.

2.1.3 How can OSA diagnosis be captured in a model?

By answering the previous questions, it becomes clear what OSA is, and what the properties of OSA diagnosis are. These insights need to be caught in a model. This is done in chapter 7: Towards an OSA Model.

2.1.4 What diagnosis strategies for OSA differentiate themselves from the traditional approach?

After obtaining a model, this model can be used to compare different diagnosis strategies. The basic analysis of a multitude of diagnosis strategies is done in chapter 8: Medical Analysis.

2.1.5 How can models be used to compare diagnosis strategies, with respect to their parameters?

As a final sub-question of the medical main question, the results should be analysed for their dependence on their model parameters. How sensitive are the results to model parameters? Does this alter the results significantly? This is answered in chapter 9: Comparisons of Diagnosis Strategies.

2.2 How to model medical strategies in UPPAAL?

The second pillar of this research is the computer science pillar. This question is the translation of the previous question into a question in the Computer Science domain.

This question is answered by the description and implementation of a modelling toolchain.

2.2.1 What characterises UPPAAL models for diagnosis strategies?

Before building a modelling infrastructure, it is required to know how UPPAAL functions.

This is answered in chapter 4: Theoretical Background.

2.2.2 How can a tool chain improve the versatility of UPPAAL models for diagnosis?

Expanding on the knowledge on how UPPAAL models function, an infrastructure is required to assess diagnosis strategies. This infrastructure is used to analyse diagnosis strategy models.

This is answered in chapter 6: Modelling Infrastructure.

2.2.3 What new insights can be obtained by utilising this infrastructure?

The tool-chain should be reviewed for usability. This is a secondary result to comparing OSA models, and is derived from the results from analysing OSA.

This is answered directly in chapter 10: conclusions and discussion.

3 Related Work and Contributions

This work is not the first time OSA diagnosis and treatment has been modelled. In this section, previous work is mentioned, and it is mentioned how this research differs from and builds upon that previous work.

3.1 Previous OSA Modelling

OSA diagnosis and treatment has previously been modelled by multiple different research groups.

Perraudin et al. [30] compare a traditional approach, led by the GP, to an approach led by pharmacists. The Pharmacy would give questionnaires to patients to assess whether they may have OSA, and refer to regular care if required. This is done in an attempt to lower the barrier to detection for the patient. This publication limits its patient population to 50-year-old male patients with symptoms highly evocative of OSA. They conclude that the pharmacist-based approach is more cost-effective. Although this approach is different from the models introduced later in this thesis, it shares similarities with the low-cost approach, as well as the questionnaire-first approaches in that an inexpensive, low-barrier diagnostics method is put at the start of the process, to make an initial filtering of patients.

Closer to home (also from the University of Twente), Geesinck et al [18] analyse the cost-effectiveness of a strategy based on questionnaires and a less expensive method of measuring interruptions in breathing. These diagnosis modelling results were later verified in practice, by Fabius et al [14] [15] . These papers share some of the same authors with the Geessinck et al. paper. These works are the basis of the statistical data of the ODI test, and also are the inspiration for the diagnosis strategy 'Questionnaire or ODI as Fast Track', in section 8.5.3.

Finally, the direct predecessor to this research was Catalyn Rus's Bachelor Thesis [32]. Rus also worked on modelling OSA diagnosis and treatment in UPPAAL. He compared multiple diagnosis strategies using UPPAAL, focussing on using treatment as a diagnosticum. Although this is not a peer-reviewed article, it should be mentioned here, because it is the direct predecessor to this research, showing the possibilities of what UPPAAL can do. This paved the way for this thesis.

3.2 Contributions

The main contribution of this Master Thesis is in the creation of a framework for systematic analysis of a larger set of OSA diagnosis models. Building blocks were created, and nine different strategies were modelled using these blocks. Since these models used the same building blocks, it enabled analysing the models in a consistent way.

In order to assist in-depth analysis of the models, a solution was found for automating the analysis of the models of diagnosis strategies. For this, a domain specific language (DSL) was specified. A DSL is a programming language that is created to fulfil a specific purpose. This DSL's purpose was to enable a systematic and automatic approach to executing diagnosis strategies, simulating them for varying parameter inputs. By using this DSL, the diagnosis strategies were compared.

4 Theoretical Background of Diagnosis Modelling

In this chapter, the modelling theory is given on which the rest of this research was built.

4.1 What is an optimal strategy?

There are numerous methods for diagnosing OSA. These methods differ in costs, waiting times, sensitivity, costs per patient, and total number of patients receiving treatment. From these methods, the best option should be chosen.

There are multiple properties for which diagnosis can be optimised, such as costs, sensitivity, or diagnosis timing. Strategies can be optimal for one or more of these, but no strategy exists that is optimal for every property. Therefore, deciding what properties have priority is a decision that is partly up to society (or politics). Thus, the goal of the modelling in this thesis is to assess the properties of different diagnosis strategies for OSA, and use this to compare these strategies. Picking a 'best' option is not something that this work aims to answer.

4.2 Basic Modelling Assumptions

In order to be able to model OSA diagnosis and treatment, assumptions have to be made about OSA.

As a first, main assumption, it is assumed that the incidence of OSA within the diagnosed/treated patient group is known. The incidence of OSA in the population is one of the main input parameters to the model.

As a second assumption, it is assumed that there is statistical independence between diagnostics results. This means that if the same patient receives the same diagnosis test twice, the second diagnosis test result has no correlation to the first, besides both being based on whether the patient has OSA or not).

4.3 UPPAAL

To model diagnosis strategies, a modelling framework is required that is able to adequately represent these strategies. A promising type of models is Timed Automata. Timed Automata are an extension of finite automata, enriched with time-based constraints [1]. One tool for using timed Automata is UPPAAL [6], developed by the universities of Uppsala (UPP) and Aalborg (AAL). UPPAAL was originally designed to verify the correctness of complex systems such as railway signalling, but also wireless network protocols. UPPAAL's strong point traditionally lies in the modelling of systems where multiple components operate in parallel, with weaving interactions between them.

Besides a verification tool, UPPAAL also added a statistical checker. The statistical checker does not provide exact answers, but instead gives probabilities and expected values. Although this yields weaker results, the benefit is that in exchange UPPAAL is more expressive. UPPAAL's statistical checker is employed in this research for answering questions about diagnosis models. An example of such a question is "How expensive is it per patient to diagnose OSA using this diagnosis strategy?". This approach has been

used before for medical modelling, such as by Wetselaar et al [41], for the modelling of tooth wear.
Uppaal has three advantages:
Firstly, UPPAAL is expressive: time, costs and uncertainty can be modelled.
Secondly, UPPAAL's models are primarily graphical. This has as an advantage when communicating with people who do not have experience with computer modelling.
Finally, UPPAAL is a tool that is mature and stable, with a fixed team behind it.

For these reasons, UPPAAL was chosen for this thesis.

4.3.1 Templating

The building blocks of an UPPAAL model are templates, which are intended to each model one component within a system. Each one of these templates is one automaton. These automata have states and transitions. The states are used to define specific stages of a process, such as 'waiting for test result', while the transitions are used to move between states.

In the case of OSA modelling, a template is made for every diagnostics test, treatment step, and one for every step-by-step process of a medical professional. There are also helper automata for tasks like setting up a patient, and administrative sub-tasks.

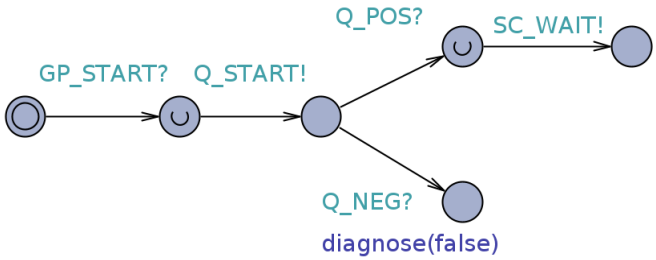

FIGURE 1: Example GP template.

The templating system in UPPAAL allows for having multiple templates prepared with the same functionality, while only having one of them enabled. This mechanism is used for composing scenarios. For instance, the task of the GP can be implemented by a template such as in figure 1. The GP automaton starts on the left, at the state with the double circle. The state right of it is Urgent (marked with an U), meaning that time cannot pass in this state. Since this state has only one successor, it will therefore immediately move to the next state.

These automata are then all put in parallel, meaning that they all run in parallel. The templates communicate using synchronisation, and through variables. For the diagnosis modelling in this Thesis, only synchronisation is used to communicate between automata, and only one automaton is progressing at the same time, with the rest waiting for input from the automaton that is still progressing.

4.3.2 States and Transitions

UPPAAL is based on the modelling paradigm of Timed Automata, which are an extension of Finate-State Automata (FSA). As with FSA's, UPPAAL's automata are a collection of states, with transitions between them. States describe a specific point in a process, and transitions describe how progress can be made between states. Unlike some other automata formats, UPPAAL automata have only one starting states, and do not have final states. Instead of final states, UPPAAL uses queries. In regular UPPAAL, these queries are encoded in Timed Computation Tree Logic (TCTL)[2]. These queries are used to answer questions on reachability, satisfiability, and more problems. In this research, UPPAAL SMC is used. UPPAAL SMC does not allow for TCTL queries but instead has its own set of queries. These allow for finding probabilities and expected values.

4.3.3 Synchronisation

Synchronisation is the main way by which UPPAAL has automata communicate with each other. Synchronisation happens on transitions. One transition in one of the templates is the broadcaster. This transition forces all other templates that are waiting on this channel to take their transition labelled with the channel. In UPPAAL, the active (broadcasting) side is marked with an exclamation mark, whereas the passive (waiting) side is marked with a question mark.

For this thesis, synchronisation channels were named using a standardised form. In this convention, the names start with an acronym that indicates what process is communicated about, followed by an underscore (_), and then have a postfix text explaining what it is.
The synchronisation channels end on one of the following: WAIT, START, POS, NEG, HIGH, MED, LOW, FAIL. This naming convention was picked because it results in channel names that are structured.

On the previous page, in figure 1, the automaton initially waits for another template to send a GP_START signal. This signal is sent by the Patient template, which sets up the properties of the individual patient. After receiving this signal, the GP instantly sends a Q_START signal, which is received by a questionnaire. This questionnaire then starts its logic, and when the questionnaire is done, it sends either a Q_POS signal (if the questionnaire is positive) or a Q_NEG signal, if it is negative. If the questionnaire was positive, the GP refers the patient to the sleep centre, using a SC_START signal.

4.3.4 Time

Time is an important factor in UPPAAL. Time is measured by clocks, which are special variables in UPPAAL that keep track of time. In UPPAAL SMC, clocks can be set to a value, and the relative rate by which a clock progresses can be adjusted. Clocks can thus be used to keep track of waiting times for an individual diagnosing step, but also for the total time a patient waits for diagnosis.

For any template, at any state, one of the following four can be true:

1. The automaton is waiting on a signal
2. The automaton is forced to progress (no time is allowed to pass while the automaton is in this state)
3. The automaton is waiting for an amount of time between two values (a minimum and a maximum)
4. The automaton will randomly progress at some rate

In the latter two cases, the clock will enforce the automaton to wait a random amount of time in the state. In the first case, the waiting time is uniformly distributed between the minimum and maximum waiting times. In the second case, the waiting is exponentially distributed. In this thesis, only uniformly distributed waiting times are used.

In principle, multiple of these options can be true at the same time. However, some combinations can result in reaching a state in which the automaton can not progress. For instance, the automaton can be forced to progress, but is also waiting for a signal.

In the diagnosis models in this Thesis, Time only progresses while waiting for diagnosis and/or treatment, and while the patient is receiving treatment. Diagnosis itself is assumed to happen instantly. This was justified by the fact that waiting times are generally much longer than diagnosis time.

4.3.5 Randomness and Branching

Synchronisation can be used to introduce randomness into a model. In a lot of models, more than just the progress of time can be random. For instance, if a model represents a guest at a theme park, the model may need to randomly decide which roller-coaster the guest will visit next.

There are two distinctly different issues here: generating random values, and branching.

4.3.5.1 Random Values UPPAAL can set variables to random values, using update functions. This is the most flexible approach that UPPAAL offers. It is only available when using the statistical model checker, which this research is using exclusively.

4.3.5.2 Branching Branching occurs when an automaton is presented with multiple options. This can be required, for instance, for differentiating the behaviour of an automaton, based on a random value. UPPAAL offers two ways of branching using a random value. The first one is by setting a variable to a random value, and then using guards to select one of the paths.

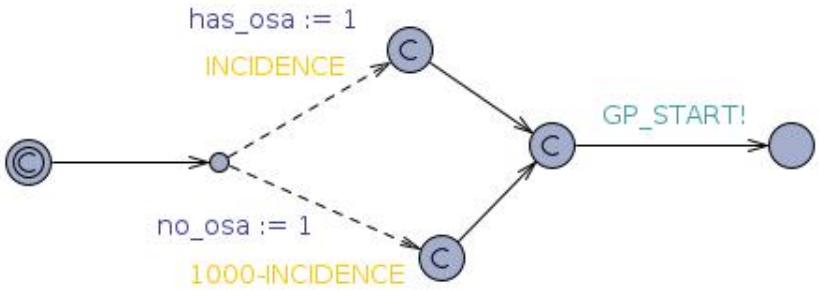

FIGURE 2: Patient generator example.

The second, and more recommended means is by annotating the transitions with their odds, as shown in figure 2. Since the data used to initialise the model is in percentages, this needs to be converted to odds. As a convention, we translated the percentages to promilles (per thousand), to mitigate UPPAAL's limitation of allowing only integer odds. In the example above, the incidence is taken as a promille value (ie. 570 for 57%), and therefore the odds of not having OSA are 1000-INCIDENCE.

5 About OSA

This chapter describes clinical information on Obstructive Sleep Apnea. This information is essential for being able to model OSA. First, a definition of OSA is given, followed by a discussion of different clinical definitions of OSA. After this, the consequences of OSA are assessed. This chapter ends with a discussion on the prevalence of OSA.

Multiple different medical issues can lead to OSA [28], of which three are listed here. Firstly, the upper airway can be too narrow. In this case, the patient's upper airway is relatively small, causing it to be more prone to collapse. Secondly, there can be an issue with the way breathing is controlled; high loop gain. This is an issue where the patient's breathing is not functioning fully automatically. While awake, the patient's brain takes over, and ensures breathing resumes normally. Finally, a low arousal threshold can be a cause of OSA becoming an issue.
Since patients differ in underlying causes, patients may require different treatments.

5.1 A definition of OSA

In this subsection a definition of OSA is given, intended to give readers without a medical background a general idea of what OSA is. This is loosely based on Dempsey et al. [11].

One can think of the upper airway as a semi-flexible tube. Where in most mammals the upper airway is solid, in humans this is much more flexible. If the upper airway is relatively narrow in certain ways, the airway can collapse. Then, a patient suffers from Obstructive Sleep Apnea, if the patient's airway is obstructed partially or entirely, while sleeping. This collapse of the airway causes the breathing to become physically hindered or impossible. The patient consequentially gets woken up, because the brain is notified of an increased CO_2 level in the bloodstream. This causes breathing to immediately start again, and the patient generally falls asleep swiftly. The patient may have no memory of this cycle. This only happens while the patient is asleep, because control over breathing is less precise while asleep, compared to when awake.

5.2 Diagnostic Definition of OSA

In this section, diagnostic definitions of OSA are explored. Ideally, such a definition is objective, inexpensive, and non-invasive to measure. Using such a definition, potential patients could easily be tested for OSA. A widely-used measurement for OSA is the Apnea-Hypopnea Index (AHI). The AHI is defined as the number of apneas (pauses in breathing) that are over 10 seconds in length, measured per hour. There are multiple differing standards for when a breathing event should be considered to be a Hypopnea. For instance, a hypopnea can both be defined as requiring an oxygen desaturation of larger than 3%, as well as 4%. Seemingly small deviations in the definition, as well as differences in measuring equipment result in large differences in the incidence statistics of increased AHI. Ho et al. [20] compare three different definitions of AHI, and find significantly different results for each. This shows that the precise value of AHI can depend highly on the exact definition of AHI.
Traditionally, the severity of OSA is defined by ranges of the AHI. However, there is more recent research showing that this categorisation is not accurate [36]. Moreover, the AHI is dependent on other patient characteristics, such as age and BMI, and fluctuates over

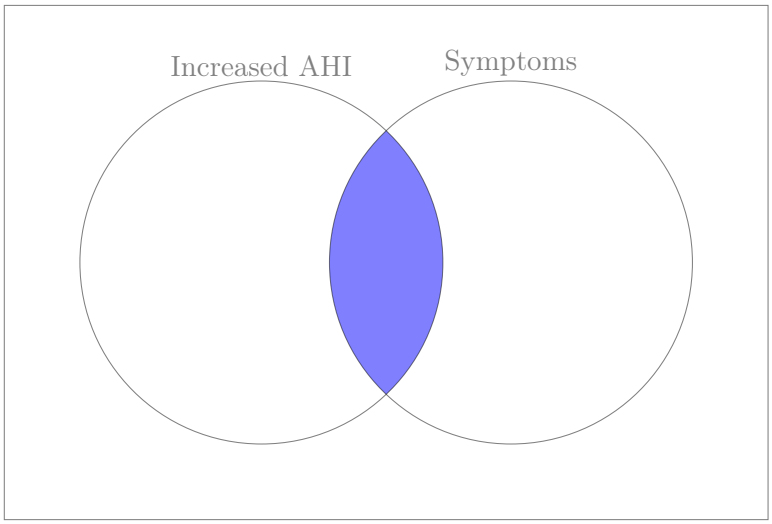

FIGURE 3: Venn-diagram showing how OSA relates to AHI. The blue area is OSA. This diagram describes the Dutch definition of OSA [36]

time [39]. Therefore, using a measurement of a patient's AHI is not sufficient to have a reliable image of the severity of the patient's OSA.

Using solely AHI is not a definition that is generally in use for diagnosing patients with OSA, because patients with high AHI may not even have any symptoms [4]. Since the severity of OSA does not always correlate well with AHI levels, it does not suffice to increase the minimal AHI required to diagnose a patient with OSA. The diagnostic definition can be made stricter by stating that the patient not only needs to have an increased AHI, but also needs to have symptoms. A definition using the conjunction of AHI and symptoms is widely used [43], and is indeed the definition of OSA in Dutch health care [36]. Formally:

> A patient has OSA if the patient is symptomatic, *and* the patient has increased AHI.

In the rest of this document, when mentioning OSA, this is the definition that is used. Figure 3 illustrates how OSA relates to increased AHI.

The differences in definitions of OSA generally make it difficult to compare research, because the inclusion of symptoms in the definition changes which types of patients get included.

5.3 Consequences of OSA

There are two categories of consequences of OSA: direct consequences and risks.

As a direct consequence of OSA, patients may suffer from lowered sleep quality. This includes such symptoms as daytime sleepiness and lowered concentration. For OSA, every patient has at least some of these symptoms (otherwise these patients would not have OSA). Excessive Daytime Sleepiness (EDS) is very prevalent in the adult population, with estimates of about 20% of the adult population of the United States of America suffering from it [29]. Prevalence among OSA-patients is much higher, at around 85% [35]. The high prevalence of EDS means that using EDS in itself is not sufficient to diagnose OSA.

OSA is linked to increased risks for Cardiovascular Diseases, as well as a plethora of other issues. It also is associated with a general increased mortality rate.

There is a correlation between motor vehicle accidents and OSA [37]. However, interestingly, only a weak link between reported daytime sleepiness and car accidents was found. This could indicate that perhaps OSA itself isn't the issue, but the fact that the driver does not know they have a problem is. If a driver knows they are likely to feel sleepy while driving, they may have developed a strategy to mitigate this (not driving at night, drinking coffee before going, ..). This also indicates that decreasing the number of undiagnosed OSA patients can lower the number of OSA-related car accidents.

5.3.1 Obesity

The relationship between Obesity and OSA is a complicated one. In general, sleep deprivation is a risk factor for the development of Obesity [5].

Obesity is a risk factor for OSA, and OSA is a risk factor for Obesity [22]. This means that a patient with OSA is more likely to develop Obesity and vice versa.

Something to take into account, however, is that there is a medical bias towards suspecting OSA in stereotypical patients, and thus there is an over-representation of obese patients in studies that base their population on patients who know they have OSA [45]. This can lead to a self-fulfilling prophecy: since doctors know that obese people are more likely to have OSA, they are more likely to look for OSA in obese people. For this reason, research about the demographics of current OSA patients is biased. When available, research into the general population has preference over research into current OSA patients.

5.4 Prevalence

A critical question to answer before making decisions on OSA treatment is how prevalent OSA is. Prevalence is defined as the proportion of patients at a moment in time, compared to a population. Since OSA is a chronic disease, this is equivalent to the percentage of a population that suffers from OSA. The effectiveness of diagnosis strategies depends on the prevalence. For instance, if the prevalence of a medical problem is low, expensive population testing is generally ineffective.

There are two fundamental problems when talking about OSA prevalence. Firstly, the definition of OSA is not standardised, and therefore prevalence numbers are not

Paper	Prevalence	Sources
[43] The occurrence of SDB among middle-aged adults	2 % to 4 %	
[26] Prevalence of symptoms of sleep apnea syndrome. (..)	7.5 %	
[17] Symptoms of sleep apnea syndrome: high prevalence and underdiagnosis in the French population	4.9 %	
[9] Diagnostic accuracy of the (sleepiness scales) in detecting OSA: (..)	1.2-28%	[25], [12], [7], [21]
[30] Cost-effectiveness of a community pharmacist-led sleep apnea screening program–a Markov model	5-10%	[44] [26] [17]

Table 1: Papers reporting OSA prevalence

considering the same medical issue. Secondly, there is no standardised method of measuring the prevalence of OSA in a population. Although there are standardized ways to test OSA, the specific testing parameters vary from research to research. Therefore, the reported prevalence statistics vary wildly from research to research. In general though, there is a trend of increasing prevalence numbers, especially in research that considers AHI a sufficient criterium for diagnosis of OSA [19]. This is caused at least in part by increased sensitivity for measuring techniques. Therefore it is difficult to come to hard conclusions based on the differing numbers.

For increased AHI, prevalence numbers were first reported by Young et al [43], estimating the prevalence of OSA to be around 24% in men, and 9% in women. Later, Heinzer et al [19] reported a prevalence of increased AHI of up to 41%, based on a population research in Lausanne, Switzerland.
Arnardottir et al. [4] tested the relationship between AHI and sleep-related symptoms in a general population sample. They also found high prevalence statistics for increased AHI, but did not find a correlation between symptoms and AHI, except for patients with an AHI over 30 (severe AHI).

The incidence of OSA among patients referred for diagnosis is much higher. In papers about the modelling of OSA diagnosis and treatment, the reported OSA incidence when referred for diagnosis is between 43% [18] and 70% [15]. The precise incidence statistics used by OSA modelling papers is given in table 2. These papers were selected based on a quick survey of available modelling papers, not a complete list of all papers involving OSA modelling. Based on these statistics, and expert consultation, the decision was made to assume the incidence of OSA among patients referred for diagnosis to 57%.

Paper	Incidence	Remarks
[38] OSAHS: modeling different diagnostic strategies	54 %	
[31] An integrated health-economic analysis of (..) OSA	50%	
[18] (..) DiagnOSAS (..) compared with polysomnography diagnosis (..)	43%	Small 77-person sample
[15] The use of oximetry and a questionnaire (..) enables exclusion (..) OSA diagnosis	70 %	Percentage OSA after referral

Table 2: OSA Incidence according to Modelling Papers

5.5 Diagnosis and Treatment Options

In this section, an overview is given of the different diagnosis options that are available for OSA, and an overview is given of the treatment options for OSA. The focus is on diagnosis options, because the modelling also focuses on diagnosis.

5.5.1 Diagnosis Options

The definitions given in this section are based on Dutch Health Care Standards [36].

5.5.1.1 Polysomnography (PSG) For diagnosis of increased AHI, the gold standard method is using polysomnography. Sensors measure an extensive set of signals, such as brain activity, oxygen levels in the blood, heart rate and breathing patterns. This data is used to identify when sleep is interrupted, and to identify the causes of these interruptions.

5.5.1.2 Polygraphy (PG) PG tests are tests that do not cover the full set of signals that are registered by the PSG tests. A PG test differs from the PSG in that brain activity is not measured with this method. As a consequence of this, sleep state, and arousals cannot be detected using this research method. These tests are less expensive, and generally more portable, facilitating at-home testing.

A limitation of PGs and other limited-sensor-data tests is that these tests generally can only detect whether the patient has increased AHI or not. These tests cannot differentiate which sleeping disorder the patient may have. This means that if the patient gets an OSA diagnosis based on such a test, but responds negatively to CPAP, the patient will still need a PSG to assess whether the patient has a problem with CPAP specifically, or whether the patient has a different sleeping disorder that also causes an increased AHI. OSA is the most prevalent among sleeping disorders that cause increased AHI, but is not the only one.

5.5.1.3 Other Tests In an attempt to lower the cost of diagnosing OSA, multiple lower-cost alternatives to PSG and PG were developed.

The Oxygen Desaturation Index (ODI) is a signal-value that can be measured instead of the AHI. Instead of measuring directly that the breathing is interrupted, the oxygen

levels in the blood are measured. In most cases, it correlates highly with the AHI, and thus it can be used as a less expensive stand-in for AHI.

There are more diagnostics tests that can replace PG and PSG, such as nFlow and NightOwl. These tests share the characteristic that they are much less expensive to give to a patient. The tests have varying statistical properties. In this research, ODI was taken as a 'standardised inexpensive test', because it has a high sensitivity (around 100%). This means that using ODI as a diagnostic test will not result in additional false negatives.

5.5.1.4 Testing at Home Traditionally, sleep apnea testing was done in Sleep Centres. This means that the patient travels to a specialised facility, where the patient sleeps for a night, while sensors monitor the patient's sleep. Having the test take place in a specialised facility has three main disadvantages. Firstly, patients will need to head elsewhere to spend a night there. This is impactful on their schedules. Secondly, since people generally sleep better at home, this results in the measurements taken not necessarily being a representative sample. Finally, specialised facilities increase the cost of diagnosis significantly.

Improvements in medicine have made it possible for tests to increasingly be taken at home. Initially, only simple tests and PG's could be organised from the home, but it is presently also possible to have the patient take a PSG at home.

Note that this paper is based on the Dutch health care standards. This means that testing at home, unless otherwise specified, is still organised by the sleep centre. Also, where American papers take a Home Test (Home Sleep Apnea Test; HSAT) to mean 'Polygraphy', in this thesis a Home Test refers to the location, and not the test type.

5.5.1.5 Questionnaires Questionnaires are an inexpensive diagnosis step that fulfils a similar function to taking a medical history. The main advantage of a questionnaire is that it is automatically gradeable. Therefore, the cost of a questionnaire does not depend on how many people take it, but only on the cost of creating the questionnaire. This means that a questionnaire can be taken by a large group of people who may have OSA, while still being comparatively inexpensive. The American Academy of Sleep Medicine (AASM) recommends against using questionnaires for diagnosing OSA, unless used in conjunction with PGs or PSGs [23], because of a relatively low correlation between questionnaire results and OSA. Thus, relying purely on questionnaires may result in a high false-positive rate.

5.5.2 Treatment Options

The most selected treatment option is Continuous Positive Airway Pressure (CPAP). CPAP prevents the airway from collapsing by ensuring that the pressure in the airway is always larger than the pressure outside. Informally, it is a machine with a tube connecting to a mask on the patient's face, providing constant air pressure (relative to the outside air) for the patient to breathe.
This is, for adults, the standard treatment option offered. In the modelling for this thesis, this is the only treatment option that is separately modelled, the rest of the treatment options are seen as 'other treatment', and the model ends when a patient requires further

treatment. Although the other options were not included as a part of the model, these options are still mentioned here, for the sake of completeness.

Another treatment option is a Mandibular Advancement Device (MAD) [24], an oral appliance used to keep the airway by holding the lower jaw in a forward position while sleeping. This option is seen as an alternative for CPAP, for mild and moderate cases of OSA, and for cases in which CPAP is either not accepted by the patient, or not working sufficiently.
Schwarz et al. [33] systematically review research in the differences between CPAP and MAD. They conclude that CPAP is, in general, significantly more effective. However, not every patient is compliant with CPAP treatment, and therefore Schwarz et al recommend offering MAD as an option in patients non-compliant with CPAP.

Yet another treatment option is surgery, which is undertaken mostly in cases where the previous two options have failed or were excluded. It is also the preferred treatment option for children. Certal et al [8] give a review of research into the effectiveness of OSA surgery.

The sleep position is also of importance for OSA [16]. Therefore, patients sleeping in the supine position (on their back) may benefit from switching to sleeping while laying on their side. There exist physical aids for assisting this switch in sleeping position. For mild cases of OSA, a change in sleep position may be sufficient as a treatment.

5.6 Contemporary Diagnosis Strategy

In figure 4, the current Dutch diagnosis strategy for OSA is shown [36]. This strategy focuses on getting as few false-negative diagnoses as possible. The number of false-negatives is kept low, by always performing a precise test before giving a negative diagnosis.

1. It is assumed that every patient starts at the General Practitioner (Huisarts; GP), If the GP considers the patient to be likely to have OSA, the patient is referred to the sleep centre.
2. Sleep centres take a medical history, and use either a PSG or a PG to measure the AHI of the patient. In the diagram, it is assumed that the Medical History (Anamnesis, AM) is taken first. In practice some sleep centres may take the medical history after the PSG or PG.
3. If the medical history shows reason to suspect OSA, the patient's AHI is measured using either a PSG or a PG.
4. If the PG fails, the patient gets a PSG. If the PSG fails, the patient gets another PSG.
5. The result of the PG and PSG then defines the diagnosis.

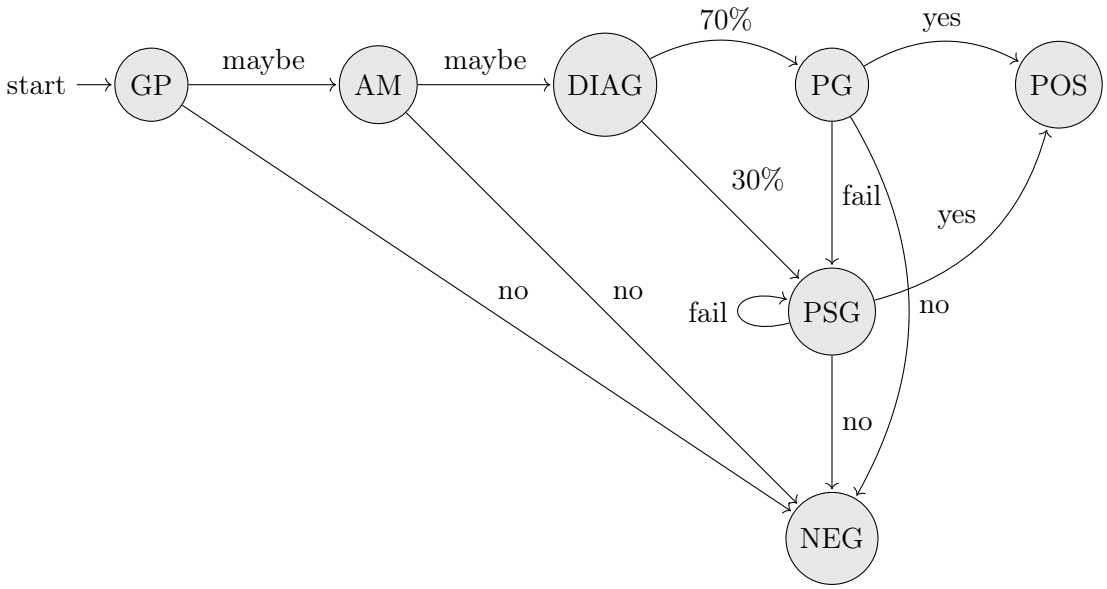

FIGURE 4: Contemporary diagnosis strategy in the Netherlands

5.6.1 Improvements on Contemporary Diagnosis Strategy

Although the contemporary strategy for OSA diagnosis is precise, the waiting times and costs are high. There are indications that the number of undiagnosed people that suffer from OSA is significant [17] [4]. Attempting to increase the diagnosed population could therefore further increase costs and waiting times.

Costs and waiting times are mainly occurring for the sleep centre, especially when a PSG is utilised. Therefore, limiting the number of patients that need to pass by the sleep centre is a means of decreasing costs for OSA diagnosis.

Questionnaires can also be used instead of full anamnesis. Questionnaires have two benefits. Firstly, the patient can take a questionnaire at home. This means that if a patient needs convincing to start the diagnosis, the first step of the process can be taken without a sense of 'commitment' to having OSA, giving the diagnosis a chance to get a foot in the door. Secondly, questionnaires are less expensive, having only initial cost of development, and the costs of maintaining a website on which the questionnaire is hosted. When compared to the hundred million euros (roughly) that is spent on OSA diagnosis in the Netherlands, every year, this is insignificant.

In chapter 8, multiple alternative diagnosis strategies are introduced. These strategies are based on the opportunities for improvement that are given in this section.

6 Modelling Infrastructure

In this section, a technical framework for evaluating medical diagnosis models is introduced. The idea behind this framework is that it results in a tool-chain for evaluating diagnosis strategies. This framework should have a model that describes OSA diagnosis in general, and a method for setting up experiments to evaluate the diagnosis strategies.

Fundamentally, the framework is comprised of three components: An UPPAAL model, a transformation setup, and a set of UPPAAL queries. The UPPAAL model provides the building blocks required for modelling diagnosis strategies, and is kept the same among all simulations. The transformation setup defines which diagnosis strategy is used, and sets the parameters for the experiment. This transformation setup is translated (unzipped) into multiple run setups, which are used to create an altered copy of the original UPPAAL model. The UPPAAL query file is used to define which results are of interest. After results are obtained from the query, a separate process is in place to generate human-readable output from the model results. In figure 5, it is shown how the infrastructure uses the components to generate results. A more precise description of the technical functionality of the toolchain can be found in the appendix.

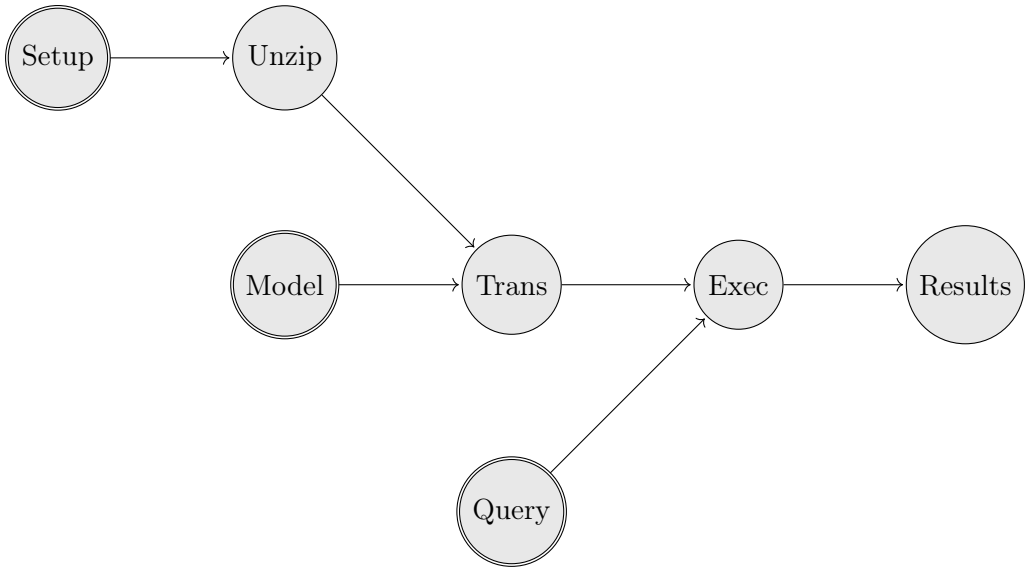

FIGURE 5: Workflow of UPPAAL translation and execution

In an attempt to clarify, let us use a metaphor: a restaurant. The spec in this model-flow can be interpreted as a menu card, with options for entrees, main dishes and deserts. The unzipping phase turns this menu card into all possible choices a customer can make. In the case of a restaurant, the model describes how the cook creates food in general. The transformation (Trans) turns a customer choice plus the model into a specific recipe for cooking the food. The query describes by which standards the customer will judge the food. The execution (Exec) then has the cook actually create the food, and has the customer judge it. Finally, the results equate to the customers taking the results of the execution, and writing a Yelp review.

6.1 Transforming Uppaal Models

In this section, a quick summary is given of how UPPAAL models were transformed in the tool-chain. Uppaal models have four components:

1. Global Declarations: set variable values that are global
2. Templates: timed automata
3. Template Declarations: set variable values for templates
4. System Declarations: set up which templates are a part of the model

The Global Declarations, Template Declarations and System Declarations are essentially text files within the model, while the Templates represent automata, and are stored in an XML format.

To keep the tool-chain simple to implement, it was decided not to create tooling to manipulate the templates themselves. Instead of manipulating the templates themselves, templates are altered by choosing between multiple alternatives for templates, each representing the same functionality. An important consideration in this was that the transformations were designed to result in an UPPAAL model that is still easy to read. Transformations to the templates alter graphs, and this can easily result in graphs that overlap in ways that make reading them very difficult.

This was used to have multiple models for the General Practitioner, and to have multiple questionnaires and tests.

To summarise, the tooling allows for the functionality as shown in table 3.

UPPAAL Part	**Functionality Implemented**
Global Declarations	Set integer values Integer value sweep
Templates	*No transformations were programmed for the templates*
Template Declarations	Set integer values Integer value sweep
System Declarations	Setup Templates Iterate over Template List

Table 3: Transformation Features

6.2 Domain Specific Language

Although UPPAAL can be used to model diagnosis processes, it has major weaknesses; UPPAAL does not include tooling for automating generating results. This means that tasks such as sensitivity analysis may require thousands of simulations, which would be simply infeasible when done by hand. Therefore, a method is needed for automating the generation of results, and turning the results into an output that can be interpreted by a person.

This illustrates a need for simplifying this process. Although UPPAAL does not provide much for interfacing with it beyond a command-line tool, UPPAAL models can still be manipulated automatically, since the format in which they are stored is an XML format. The toolchain uses this fact to alter (a copy of) the input UPPAAL model, and replace some lines of the specification. UPPAAL's command line tool is then used to automatically obtain results.

For specifying *what* changes should be made to an UPPAAL model, these should be written down in some way. A choice was made here to use a Domain Specific Language; a limited programming language built for a specific purpose. The choice was made for a DSL, instead of building a library for a programming language, because it results in input that is more concise. This was done to prevent creating a DSL that is overly expressive and therefore inefficient.

The language is designed to fulfil the following main goals:

1. To be able to transform lines in the UPPAAL Systems Declarations
2. To be able to set variables
3. To be able to set up multiple experiments in one file
4. To have some sort of importing mechanism to load another specification file within the specification
5. To be guaranteed to always generate the same set of UPPAAL transformations

In the next subsections, first, the individual commands of the language are described, and then it is shown how the language allows for multiple experiments to be set up in one file.

6.2.1 Run Setup

The primary task of the DSL is to set up the UPPAAL model. The DSL therefore primarily contains commands that manipulate specific lines in the UPPAAL model. The primary manipulations the DSL does are the following:

1. Setting local and global integer (number) variables
2. Sweeping over local and global integer (number) variables
3. Setting local and global variables of other types
4. Selecting templates

The precise specification of the commands of the DSL is given in the appendix. Using this technology, the setup of a simulation can be fully automated.

```
{
    setLocalValue("Patient", "const int INCIDENCE", 700)
    setTemplate("GP", "GPbaseCase()", "Traditional")
    setTemplate("SC", "SleepCentre(TREATMENT_START)", "SOMNO")
}
```

Above is an example of a run setup. It is surrounded by brackets, for a reason that should become clear in the next section. On the second line, the INCIDENCE of OSA is set for the simulation, at 70% (700 per 1000). On the lines after that, a selection is made for a template for the General Practitioner (GP), and for the Sleep Centre.

6.2.2 Multiple Runs

Using the UPPAAL manipulation options of the previous subsection, a single simulation run can be set up and executed automatically. For tasks such as sensitivity analysis, a multitude of runs have to be simulated. Although it is possible to do this by hand, automating the execution of multiple runs greatly increases the efficiency of the modelling process, allowing more work to be done in the same time. Therefore, the DSL was extended in such a way that it allows for setting up multiple runs. The DSL is based around a tree structure, where, the deeper you go into the tree, the more the simulation setup is specified.

```
{
setLocalIntSweep("Patient", "const int INCIDENCE", 10, 1000, 10)
    { setTemplate("GP", "GP2()", "Traditional GP") }
    {
        setTemplate("GP", "GP3()", "GP with Questionnaire")
        { setTemplate("Q", "StopBang(Q_START)", "Stop Bang") }
        { setTemplate("Q", "BerlinQ(Q_START)", "BerlinQ") }
        { setTemplate("Q", "PhilLow(Q_START)", "Phillips Low") }
    }
}
```

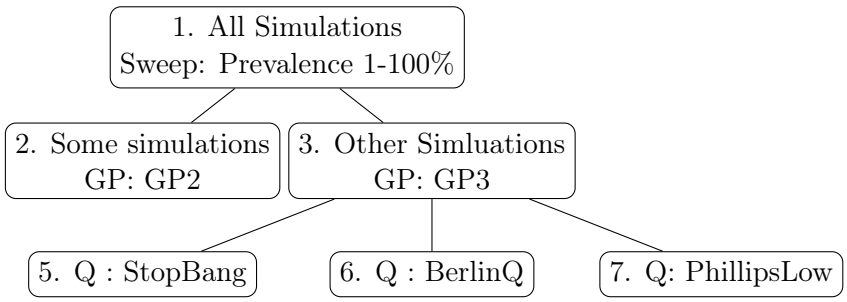

FIGURE 6: Example of a DSL setup Tree

Consider the example above, with multiple levels of parenthesis blocks within each other. This structure represents a tree structure; the tree represented by it is shown in a more readable way in figure 6. One can see every node in the tree as partly specifying the properties of a run (or set of runs, based on the contents of the nodes). The tree is traversed, and every child of a node builds upon the properties of their parent.

Node	Parent	Is Leaf?	Setup
1	-	No	Prevalence 1 to 100%.
2	1	Yes	Prevalence 1 to 100%; GP := GP2
3	1	No	Prevalence 1 to 100%; GP := GP3
4	3	Yes	Prevalence 1 to 100%; GP := GP3; Q : StopBang
5	3	Yes	Prevalence 1 to 100%; GP := GP3; Q : BerlinQ
6	3	Yes	Prevalence 1 to 100%; GP := GP3; Q : PhillipsLow

Table 4: DSL Tree Interpretation Example.

In table 4, the setup is described for every node of the example tree, in order of traversal of the tree. Nodes 3, 4, 5 and 6 are leafs, and are therefore starting points for running the model. Thus, the model needs to be run 400 times to execute this example specification. It needs to run a hundred times with GP set to GP2, for varying prevalence levels. Similarly, it needs to run a hundred times for each of the questionnaires, with GP set to GP3.

This shows two things. Firstly, it shows that this setup language can be used to set up complex scenarios, and can generate very specific datasets this way. Secondly, it shows that careless modelling with this setup language can easily create high numbers of scenarios. Although this does not require manual work, running one simulation takes between a minute and four minutes, and thus on a quadcore computer (the simulations can operate in parallel) this can still result in hours upon hours of compute time. Indeed, since all combinations of parameters are tried, iterating over multiple parameters may well result in years if not decades of compute time. Thus, some intelligence is still required when using this DSL.

6.2.3 Import Methods

The DSL has two different import methods: import and merge. Recall that the system is based on a tree. Import takes the contents of another specification file, and puts the tree that can be generated from that file as a child of the node on which the import is added. Merge is similar to import, but instead of making these nodes a child of the node itself, the merge command adds the children as children to all leafs underneath the node on which the merge command is put. Below is an example of how this importing works. In this example, the import and merge commands are expanded one by one:

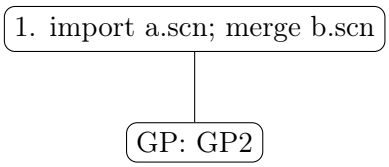

FIGURE 7: Example of a DSL setup Tree

FIGURE 8: Example: a.scn

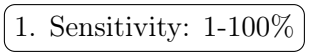

FIGURE 9: Example: b.scn

Consider the examples of DSL graphs above. The commands on a node are executed in order, and thus the import is handled first. The resulting graph is the following:

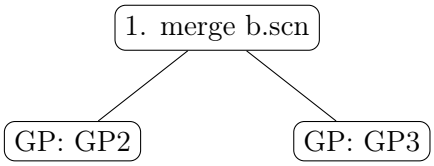

FIGURE 10: Intermediate Tree after Import

Now, the merge is executed. The top node, with the merge, has two children, so each of these children gets the tree of b.scn underneath it.

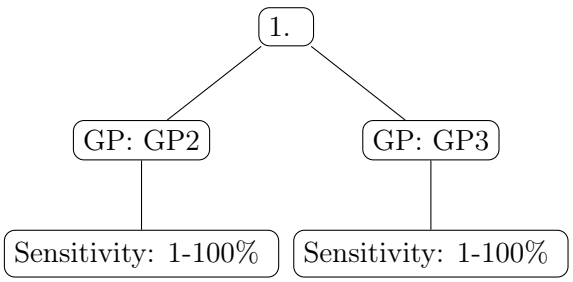

FIGURE 11: Final Tree of import example

The combination of these two methods allows for flexibility in importing files.

6.3 UPPAAL Queries

UPPAAL uses Queries to obtain statistical results on a model. The queries, in the Statistical Model Checker of UPPAAL, can be used to answer two different types of questions:

1. Expected value of a formula
2. Probability that a statement is true

6.3.1 Expected Value

```
E[<=50000; 70000] (max:TOTAL_COST)\
```

This type of query calculates the expected value ('average') of a formula. The example formula is interpreted in the following way: It calculates the expected value, within the first 50 000 time-units (days), based on 70 000 model simulations. The result of this query is the maximum of the TOTAL_COST variable. The maximum is a required addition to this formula, because the value of a variable changes during a run. Observe that the minimum value also exists, but when using this, care should be taken that the value is not at its minimum value at the start of the automaton.

6.3.2 Probabilities

```
Pr[<=50000; 70000] (<> ( diagnosed_has_osa && has_osa ))\
```

The formula above shows a probability formula in UPPAAL's query language. The example formula queries the model for the odds that a patient receives a true-positive diagnosis.

6.4 Output Stage

To generate output data, multiple queries are executed on the model, creating a set of statistical results. This set of statistical results is stored in a special save format, to allow for further analysis.

6.4.1 Table Generation

As a final part of the tool-chain, scripts were created that generate latex tables and graphs from the results of the model. A set of selection functions was created as part of this research, to allow for the swift generation of output tables and graphs.

7 Towards an OSA Model

In the previous section, a new modelling framework was introduced. To use this model for OSA diagnosis, this needs to be initialised with model parameters, which is done in this chapter.

In this section, both the building blocks and the structure of the model are described. Since this research focuses on diagnosis, first the building blocks for diagnosis of OSA are described. Next, the template for CPAP is described, followed by the general model structure that was used for this research.

7.1 Diagnosis Tests

This research uses multiple OSA diagnosis methods, and multiple OSA treatments. To model these, the model requires statistical parameters to represent them. These parameters are based on literature research, with, where required, estimations for parameters that cannot directly be taken from literature.

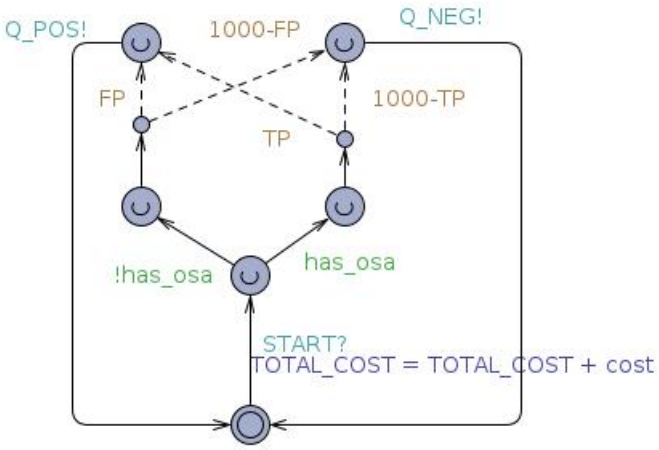

FIGURE 12: Example of a test setup.

Figure 12 shows the setup of a diagnosis test. These tests are modelled based on the sensitivity and specificity of the tests, which are taken from medical research. The automaton starts at the bottom state, by waiting for a signal on the 'START' channel. When it receives such a signal, it branches off based on whether the patient has OSA or not. Then, based on true positive and false positive rates the test randomly either results in a positive (Q_POS) or negative (Q_NEG) result. These channels are named starting with Q, because this automaton was lifted from a questionnaire template. Observe that the true positive rate is equivalent to sensitivity, and that the specificity is equivalent to 100

There are two types of diagnosis tests: AHI measurement options, and symptom detection options. Both of these categories have their subsection below.

7.1.1 AHI Measurement Options

The model is based on the traditional cohort of OSA patients. It was assumed that PSG is a gold-standard test. Since the statistics of the other methods are measured relative to PSG, the sensitivity and specificity of PSG were set to 100%. The rest of the parameters are based on literature research, and the values are in table 5. The waiting times are not based on literature research, but are based on the expertise of the sleep apnea experts that supervised this thesis.

It was assumed that PG and PSG have 95% success rate. For ODI, there was no data available that separated the Specificity from the failure rate. Therefore, the success rate for ODI was set to 100%, and the specificity was set to 50%. For PSG and PG it was assumed that it has a 5% chance of being inconclusive. In these cases, a PSG is needed to diagnose the patient.

Diagnosis	Success	Sensitivity	Specificity	Cost	Waiting Times	Sources
PSG	95	100	100	1250	90 to 120 days	Baseline
PG	95	100	95	650	5 to 14 days	Baseline
ODI	100	100	50	120	0 to 10 days	[15]

Table 5: Statistical parameters for AHI measurement options

7.1.2 Symptom Measurement Options

As seen in the chapter about OSA, questionnaires can be used in the diagnosis of OSA. The sensitivity and specificity of such questionnaires has been researched before. Table 6 lists sensitivity and specificity numbers for questionnaires, which are taken from that research.

Questionnaire	Sensitivity	Specificity	Cost	Waiting Time	Sources
Anamnesis	100	40	350	7 to 14 days	Baseline
BerlinQ	46	70	0	0 days	[32]
StopBang	88	42	0	0 days	[9] [32]
PhillipsLow	78	70	0	0 days	[13]
PhillipsHi	33	95	0	0 days	[13]

Table 6: Statistical parameters for Symptom measurement options

7.1.2.1 Three-level Phillips Questionnaire Beyond a positive-negative differentiation, the Phillips questionnaire can also be used with three levels of result (high/medium/low risk of OSA) [13]. The patient fills in the questionnaire as normal. If the patient scores too low to test positive on the low-threshold set-up of the Phillips questionnaire, the test results in a negative result (NEGATIVE). If the patient scores above the threshold for the low-threshold Phillips questionnaire, but below the threshold for the high-threshold Phillips Questionnaire, the patient scores a medium result (MAYBE). If the patient also scores above the threshold for the high-threshold Phillips questionnaire, the patient scores a positive result (POSITIVE). This test has as it's unique feature that the patients with a low to medium risk of OSA can be given a

different diagnostics process, compared to patients who, based on their questionnaire result, have a higher risk of having OSA.

7.1.2.2 ODI or Phillips Fabius et al [14] suggest a strategy based on ODI and the Phillips Questionnaire. The strategy brought forward in this paper is that the patient gets referred for further diagnosis or treatment if the patient either has a positive score from an ODI measurement, *or* a positive score from a Phillips Questionnaire. Instead of using the definition that the patient needs both to continue, this research states that either is sufficient to consider continuing the diagnosis process.

7.2 Modelling CPAP

CPAP is used as the primary type of treatment in this research. The most important factors in modelling CPAP are costs, conformation to treatment and odds of CPAP being the right treatment for the patient.

The assumption was made that the CPAP used is an automated titration machine that can give results to the medical professional that assists the trial period of CPAP. Therefore, the medical professional can read out data on the usage of CPAP, and on the AHI of the patient during usage. This means that the medical professional gets objective insight in whether the treatment worked. This, combined with the patient's experiences, can give a precise insight in whether the patient is helped with using CPAP, and means that the CPAP can be used to diagnose whether the patient has OSA, or at least to verify the assessment that the patient is helped with CPAP.

The assumption is made that this detection of the usefulness of CPAP will not falsely report that CPAP worked, nor will it falsely report that CPAP doesn't work. If a patient has OSA, CPAP will either work, or be rejected. If a patient doesn't have OSA, CPAP either doesn't work, or it will be rejected. Based on literature research, therapy acceptance is set to be 70%. Table 7 shows the statistical parameters that were used for CPAP. These parameters are based on expert consultation.

Property	**Value**
Acceptance	70%
Detected Rejection	70%
Cost for trial period	350 €
Trial period length	2 months
Waiting Time	21 to 30 days

Table 7: Statistical parameters for CPAP

Figure 13 (next page) shows the UPPAAL template for the CPAP treatment. First, the model differentiates between patients with OSA, and those without. Then, based on the data from table 7, the patient either accepts CPAP forever, the CPAP yields a negative result (which is due to the patient not benefiting from CPAP), or the CPAP fails to be effective, without any knowledge on whether the patient would have benefited from CPAP or not. In the simulation models in the next section, there is no differentiation between a negative and a failed result.

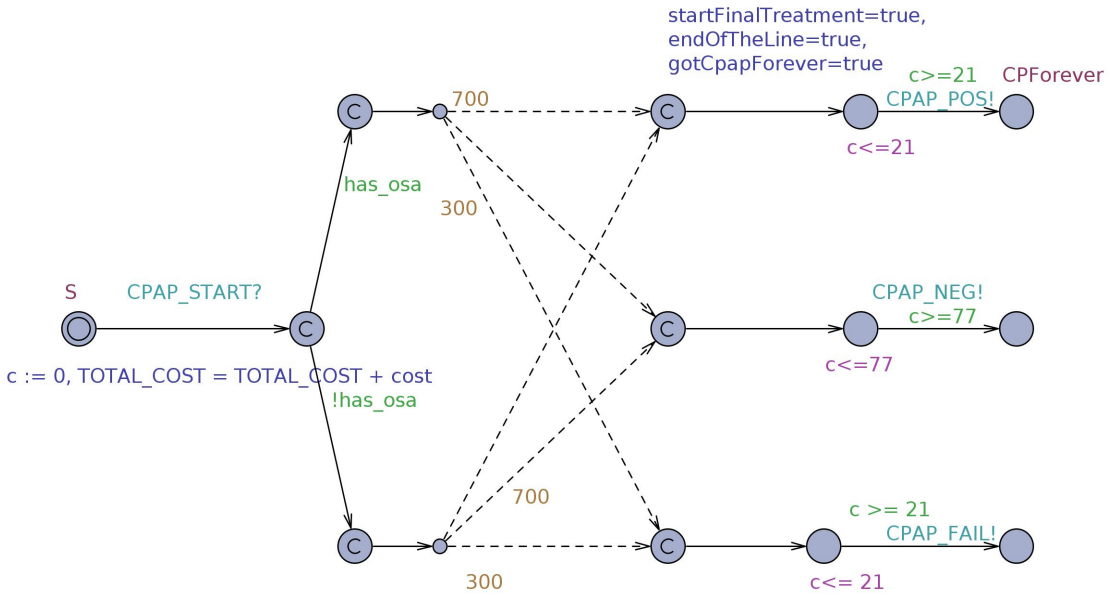

FIGURE 13: CPAP treatment model.

7.3 UPPAAL Model Structure

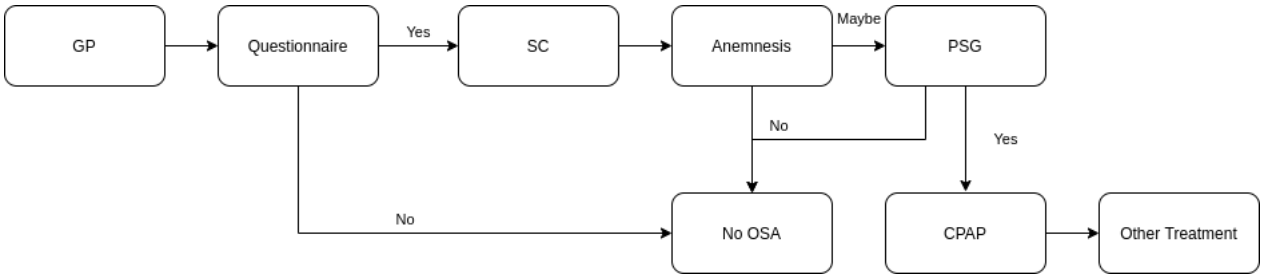

FIGURE 14: Example of diagnosis strategy: Model of Hard Filter Approach.

The model is based on two levels of abstraction: GP/Sleep Centre Level and test / treatment level. Figure 14 shows a diagnosis strategy, in abstract. Here, the GP and Questionnaire states are a part of the GP's responsibility, and SC, Anamnesis, PSG and CPAP are the Sleep Centre's responsibility.

For the diagnosis strategies in this thesis, the diagnosis process always starts at the GP. Depending on the strategy, more or less of the diagnosis strategy is done by the GP, before the patient gets referred to a Sleep Centre. In general, steps taken by the GP are less expensive than those taken by the Sleep Centre.

In cases where the diagnosis is unclear, the patient needs to be referred to the Sleep Centre, regardless of what steps the GP is taking. The Sleep Centre is assumed to always take the same steps, regardless of what the GP does.

7.3.1 Sleep Centre Model

In this section, the medical protocol of the sleep centre is described. It is assumed that first a medical history of the patient is taken, to assess whether it is likely that the patient has OSA. If it is deemed unlikely, then the patient receives a negative diagnosis for OSA, without any further testing being required. If suspicion of OSA remains, then the patient receives either a PSG or a PG.

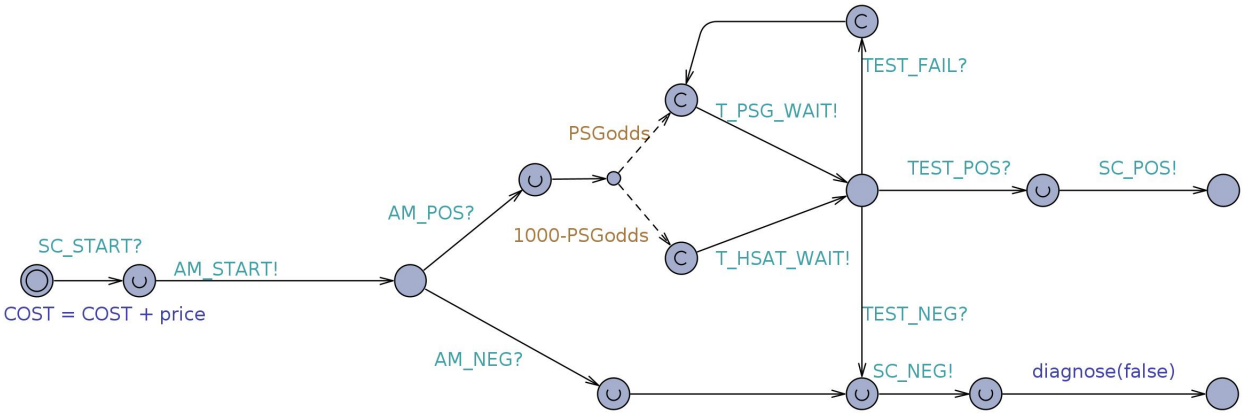

FIGURE 15: Sleep Centre Model.

Figure 15 shows a cleaned-up version of the template used for modelling the Sleep Centre. It was altered to improve the legibility of the model. Omitted are the administrative steps after the sleep centre has given a positive diagnosis. The model functions as follows:

1. The patient arrives at the sleep centre; this is modelled by receiving a signal on the SC_START channel.
2. Costs are incurred for arriving at the sleep centre, and a medical history is taken (Anamnesis; AM_START).
3. If the Medical History gives no indication of OSA, the model moves on towards the branch where a negative diagnosis is emitted (SC_NEG), and the diagnosis variable is set to false.
4. If the Medical History gives some indication of OSA, the patient receives a sleep test.
5. Randomly, the patient either gets assigned PG or PSG. These odds are a model-parameter; in most in this research it is assumed that 70% of cases initially receive PG.
6. If the test is positive, give a positive diagnosis.
7. If the test is negative, give a negative diagnosis.
8. If the test has failed, give the patient a PSG and assess the results of this retried PSG. This repeat at failure happens until the patient receives either a positive or negative diagnosis.

8 Analysis of Diagnosis Strategies

In the previous sections, the ground work for a model of OSA diagnosis was described, and a methodology for modelling OSA diagnosis was given. In this chapter, this is combined and used to model and analyse a set of diagnosis strategies for OSA. Nine strategies were modelled, spread over five categories:

1. Traditional Approaches: This category has one model, which represents the current diagnosis strategy for OSA in the Netherlands.
2. CPAP First: This category has two models, which are based on the idea that CPAP can be used as a diagnosticum.
3. Questionnaires as Hard Filter: This category has two models, based on the idea of limiting the number of patients that end up at the Sleep Centre, based on a questionnaire.
4. Questionnaire as Fast Track: This category has three models. These are based on the idea of short-cutting the sleep centre if the patient has symptoms and a positive questionnaire.
5. Ultra-Inexpensive : This category has one approach, which is a hard-filter approach that only uses the Sleep Centre in rare cases. This approach is intended as the least expensive conceivable approach.

The goal of the nine strategies is to pick some options for further analysis. These options will be further explored in the next chapter.

8.1 Definitions of Output Parameters

In this chapter, multiple diagnosis strategies are compared. To compare these strategies structurally, a set of results was defined. The names of these results, with their definition, is given in table 8. The total costs and total on CPAP are based on a population of 70 000 patients, which is a rounded estimate of the number of patients that the GP refers for OSA diagnosis, per year. These numbers thus give a rough estimate of the total size of OSA diagnosis, as well as the number of patients treated.

Result	**Description**	Unit
Sensitivity	Sensitivity of Diagnosis Process	%
Specificity	Specificity of Diagnosis Process	%
CPAP Forever	Patients that get CPAP as final treatment	%
Percentage Other Treatment	Patients that are diagnosed positive, but don't get CPAP	%
Time to Diagnosis	Time from start of the process till diagnosis of OSA	days
Time to CPAP Forever	How long did it take to get to CPAP, if the patient accepted?	days
Cost per Diagnosis	Cost per patient	€
Cost per Treatment	Cost per patient, divided over patients that receive treatment	€
Total Cost	Cost times number of patients	€
Total on CPAP	Number of patients that end up on CPAP	patients

Table 8: Description of the definitions of model results.

8.2 Model of the Traditional Approach

In this section, the traditional OSA diagnosis approach is described, and simulation results are presented.

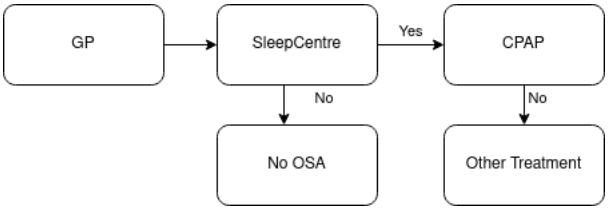

FIGURE 16: Model of Traditional Approach.

In figure 16, an abstract representation of the steps of the traditional approach is displayed. This approach has the GP refer all patients to the sleep centre. If the Sleep Centre considers the patient to have OSA, the patient receives CPAP. If the CPAP then doesn't succeed, the patient receives another treatment.

In table 9, the numerical results for this method are shown. The sensitivity and the specificity of this method are both very high; 100% and 98% respectively. Note that the percentage of CPAP, in this case, is equal to the maximum percentage of CPAP patients. This is caused by the incidence of OSA in the model (57%), combined with the CPAP adherence (set at 70%). The maximum number of patients that stay on CPAP is equal to these two numbers multiplied by each other.

Result	**Value**	
Sensitivity	100	%
Specificity	98	%
CPAP Forever	40	%
Percentage other treatment	17	%
Time to Diagnosis	41	Days
Time to CPAP Forever	79	Days
Cost per Diagnosis	1170	€
Cost per Treatment	2900	€
Total Cost	81 700 000	€
Total on CPAP	28000	Persons

TABLE 9: Results of the traditional approach.

8.3 CPAP as Diagnosis

In earlier phases of the research, the option for using CPAP as a diagnosticum was also considered. This was done, because the idea was of interest, and it is also in line with what Catalyn Rus has researched during his Bachelor thesis. These strategies are copied directly from Catalyn Rus' thesis. These methods are included, because this way they are researched using the same methodology as the scenarios introduced newly in this research.

In the end, this approach was not pursued further for this research, because the approach differs so much from the traditional approach that it was considered unlikely to be implemented in practice. There are also practical issues with this approach. For instance, the idea that a patient would take a treatment for the rest of their life, because of filling in a questionnaire and scoring positive, sounds unlikely.

8.3.1 CPAP First

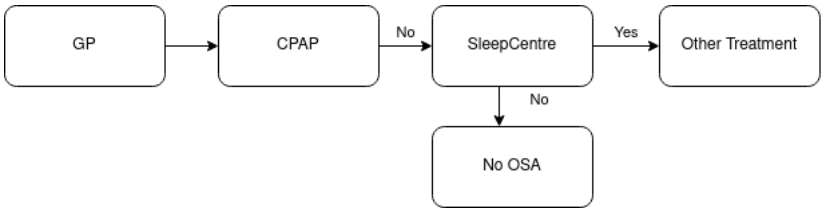

FIGURE 17: Model of CPAP First Approach.

This diagnosis strategy is displayed in figure 17. In this diagnosis strategy, CPAP is given as soon as the GP has suspicion that the patient may have OSA. This means that, if the patient would have gotten a referral to the sleep centre in the traditional approach, the patient now receives a CPAP instead. This method is intended to illustrate the range of possible diagnosis strategies. Since this method does not come to a diagnosis before starting treatment, it may not fit well with evidence-based medicine.

The results of this diagnosis method are given in table 10. Observe that the average time to diagnosis here is more than double that of the traditional model (83 days instead of 41 days). This is caused by the fact that over half of all patients either do not have OSA, or do not respond positively to CPAP. In all these cases, diagnosis will only be reached after both a trial period with CPAP and after waiting for the sleep centre. For the patients who end up on CPAP though, the waiting time of this strategy is at the absolute minimum, because they get treatment right away.

The results show that this flow results in the same sensitivity and specificity, and thus patient numbers, while having much lower total costs, showing the potential of this method.

Result	**Value**	
Sensitivity	100	%
Specificity	99	%
CPAP Forever	40	%
Percentage other treatment	18	%
Time to Diagnosis	83	Days
Time to CPAP Forever	26	Days
Cost per Diagnosis	826	€
Cost per Treatment	2100	€
Total Cost	57 800 000	€
Total on CPAP	28000	Persons

TABLE 10: Results of the CPAP-first approach.

8.3.2 Questionnaire then CPAP

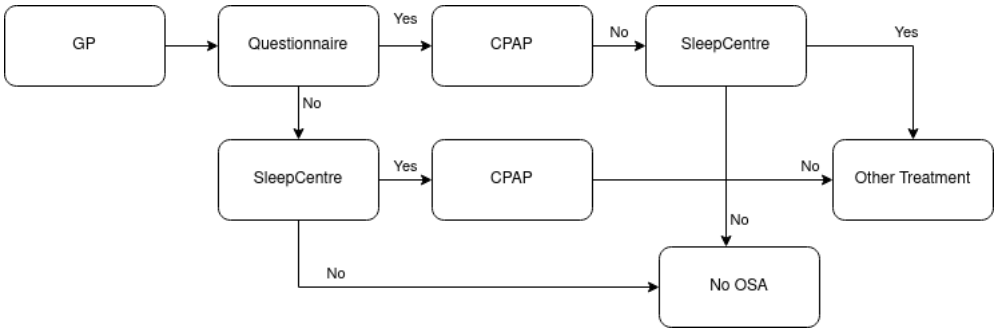

FIGURE 18: Model of CPAP after Questionnaire Approach.

In this approach, the GP has more responsibility. Instead of merely giving a CPAP, the GP has the patient take a questionnaire first. If the questionnaire result is positive, the patient receives a CPAP, continuing the same way as the previous approach. If the questionnaire yields a negative result, the patient follows the traditional approach instead, and is referred to the Sleep Centre.

In table 11, the results of this method are displayed. The columns are labelled for the four different questionnaires that were selected for modelling in this thesis. The sensitivity and specificity are again at their maximums. This is as expected, because in this strategy the patient always visits the sleep centre before a negative diagnosis is given.

The questionnaires with a higher sensitivity (StopBang, Phillips Low) result in an increased Time to Diagnosis, but a decreased time to treatment, and a decreased cost. This is caused by the fact that patients that score positively on the questionnaire are tested by giving the patient a trial treatment, whereas the other patients are referred to the Sleep Centre. Since CPAP requires a two month trial period before the results are in, this means that the Sleep Centre is quicker at giving a diagnosis. Naturally, not having to wait for the sleep centre causes a lower time to treatment.

Result	**Value**				
Scenario	BQ	SB	Phillips Low	Phillips High	
Sensitivity	99	100	100	99	%
Specificity	99	99	99	99	%
CPAP Forever	40	40	40	40	%
Percentage other treatment	17	17	17	17	%
Time to Diagnosis	54	67	60	47	Days
Time to CPAP Forever	54	32	36	52	Days
Cost per Diagnosis	1020	824	836	937	€
Cost per Treatment	2600	2100	2100	2300	€
Total Cost	71 300 000	57 700 000	58 500 000	65 600 000	€
Total on CPAP	28000	28000	28000	28000	Persons

TABLE 11: Results of the Q then CPAP Approach.

8.4 Hard Filter Approaches

The hard filter approaches are characterised by the GP administering extra tests to the patient, before the patient is referred to the Sleep Centre. These approaches are named as hard filter approaches in this report, because they add an extra filtering stage to the diagnosis process, before continuing with the traditional approach. Two hard filter approaches are modelled in this research. Firstly, a questionnaire is applied as a hard filter. Secondly, the patient was referred for further diagnosis if either a questionnaire, or an ODI measurement showed that the patient potentially had OSA.

8.4.1 Questionnaire Only

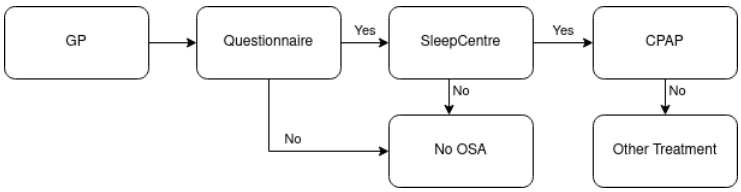

FIGURE 19: Model of Hard Filter Approach.

The first hard filter approach has the patient take a questionnaire at the GP. If the questionnaire is positive, the diagnosis strategy continues in the same way as the traditional approach. However, if it fails, the GP concludes that the patient has no OSA. Figure 19 describes the flow of this approach; table 12 shows the results.

Result	**Value**				
Scenario	BQ	SB	Phillips Low	Phillips High	
Sensitivity	46	88	80	50	%
Specificity	100	99	100	100	%
CPAP Forever	18	35	32	20	%
Percentage other treatment	8	15	14	9	%
Time to Diagnosis	17	33	28	16	Days
Time to CPAP Forever	80	79	79	79	Days
Cost per Diagnosis	522	943	822	472	€
Cost per Treatment	2900	2700	2600	2400	€
Total Cost	36 600 000	66 000 000	57 500 000	33 100 000	€
Total on CPAP	13000	24000	22000	14000	Persons

TABLE 12: Results CPAP after Q Approach.

The sensitivity is shown to be equal to the sensitivities of the questionnaires, as shown in table 6. The specificity is maximal. This shows that, as expected, adding a filtering step to the start of the diagnosis process negatively impacts the total sensitivity, but maintains (or improves) specificity.
The percentage of patients receiving treatment is much lower in this approach, compared to the traditional approach. This also directly results in a lower number of total patients, especially for the BerlinQ and Phillips High questionnaires, which has lower sensitivity. The cost per treatment is lower than that of the traditional approach, but not by much.

8.4.2 Questionnaire OR ODI

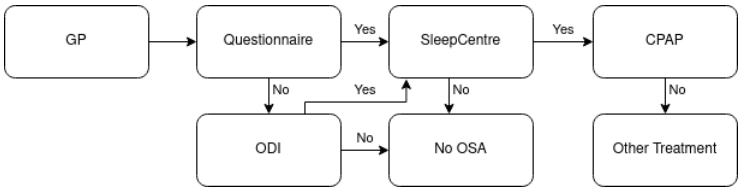

FIGURE 20: Model of Conditional Track Approach with either questionnaire or ODI positive as a condition for SC.

In the diagnosis scenarios of the first hard-filter approach, the diagnosis sensitivity dropped. In this strategy, a variation is made to the first approach, in an attempt to mitigate this drop in sensitivity. This method was inspired by Fabius et al [15].

This diagnosis strategy has the GP give the patient a questionnaire, and an ODI measurement. If either of the two is positive, the patient is referred to the sleep centre for further diagnosis. If none of the two is true, the patient is said to have no OSA. Since it was assumed in this research that ODI measurement is highly sensitive, the sensitivity of this method should therefore be high again.
Figure 20 shows the method, and the results are in table 13.

Result	**Value**				
Scenario	BQ	SB	Phillips Low	Phillips High	
Sensitivity	100	99	100	99	%
Specificity	99	99	99	100	%
CPAP Forever	40	40	40	40	%
Percentage other treatment	17	17	17	17	%
Time to Diagnosis	31	30	31	31	Days
Time to CPAP Forever	71	69	69	71	Days
Cost per Diagnosis	1170	1140	1130	1130	€
Cost per Treatment	3000	2900	2800	2800	€
Total Cost	82 200 000	79 800 000	79 200 000	78 800 000	€
Total on CPAP	28000	28000	28000	28000	Persons

TABLE 13: Results of the Hard Filter Either Q or ODI approach.

When comparing this method to the traditional approach, most statistics are very similar. For BerlinQ the costs are mildly higher, for the other questionnaires the costs are mildly lower. However, this is ten days quicker on average. This shows that this method gives the same results, for the same costs, but in less time.

8.5 Questionnaires as Fast Track

This category of diagnosis strategies is characterised by keeping the traditional approach as a fall-back diagnosis strategy. This means that, instead of giving a negative diagnosis after a questionnaire, or ODI measurement gives a negative result, the patient gets sent to a Sleep Centre to verify the diagnosis. In case of a positive diagnosis based on the inexpensive diagnosis path, the patient directly receives CPAP. The idea is that this approach does not result in lower sensitivity, but the number of patients at the Sleep Centre is lowered.

8.5.1 Two Level Questionnaire

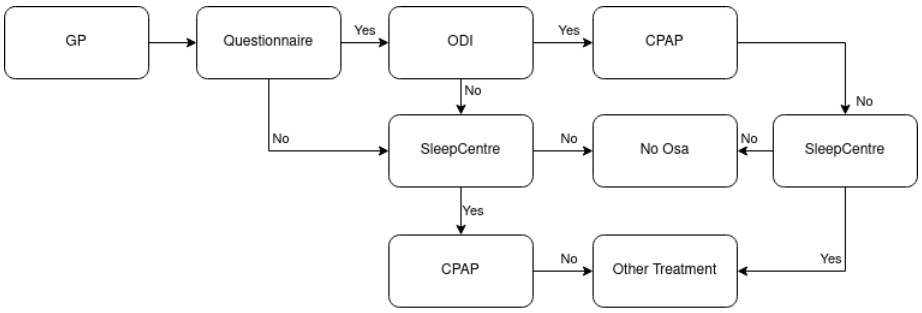

FIGURE 21: Model of Fast Track Approach with Two Level Questionnaire.

This diagnosis strategy uses a questionnaire, in combination with ODI measurement as a fast track for patients. If either of these does not yield a positive diagnosis, the patient is referred to the sleep centre for further diagnosis. Figure 21 describes this approach; table 14 gives the results of this approach.

Result	**Value**				
Scenario	BQ	SB	Phillips Low	Phillips High	
Sensitivity	100	100	100	100	%
Specificity	84	70	79	94	%
CPAP Forever	40	40	40	40	%
Percentage other treatment	19	21	20	18	%
Time to Diagnosis	20	11	13	20	Days
Time to CPAP Forever	51	35	38	49	Days
Cost per Diagnosis	905	610	661	852	€
Cost per Treatment	2300	1500	1700	2100	€
Total Cost	63 400 000	42 700 000	46 300 000	59 700 000	€
Total on CPAP	28000	28000	28000	28000	Persons

TABLE 14: Results of the Fast Track Approach with Two Level Questionnaire.

The sensitivity of this method is at maximum, but the specificity is lower. This is caused by the lower specificity of the Questionnaire and ODI measurement, compared to the Sleep Centre. This results in false-positive diagnoses. Also visible is that StopBang and Phillips Low, the questionnaires with the highest sensitivity (and lowest specificity) are less expensive, but also have a lower specificity, causing more patients to needlessly get a CPAP. If this is acceptable, then this approach is a good candidate.

8.5.2 Three-level Phillips

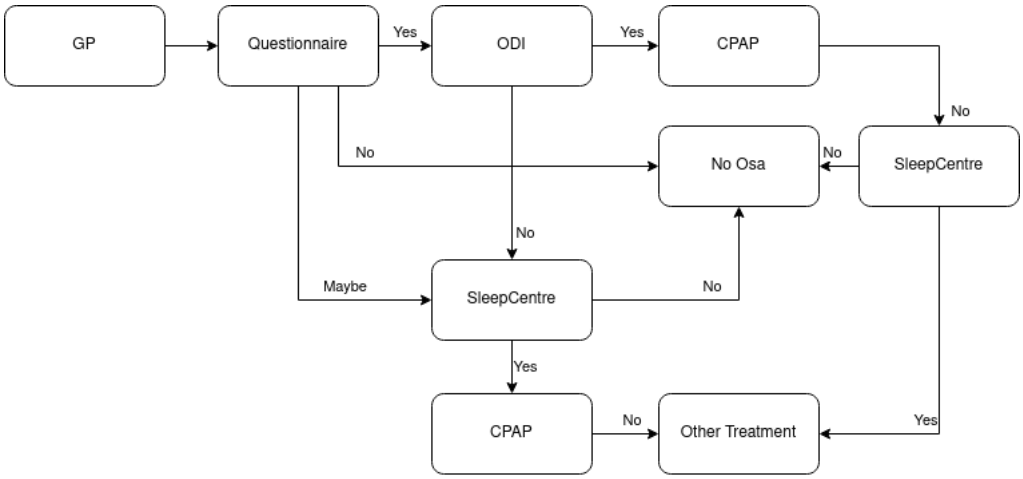

FIGURE 22: Model of Fast Track Approach with Three Level Questionnaire.

This approach utilises the three-level Phillips Questionnaire. This questionnaire either considers a patient highly likely, medium likely, or unlikely to have OSA. In this approach, if the patient receives a 'highly likely' result, the patient gets an ODI test, in the same way as the previous fast-track approach. If the patient is considered medium likely to have OSA, the patient is sent to the Sleep Centre, just like in the traditional approach. If the patient is considered unlikely likely to have OSA, the patient receives a negative diagnosis at that very moment. Figure 22 describes this approach; table 15 gives the results of this approach.

Result	**Value**	
Sensitivity	80	%
Specificity	94	%
CPAP Forever	32	%
Percentage other treatment	5	%
Time to Diagnosis	13	Days
Time to CPAP Forever	45	Days
Cost per Diagnosis	509	€
Cost per Treatment	1600	€
Total Cost	35 600 000	€
Total on CPAP	22000	Persons

TABLE 15: Results of the Three Level Approach.

Compared to the traditional approach, this method is much less expensive. Indeed, this method is among the least expensive methods, when considering total costs. However, sensitivity drops down to 80%, meaning that fewer patients receive a diagnosis. The cost and waiting time are significantly lower. The cost per diagnosis is similar to the previous fast-track approach, when using StopBang.

8.5.3 Questionnaire or ODI as Fast Track

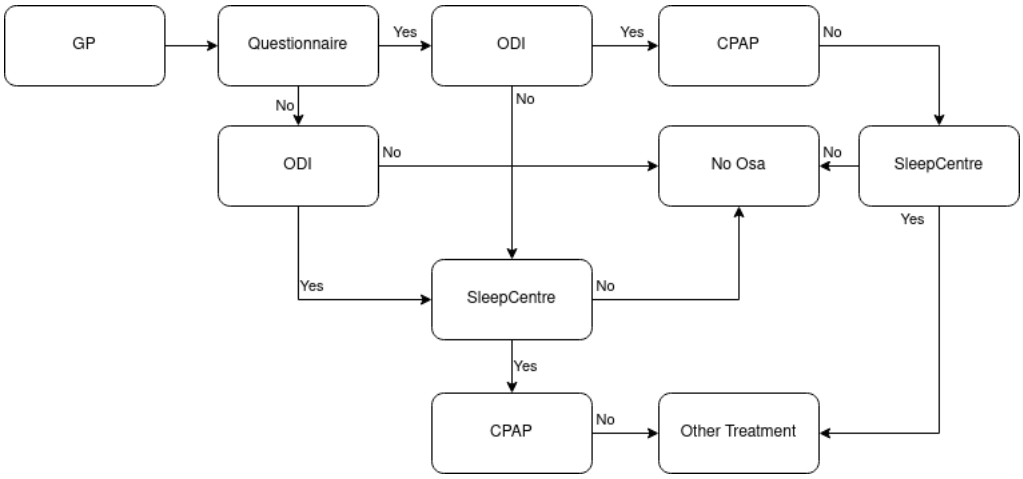

FIGURE 23: Model of a hybrid of a Fast Track and a Hard Filter, based on Questionnaire and ODI.

As a third and final medical strategy in the fast-track category, again the combination of ODI measurement and a Questionnaire is used to diagnose the patient. This strategy uses the diagnosis method as introduced by Fabius et al. in 2019 [15]. In this strategy, the patient always receives both. Figure 23 shows this strategy. The result of the questionnaire and ODI together are translated into a decision as follows:

1. If both ODI and Questionnaire are positive, the patient is fast-tracked to CPAP Treatment.
2. If one of the two is positive, the patient gets referred to the sleep centre.
3. If neither of the two is positive, the patient gets a negative diagnosis.

Result	**Value**				
Scenario	BQ	SB	Phillips Low	Phillips High	
Sensitivity	100	100	100	100	%
Specificity	85	71	79	95	%
CPAP Forever	40	40	40	40	%
Percentage other treatment	17	17	17	17	%
Time to Diagnosis	21	11	13	20	Days
Time to CPAP Forever	54	36	39	52	Days
Cost per Diagnosis	990	789	806	921	€
Cost per Treatment	2500	2000	2000	2300	€
Total Cost	69 300 000	55 200 000	56 400 000	64 400 000	€
Total on CPAP	28000	28000	28000	28000	Persons

TABLE 16: Results of the Fasttrack Either Q or ODI approach.

In table 16, the results of this diagnosis strategy are displayed. Again, as with the previous fast-track options, the sensitivity is maximal, but the specificity drops. The number of patients receiving treatment does not drop for this approach, when compared to the traditional approach. This approach is also very fast, giving diagnoses in between 11 and 21 days. Total costs, as well as costs per diagnosis are significantly lower than with the traditional approach.

These results show that this approach has merit, and should be looked into further.

8.6 Ultra-Inexpensive

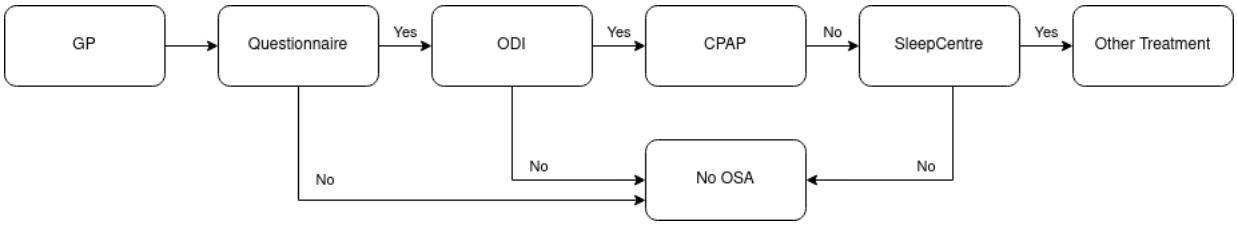

FIGURE 24: Model of Inexpensive Approach.

In this approach, any and all expensive steps are omitted for the primary diagnosis path. As a replacement for the Medical History (Anamnesis), a questionnaire is given, and as a replacement for the PSG, an ODI measurement is taken. This means that the diagnosis of OSA in this approach is as inexpensive as possible. The results of this method are shown in table 17. The results show that the total costs again go down if the questionnaire is less sensitive. This is caused by the fact that false-negatives can result in lower total costs. The StopBang method is the most expensive, but also results in the highest number of patients treated.

This method has a lower sensitivity than the fast-track options, because patients are sent home after a negative questionnaire result. However, this does result in a lower total cost. Since this diagnosis strategy has a low time to diagnosis, and relatively low costs, this diagnosis strategy was also chosen to be analysed further.

Result	**Value**				
Scenario	BQ	SB	Phillips Low	Phillips High	
Sensitivity	46	88	80	50	%
Specificity	85	71	80	95	%
CPAP Forever	18	35	32	20	%
Percentage other treatment	8	15	14	9	%
Time to Diagnosis	2	4	3	2	Days
Time to CPAP Forever	31	31	31	31	Days
Cost per Diagnosis	327	573	486	264	€
Cost per Treatment	1800	1600	1500	1300	€
Total Cost	22 900 000	40 100 000	34 000 000	18 500 000	€
Total on CPAP	13000	25000	22000	14000	Persons

TABLE 17: Results of the Ultra-Inexpensive approach.

9 Comparisons of OSA Diagnosis Strategies

In this section, a more advanced comparison is made of a selection of diagnosis strategies. The selected strategies are displayed in table 18. For each of the strategies, one questionnaire was selected, based on which questionnaire fit best with the reason the strategy was included. Here, the Hard-Filter Approach is listed as easy to implement, because it merely requires altering when the GP refers patients to the Sleep Centre. The other alternatives included require that more alterations are made to the protocols. In the other alternatives, some patients are not referred to the sleep centre for diagnosis, instead having the GP directly refer some of the patients for treatment. In the case of the ultra-inexpensive the sleep centre is only ever used after CPAP, if the CPAP is unsuccessful. Such changes can bring larger change, but these changes also require more alterations to the entire OSA diagnosis and treatment chain.

Strategy	Questionnaire	**Reason for Selection**
Traditional Approach	-	Contemporary option
Hard Filter Approach	Stop-Bang	Inexpensive and easy to implement
Fast Track Two Level Approach	Stop-Bang	Inexpensive, high sensitivity
Fast-Track Either Q or ODI Approach	Phillips High	Mid-tier expensive, higher specificity
Ultra-Inexpensive Approach	Stop-Bang	Least expensive approach.

Table 18: Strategies chosen for further analysis

The goal of this section is to provide insight in how these alternatives compare. To this end, first, a direct comparison is made between the alternative diagnosis strategies, and the traditional approach. This comparison is done by first creating a plusses-minuses summary, to show where the diagnosis strategies have an edge over the traditional approach.
After the direct comparison, individual parameters of the model results were then iterated over, to assess how sensitive the results are to the parameters of the model.

Finally, the distribution of waiting times is compared for each of the diagnosis strategies selected for this chapter.

9.1 Direct Comparison of Represented Methods

In this section, the selected methods are compared directly, to assess how they function under different circumstances. Four alternatives to the contemporary approach are assessed by their modelling results. They are compared in three different ways:

1. Comparing how the new strategies compare to the traditional approach
2. Altering the percentage of patients that receive PSG, compared to PG.
3. Calculating what percentage of patients received a diagnosis after what time

9.1.1 Comparing the New Strategies to the Traditional Approach

Four alternatives were selected for further analysis, to compare these alternatives to the traditional approach. In this section, a summary is given on how these alternatives compare to the traditional approach. This summary is a direct translation of the results obtained in chapter 8. In table 19, a comparison is made between the four proposed

Result	**Value**			
Scenario	Hard Filter	Fast Track Two Level	Fast Track EitherOr	Ultra-Inexpensive
Sensitivity	-	=	=	-
Specificity	=	-	=	-
CPAP Forever	-	=	=	-
% other treatment	-	=	=	-
Time to Diagnosis	+	++	++	+++
Time to CPAP Forever	=	+	+	+
Cost per Diagnosis	=	++	+	+
Cost per Treatment	+	++	+	++
Total Cost	+	++	+	++
Total on CPAP	-	=	=	-

TABLE 19: Comparison of Alternatives, compared to Traditional Approach + means better, not higher, thus seeing a + in the cost column means the cost is lower.

alternatives to the traditional diagnosis method. The comparison is made by comparing for every result to the results of the traditional method. If the results are similar or the same, they are reported with =, + means a bit better, ++ means a lot better, - means a bit worse. This shows that two of the four methods do not lose any sensitivity, and therefore retain the same number of patients. It shows that the 'ultra-inexpensive' method scores worse than the others on nearly every aspect, except for cost and waiting time. This is expected, because the sensitivity of the questionnaire directly influences the maximum sensitivity of that scenario.

From this comparison, the Fast Track Two Level approach looks to be a great option.

9.1.2 PSG vs PG

Polysomnography and Polygraphy are both tests that assess the AHI of a patient, but these methods differ in price, waiting time and specificity. The precise parameters of PSG and PG are given in table 5. Since the decision on which percentage of patients is referred to either PSG or PG is a strategic decision, the consequences of this decision are important to analyse.

In this subsection, the selected strategies are compared for the full range of possible splits between PSG and PG, from 0% PSG and 100% PG to 100% PSG and 0% PG. The total costs are given are given in figure 25.

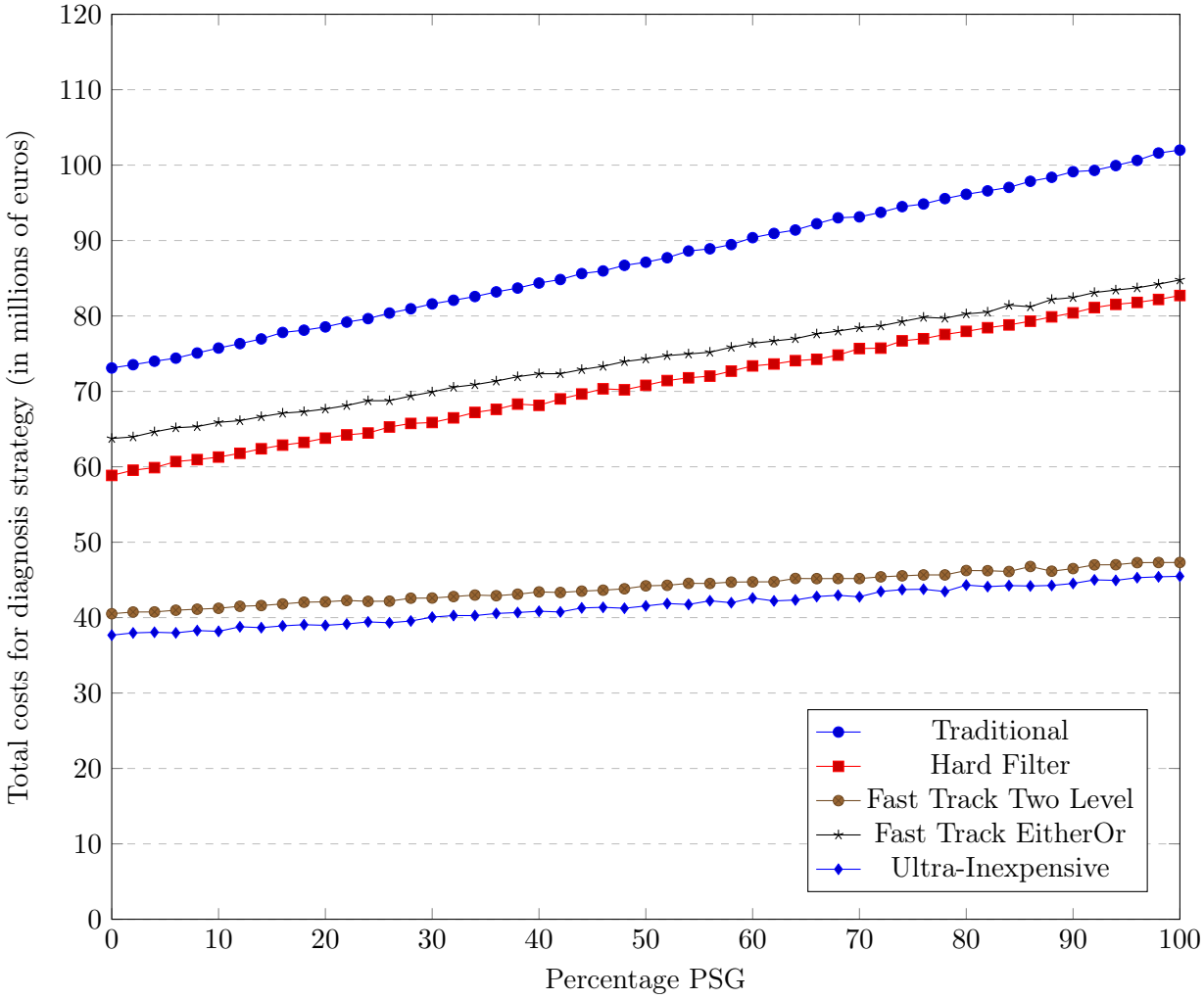

FIGURE 25: Comparison of costs increases per diagnostic strategy, based on the split between PSG and PG at the Sleep Centre.

The first thing that is visible is that the traditional approach, Fast Track EitherOr approach, and the Hard Filter approach yield a much higher total cost, no matter what percentage of patients receive PG. The Fast Track Two Level approach is very similar in cost to the Ultra-Inexpensive approach, with both of these methods having a much lower cost than the other methods.

In figure 26, the time to diagnosis is given for each of the diagnosis strategies. The

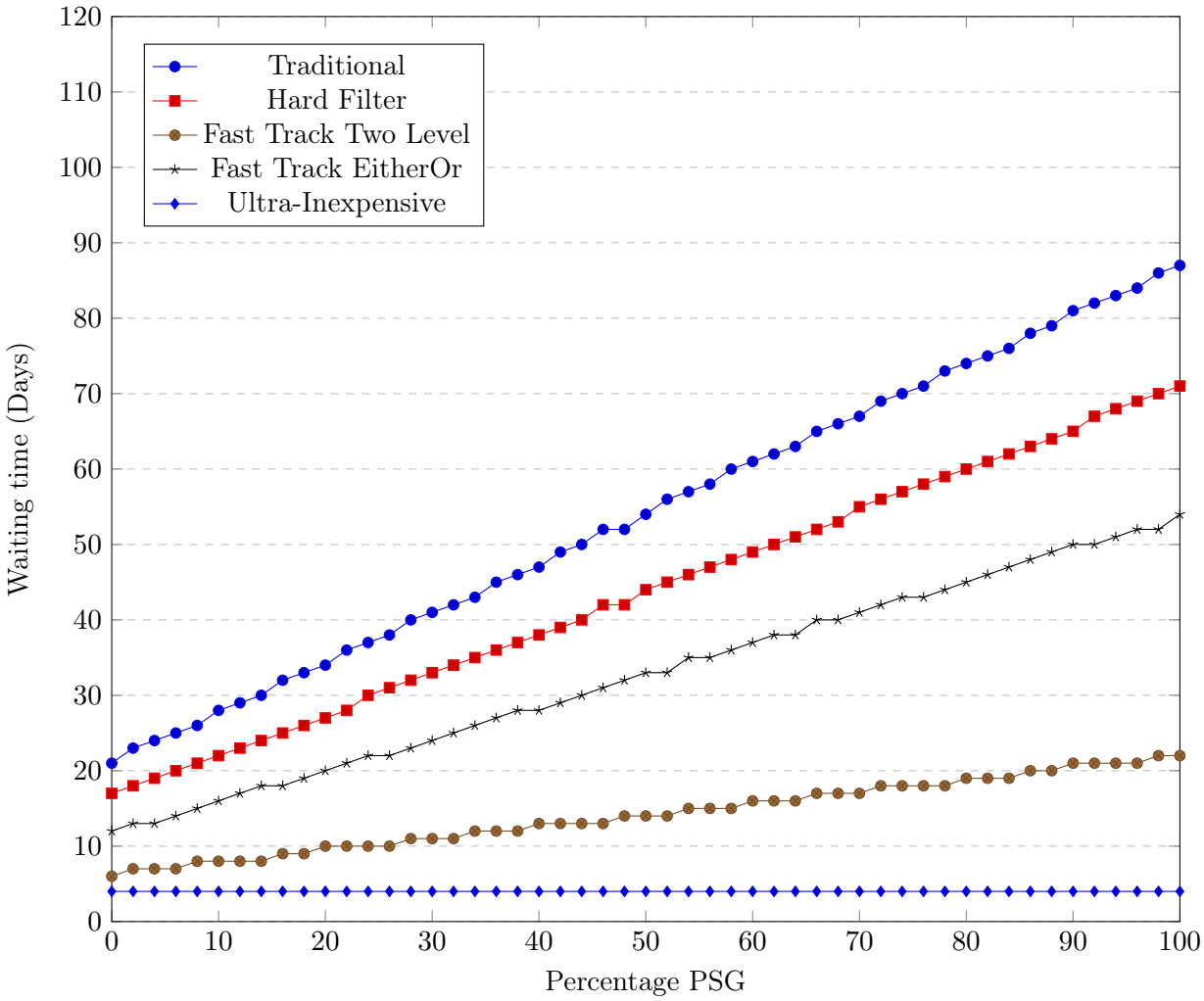

FIGURE 26: Comparison of time to diagnosis per diagnostic strategy, based on the split between PSG and PG at the Sleep Centre.

Ultra-Inexpensive option is the superior option here; this strategy starts at a very low waiting time, and remains there. The other methods have an increase in waiting time with an increased PSG percentage. Observe that the slope of the line is correlated to the percentage of patients that end up in the sleep centre. This shows that the Fast Track Two Level approach has a much lower number of patients that end up at the sleep centre.

This section shows that by using more PG instead of PSG, the waiting times of all approaches, including the traditional approach, can be kept under a month. Also, if all current PSG's would be replaced by PG's, this would save 12 million Euros on its own.

9.1.3 Analysis of the distribution of diagnosis timings

The time to diagnosis is an important property of a diagnosis strategy, and the average time to diagnosis was compared in previous sections. In this section, instead of looking at the average waiting time, the waiting time is given as a percentage of patients that received a diagnosis after a certain amount of time, in a graph. These graphs show how many patients receive a diagnosis quickly, and how many patients have to wait long.

In principle, this same method can be used for any numerical result, such as time to diagnosis, but also costs.

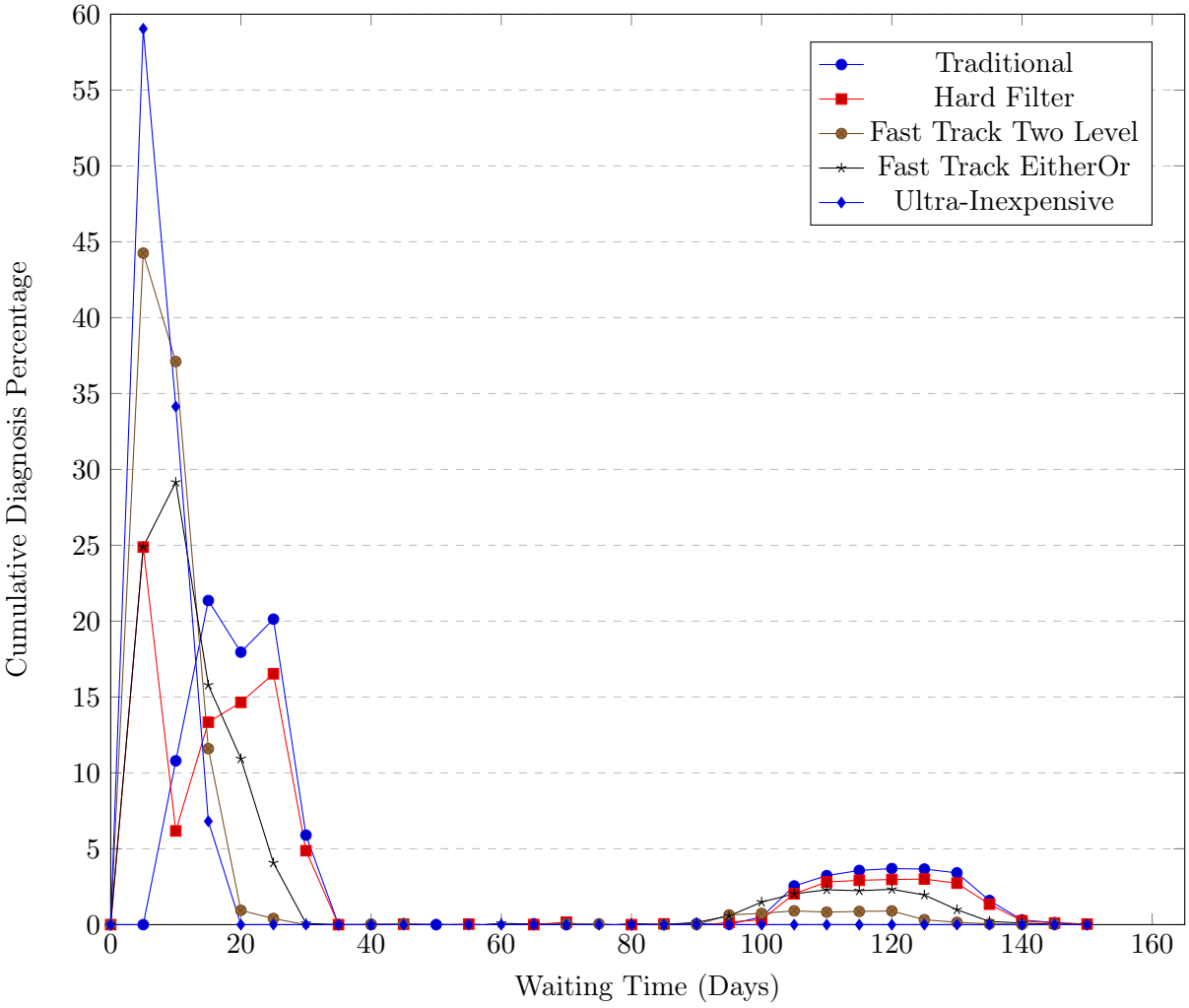

FIGURE 27: Percentage of patients receiving a diagnosis after waiting for a given amount of time.

In graph 27, the distribution of waiting times is shown. What can be seen is that all methods are quick to diagnose some of the patients. After this initial phase, no patients finish their diagnosis and treatment plan. This indicates that all patients that haven't had a diagnosis after that amount of time will have to wait for some time. This is caused by the fact that these patients are all waiting for getting a PSG.

This graph gives an interesting result: patients have to either wait less than 40 days, or more than 90. Therefore, an analysis was made between 40 days and 140 days.

Scenario	40 days		140 days	
	Finished	Correct	Finished	Correct
Traditional	76%	75%	98%	98%
Hard Filter	80%	73%	98%	91%
Fast Track Two Level	94%	81%	99%	86%
Fast Track Either Or	84%	82%	99%	96%
Ultra-Inexpensive	100%	80%	100%	80%

TABLE 20: Percentage of patients finished diagnosis after 40 and 140 days, per diagnosis strategy.

In table 20, the percentage of patients that have finished their diagnosis and treatment path after 40 and 140 days is given. This shows that the Ultra-Inexpensive method is much much faster than the alternatives, with patients never having to wait more than 40 days before treatment. This table also shows that no method can diagnose more than 82% of patients correctly within 40 days. However, eventually, the Fast Track EitherOr method approximates the traditional approach in the percentage of correct diagnoses.

This shows that after 40 days, the fast-track methods give a similar number of correct diagnoses, compared to the UltraInexpensive method, but the fast track methods give more correct diagnoses after 140 days.

9.2 Sensitivity Analysis

In the previous sections, diagnosis strategies were compared, and conclusions were drawn on how these strategies differ. To make these comparisons, parameters were chosen. In this section, the effects some of these model parameters have on the results is measured.

The following model parameters were assessed for sensitivity analysis:

1. Sensitivity and Specificity of ODI diagnosis
2. Number of Yearly Patients
3. OSA Incidence

The sensitivity and Specificity of the ODI test were chosen to be analysed, because the ODI replaces the PSG and PG in some scenarios. Therefore, the ODI test is a candidate for having a large impact on the quality of the diagnosis strategies.
The questionnaires were not analysed, because multiple questionnaires were already analysed, meaning that through the results for different diagnosis tests the sensitivity of these parameters was already covered. The number of yearly patients was chosen, because this gives an idea of what could happen to the total costs and number of treatments if the number of patients goes up.
The OSA incidence was chosen as a parameter to analyse, because this assesses how these strategies function in populations in which the incidence of OSA is different.

9.2.1 Sensitivity analysis of ODI parameter

ODI measurement is a part of the Fast-Track and Ultra-Inexpensive methods. It was assumed in the results above that ODI measurements have a sensitivity of 100%, and a specificity of 50%. In this section, the sensitivity, costs and time to diagnosis are analysed for ODI measurement sensitivity values between 50% and 100%.

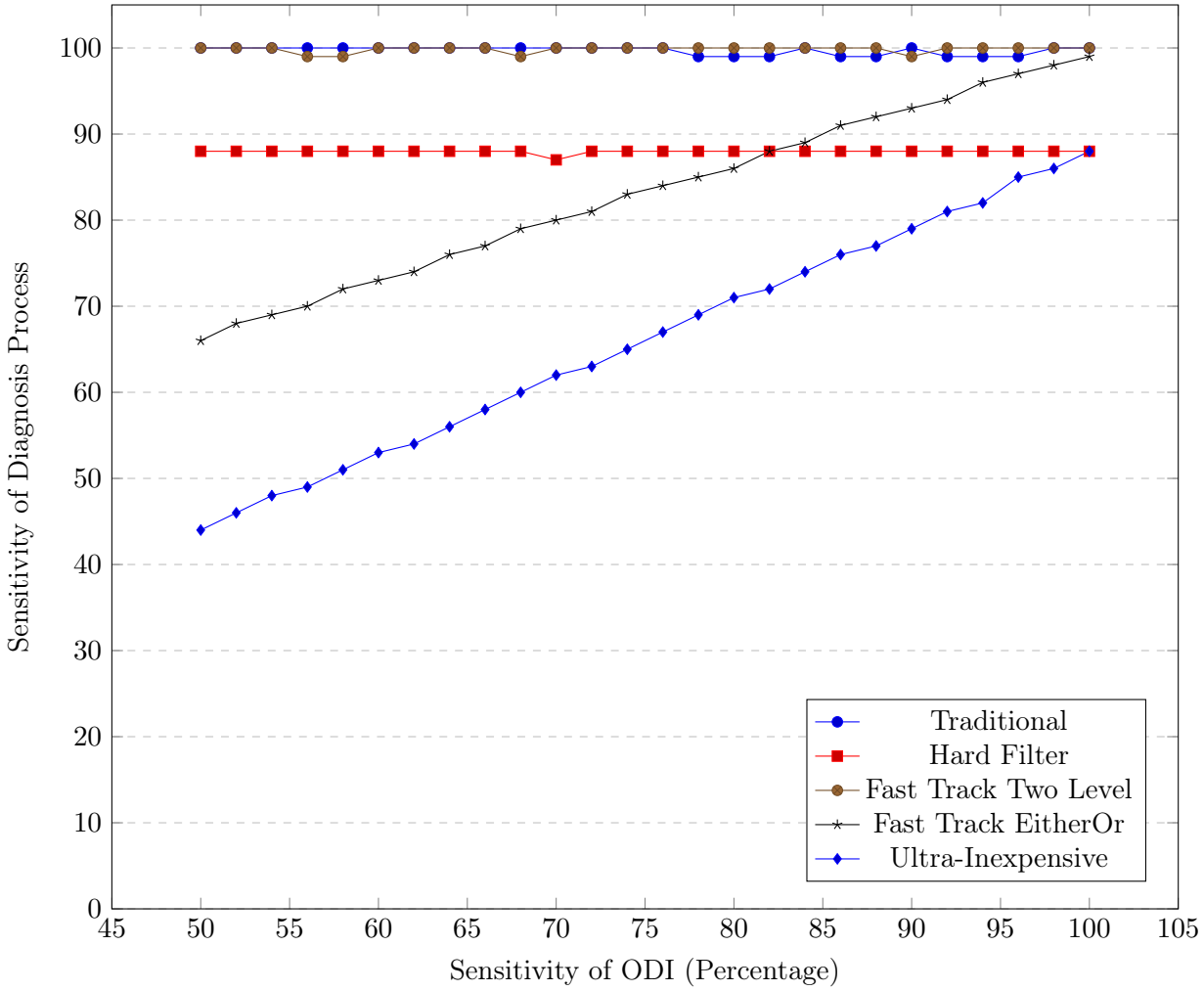

FIGURE 28: Comparison of sensitivity of diagnosis, based on input sensitivity of ODI.

In figure 28, the diagnosis sensitivity is shown for the five selected methods. This is done by simulating the selected methods for different ODI sensitivity. Visible is that the sensitivity of the Fast Track EitherOr, and Ultra-Inexpensive methods decreases with decreasing ODI measurement sensitivity.

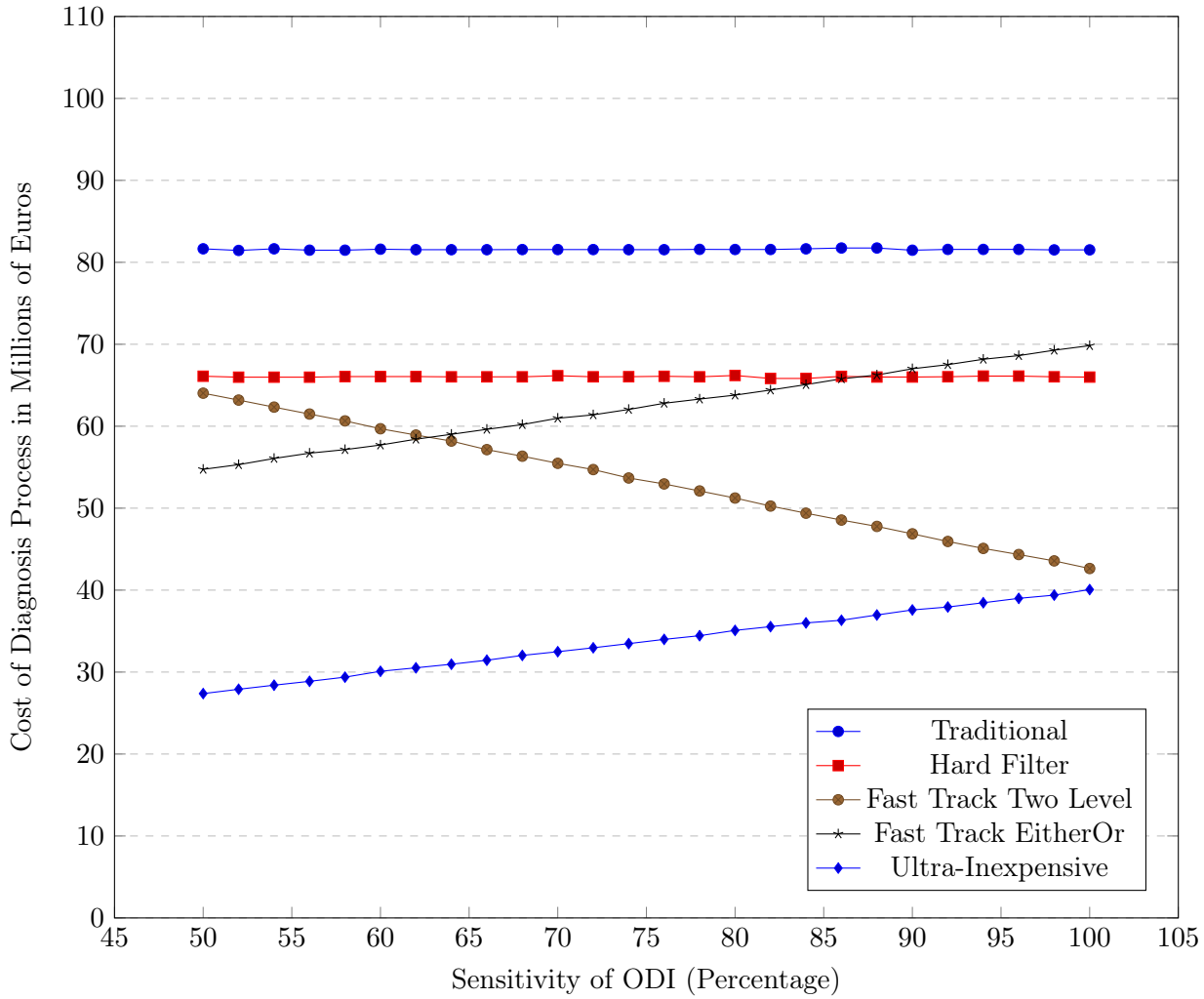

FIGURE 29: Comparison of total OSA Cost for new patients, per year, based on input sensitivity of ODI.

In figure 29 the total treatment costs are given, for assumed ODI sensitivity. The approaches that have a horizontal line are approaches that do not use ODI. The Fast Track Two Level approach is less expensive for increased ODI sensitivity. This is caused by the fact that if the ODI measurement is negative, this approach refers the patient to the Sleep Centre. The Fast Track EitherOR option becomes more expensive for increasing ODI measurement sensitivity. This is caused by the fact that this method was set up with a questionnaire with low sensitivity, and thus increased ODI sensitivity causes an increased number of patients getting a (true) positive result, and thus increased costs. Patients receiving a false-negative result from the ODI are likely to receive a false-negative diagnosis for OSA with this method, and therefore the costs for treatment and diagnosis stay low. This is not a desired outcome, unless lowering costs are more important than helping patients.

Finally, for the Ultra Inexpensive approach, the number of patients receiving treatment increases with the ODI measurement sensitivity, and therefore the costs increase. Again, the next graph, showing costs per treatment, will give more clarity.

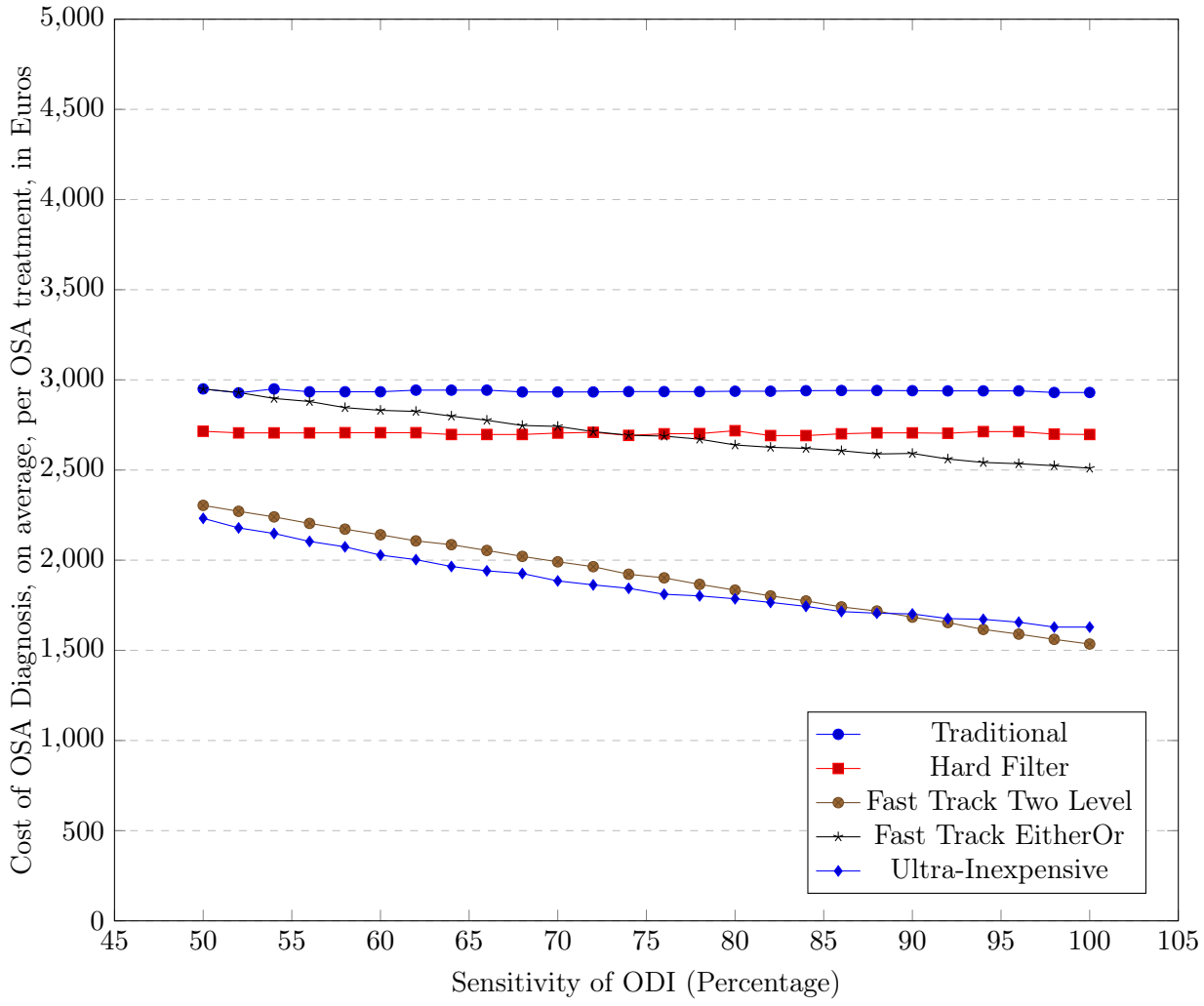

FIGURE 30: Comparison of total OSA Cost per treatment for new patients, per year, based on input sensitivity of ODI.

Figure 30 shows the average cost per treatment, graphed to sensitivity of ODI measurement. Visible here is that if ODI measurement is not very sensitive, some of the new strategies lose part of their advantage. If ODI measurement is very sensitive, the Fast Track Two Level and Ultra Inexpensive approach are much less expensive per treament. This graph also shows that while, as seen on the previous page, increased ODI sensitivity causes the FastTrack EitherOr option to have increased costs in absolute sense, the cost per treatment does go down.

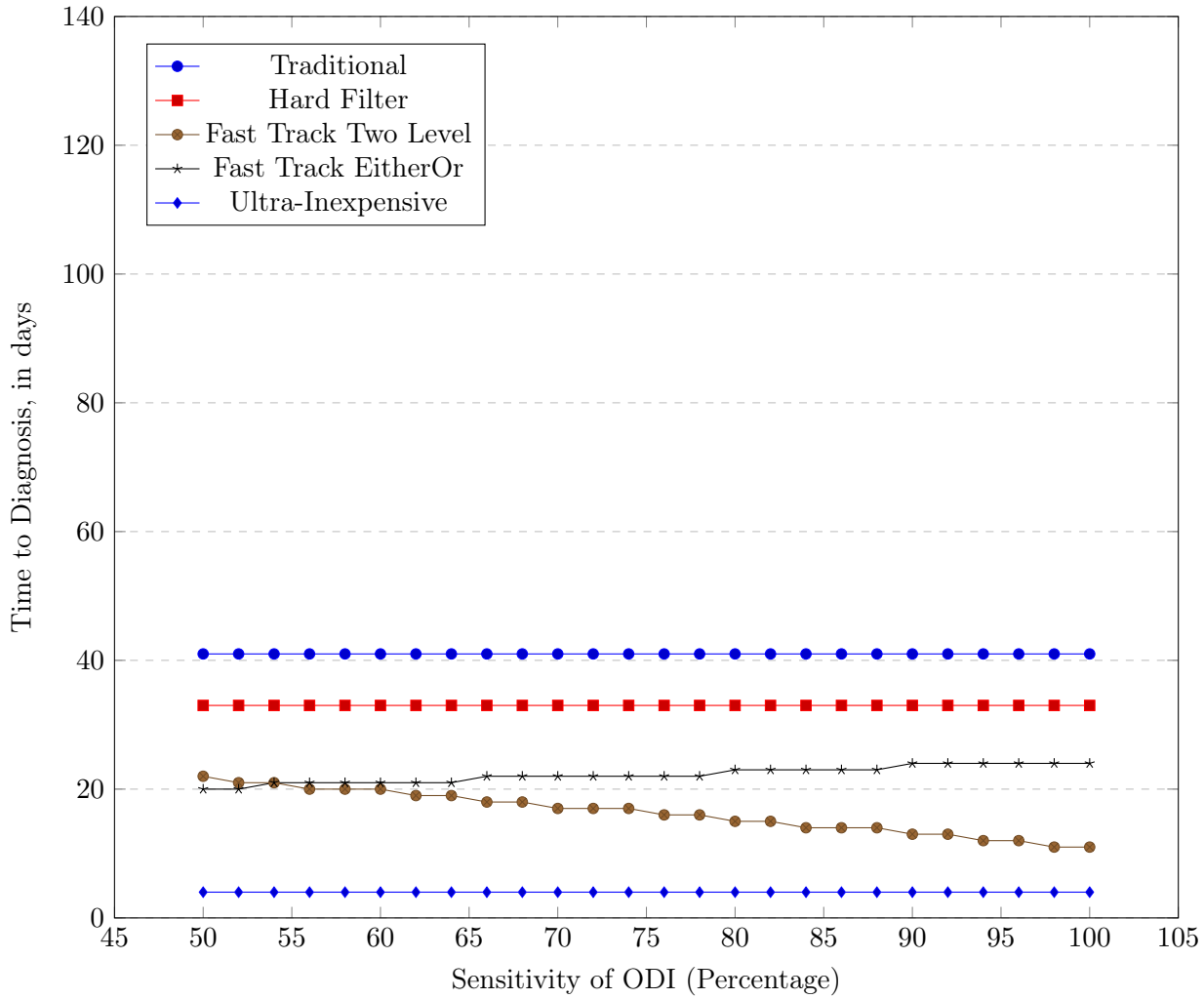

FIGURE 31: Comparison of Diagnosis Waiting Times, based on input sensitivity of ODI.

Figure 31 shows the time to diagnosis, graphed to sensitivity of ODI measurement. The Hard Filter and Traditional approaches always have the highest time to diagnosis, and the Ultra-Inexpensive method always has the lowest. The other two methods have their time to diagnosis somewhere in the middle, with the Fast Track Two Level method significantly decreasing in time to diagnosis for higher sensitivity of ODI measurement. This is caused by the fact that the patient is fast-tracked if the ODI measurement gives a positive result. Thus, the more positive results the ODI measurement gives, the more patients are put on the fast track, and receive a diagnosis (and treatment) sooner. Even at 50% ODI measurement sensitivity, this method still results in a much lower time to diagnosis, when compared to the traditional method.

What this section shows is that, regardless of what the sensitivity of ODI measurement is, the Ultra-Inexpensive method will always be the least expensive, but it will become much less sensitive if the sensitivity of ODI measurement is lower. The Fast Track Two Level approach does not have this issue, and has a similar price per treatment to the Ultra-Inexpensive option. This suggests that the Fast Track Two Level approach may be superior to the Ultra-Inexpensive method, if costs are not the only factor considered.

9.2.2 Analysis of ODI specificity parameter

Sensitivity and specificity together give a statistical model of a diagnosis test. Therefore, the same analysis that was done for the sensitivity of ODI measurement is also done for the specificity of ODI measurement.

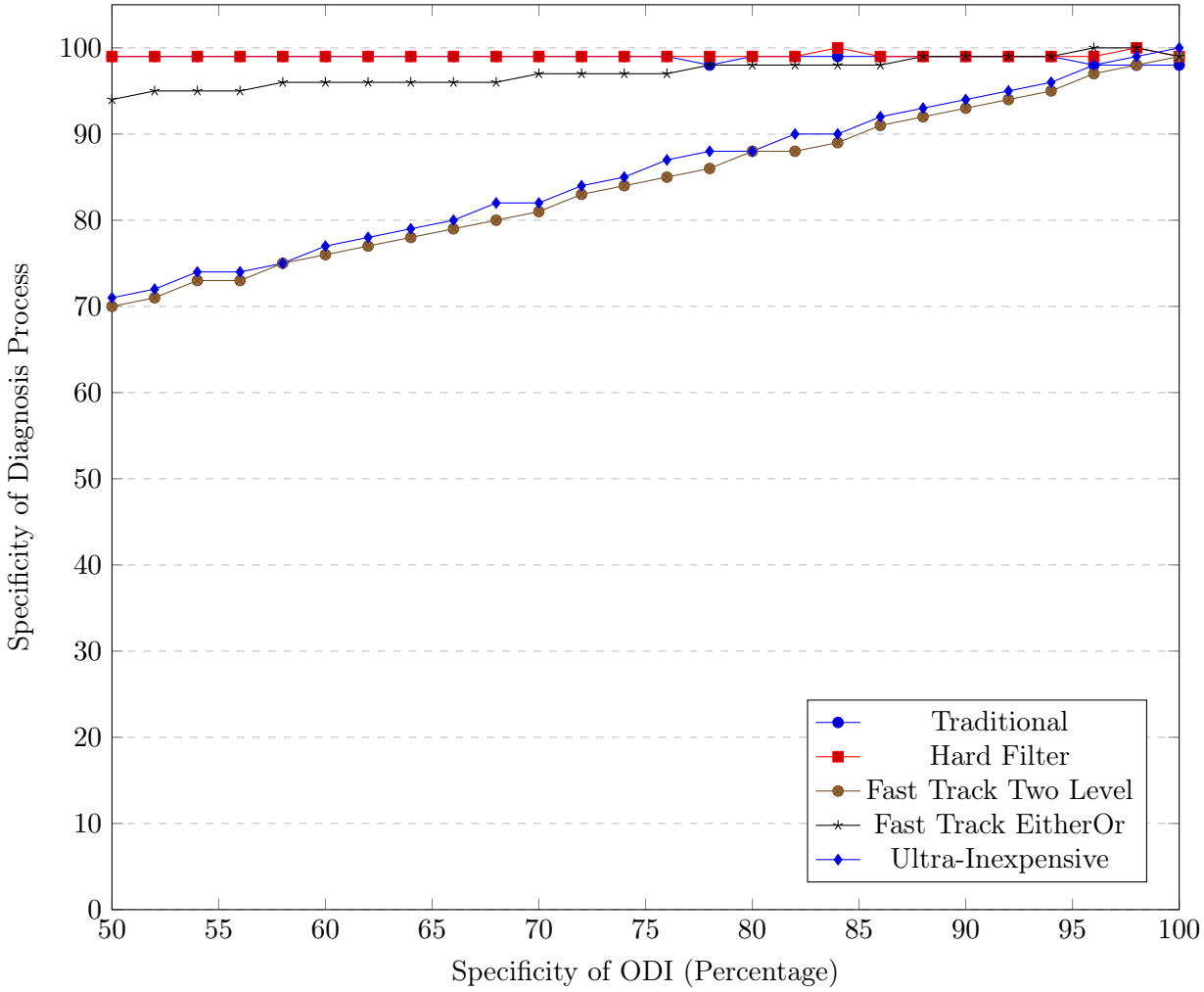

FIGURE 32: Comparison of specificity of diagnosis, based on input specificity of ODI.

In graph 32, the specificity of the diagnosis strategies are plotted, as a function of the specificity of the specificity of ODI tests. The Traditional and Hard Filter approach do not depend on ODI for their results, as they do not use ODI measurement.
The Fast Track Two Level and Ultra-Inexpensive methods have a very similar curve. This is caused by the fact that these methods both assign a positive diagnosis to all patients with a positive test result and a positive ODI result. Observe that, although these methods have the same specificity, the Fast Track Two Level method has a much higher sensitivity, as seen in the previous section.
The diagnosis specificity of Fast Track EitherOr option depends on the specificity of ODI measurement, but less so than the other methods. This is caused by the fact that patients only receive false positives in this scenario if the questionnaire and the ODI measurement both generate a false positive.

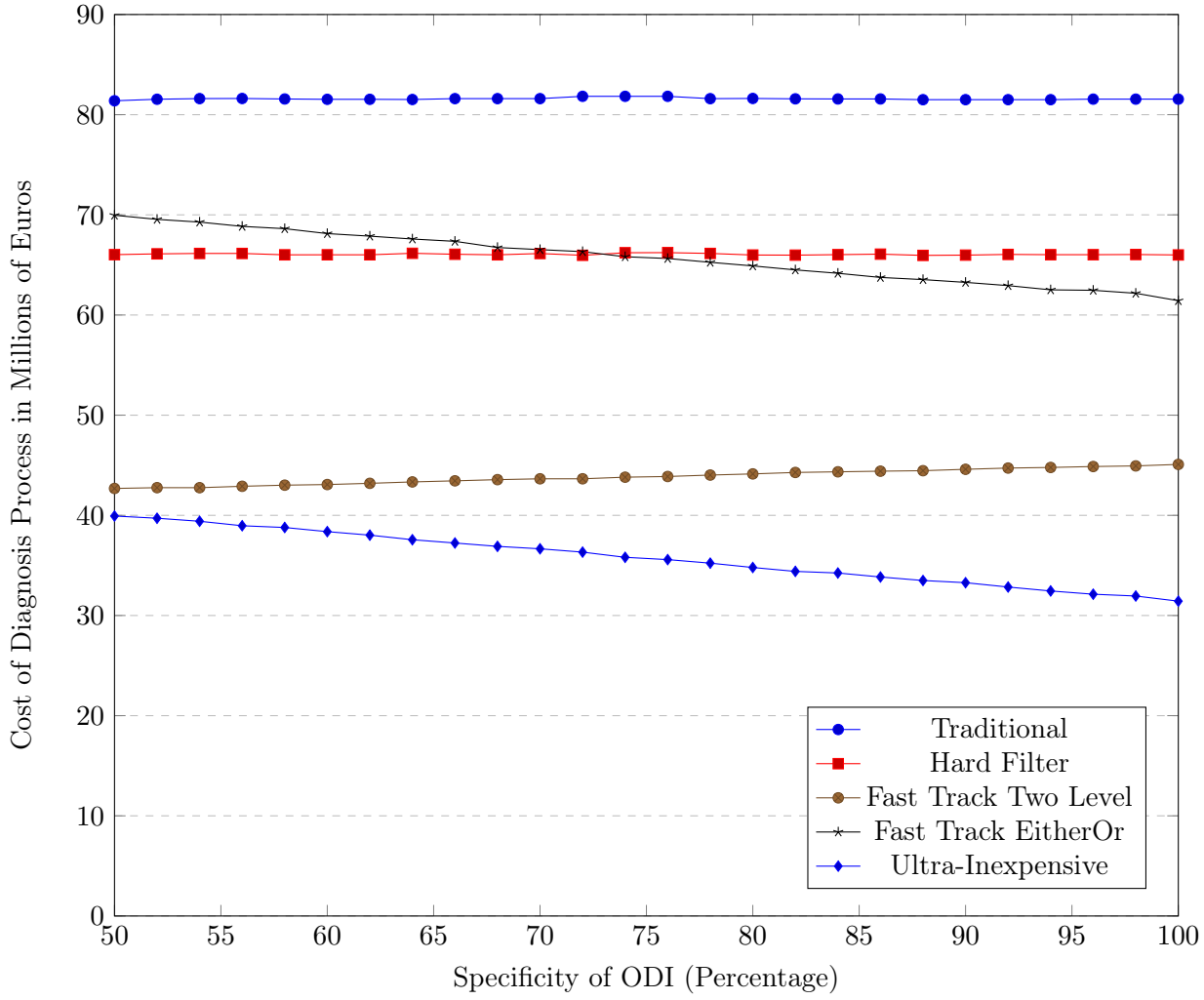

FIGURE 33: Comparison of total OSA Cost for new patients, per year, based on input specificity of ODI.

In figure 33, the total costs of OSA diagnosis is given. The methods that do not depend on ODI measurement have a horizontal line, as expected. The Ultra-Inexpensive, and Fast Track EitherOr options become less expensive when the specificity of ODI measurement increases. This is caused by the fact that this increases the odds of a true negative result, without sending the patient either to CPAP or the Sleep Centre. In the case of the Fast Track Two Level approach, the total costs increase for higher specificity of ODI measurement. This is caused by the fact that patients that score a false-negative on both the questionnaire and the ODI measurement get referred for treatment, whereas the patients who score a false-negative on only one of the two get sent to the Sleep Centre. Thus, increased specificity of ODI measurement results in patients with a false-negative result on the questionnaire are more likely to be sent to the sleep centre. Essentially, this means that for lower ODI measurement specificity, the CPAP treatment is used as a sort of second diagnosis step, to filter out the patients that get a false-positive diagnosis.

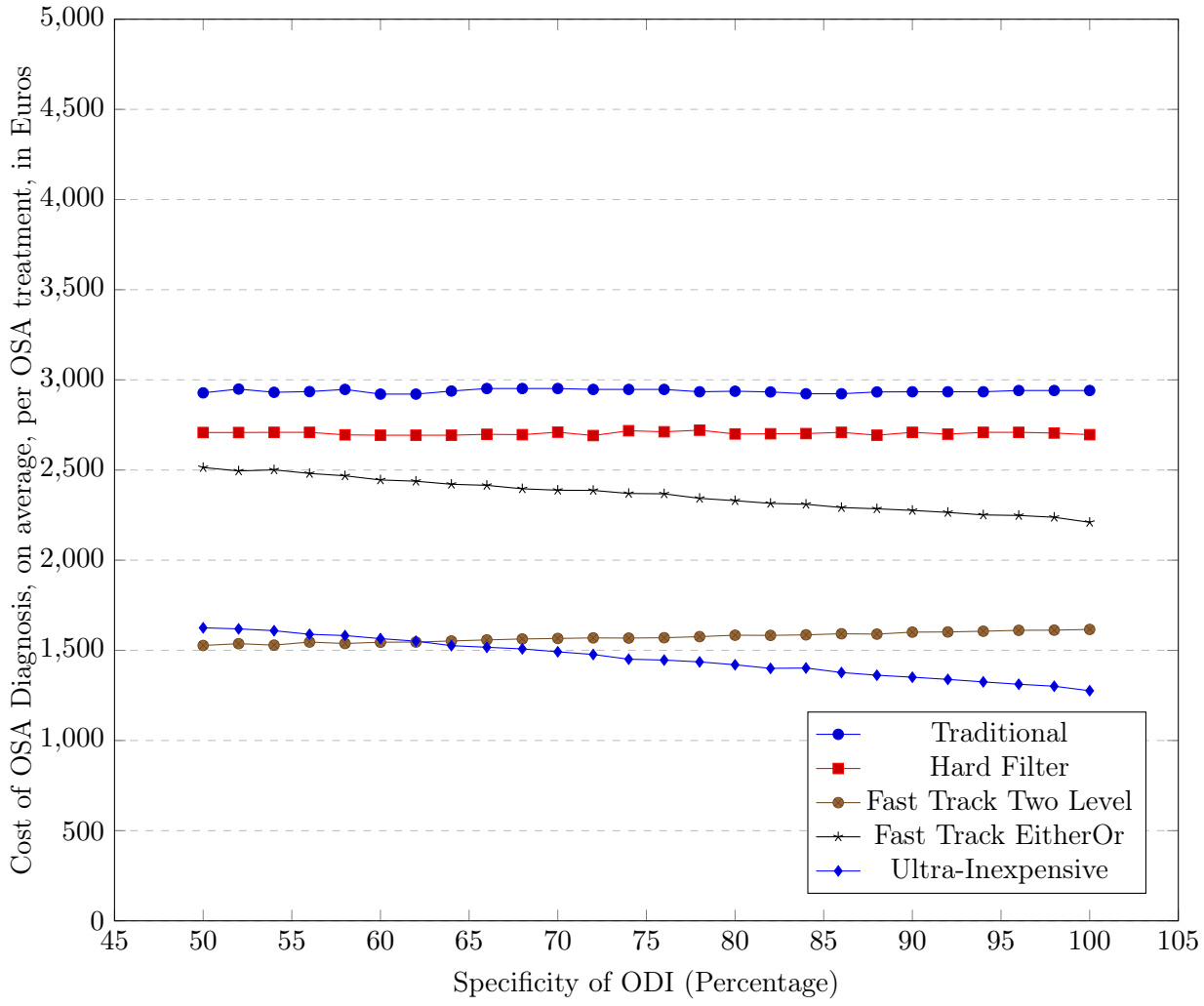

FIGURE 34: Comparison of total OSA Cost per treatment for new patients, per year, based on input specificity of ODI.

Figure 34 shows how much, on average, is spent for each patient that ends up getting treatment. This is again graphed against the specificity of ODI measurement. This shows the same results as the previous graph, for the same reasons.

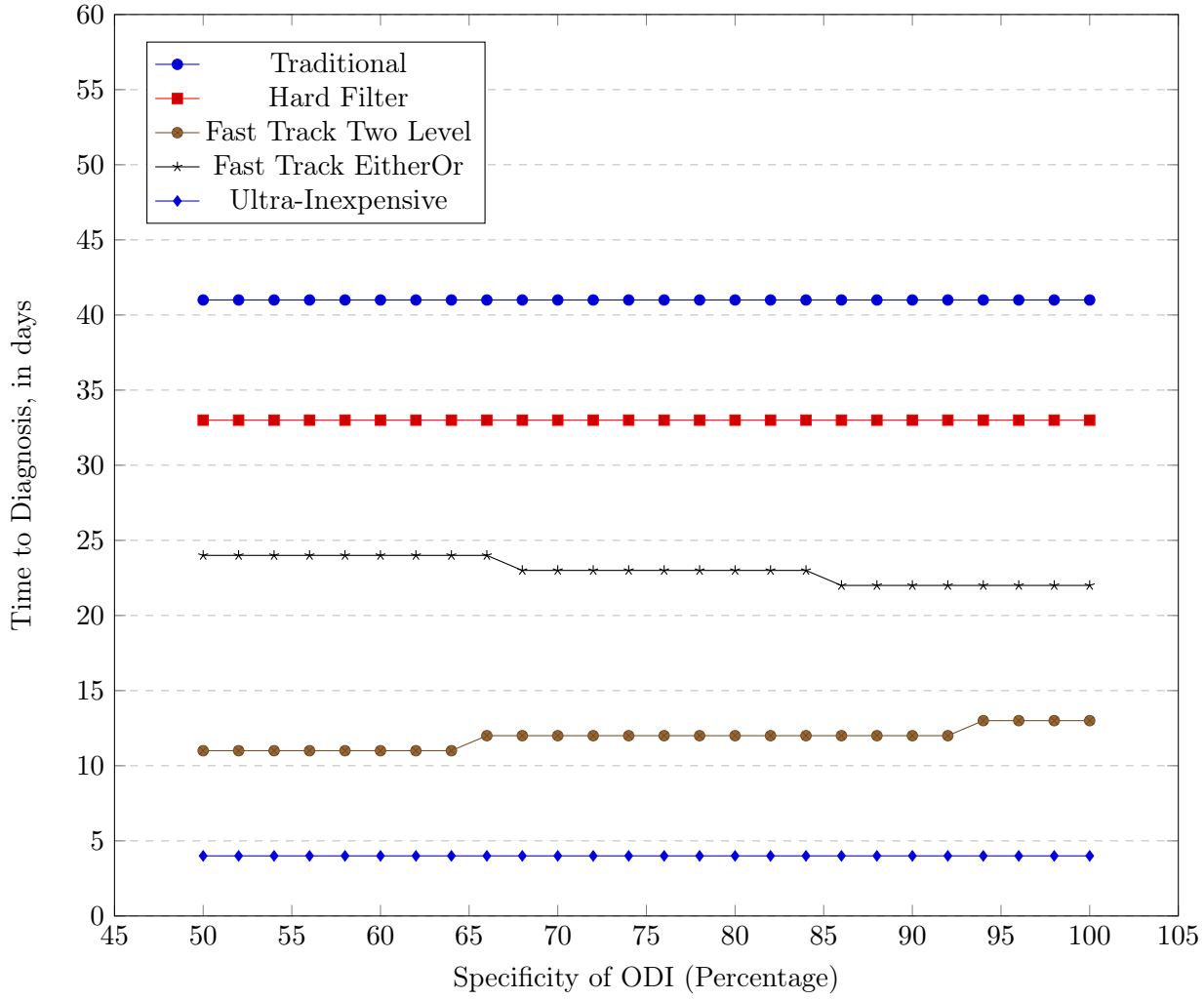

FIGURE 35: Comparison of Diagnosis Waiting Times, based on input specificity of ODI.

Figure 35 shows the Time to Diagnosis for the selected diagnosis methods. This shows that, although the Ultra-Inexpensive method uses ODI measurement, this is not of influence on the Time to Diagnosis. This is caused by the fact that, with this diagnosis method, the specificity of ODI measurement changes the outcome of the diagnosis, but not how long it takes for a patient to receive one.
The Time to Diagnosis for the two Fast Track methods depends on the specificity of ODI measurement, but not enough to alter which options have the lower Time to Diagnosis.

This shows that the ODI measurement specificity does not have a significant influence on the Time to Diagnosis.

9.2.3 Increased numbers of patients

The analysis in the section above assumes that the number of patients stays the same, regardless of the diagnosis strategy taken. In this subsection we evaluate the consequence of increasing and/or decreasing the number of patients that are diagnosed. It was assumed that the incidence of OSA in this population stays the same.

	Total number of Patients			Total Costs		
Number of patients	70 000	100 000	140 000	70 000	100 000	140 000
Traditional	27 800	39 700	55 600	81 mil €	116 mil €	163 mil €
Hard Filter	24 500	35 000	49 000	66 mil €	94 mil €	132 mil €
Two-Level Fast	27 800	39 800	55 600	42 mil €	60 mil €	85 mil €
QorODI Fast	27 800	39 800	55 600	55 mil €	78 mil €	110 mil €
UltraInexpensive	24 400	35 200	49 200	39 mil €	57 mil €	79 mil €

TABLE 21: Results for patient numbers and total costs, when the numbers of patients referred for OSA diagnosis increases.

In table 21, the total number of CPAP patients and total costs for OSA diagnosis are given, for 70 000, 100 000 and 140 000 patients referred by the GP. This corresponds to the current number of OSA patients, a middle point, and two times the current number of patients referred for OSA diagnosis.

Both the total number of patients, as well as the total costs, grow linearly with the number of patients. This is a direct consequence of the model used in this thesis; higher patient populations is modelled to neither cause advantages nor disadvantages.

The data in table 21 shows that the cost advantage of the Two Level Fast Track and Ultra-Inexpensive methods increases if the number of patients increases. This is expected from the per-patient costs, and highlights that if the number of patients increases, the possible cost savings increase.

9.2.4 Variations in OSA Incidence

In this section the per-patient costs, sensitivity and specificity of the selected methods are analysed, while altering the value of OSA Incidence.

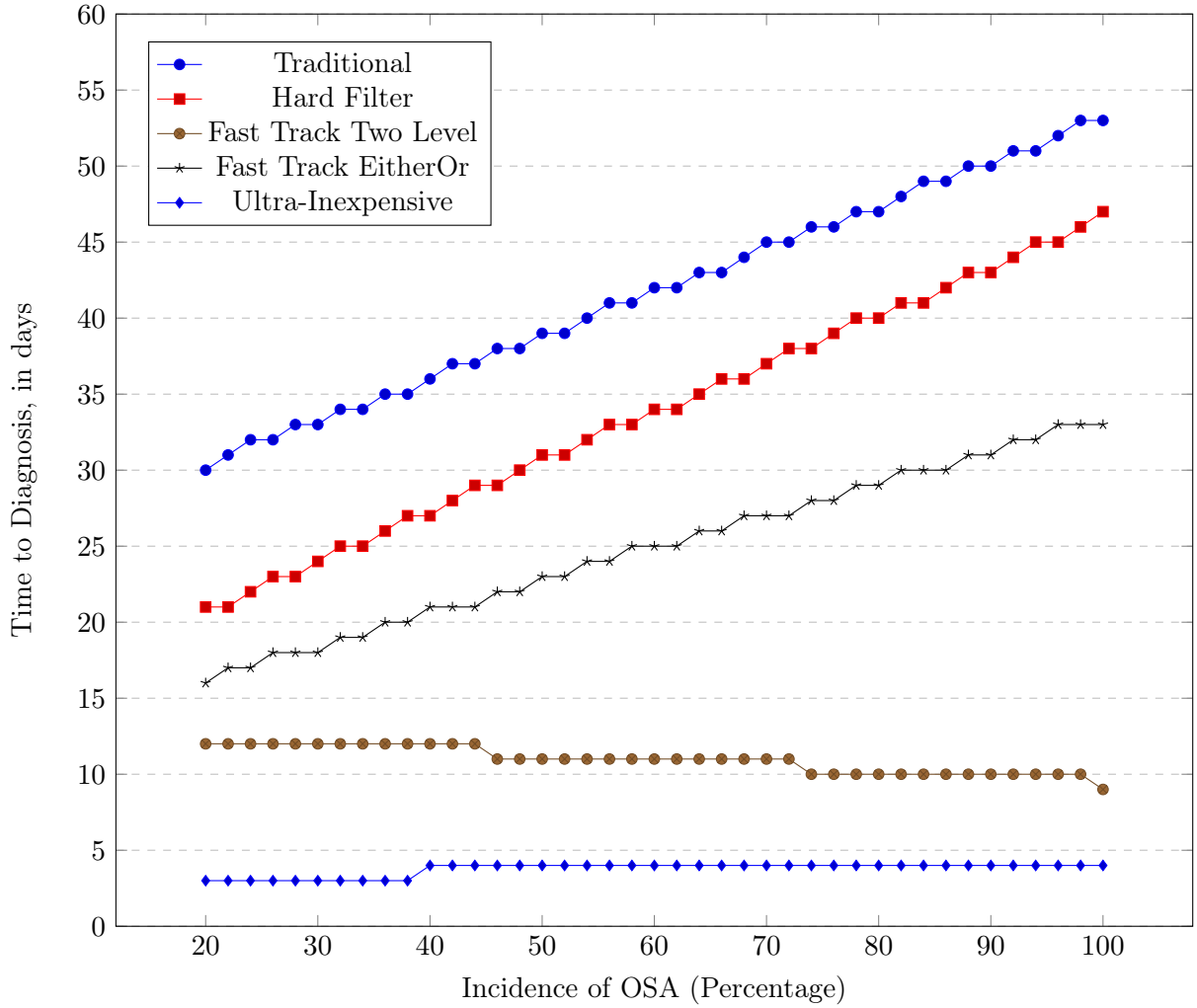

FIGURE 36: Comparison of Diagnosis Waiting Times, based on incidence of OSA.

The Traditional and Hard Filter approach see increased time to diagnosis with increased OSA incidence. This is caused by the fact that the Anamnesis filters out some of the patients without OSA. Therefore, the patients with OSA are more likely to require further testing. The same applies to the Hard Filter and Fast Track Either Or approaches.

On the other hand, in the Fast Track Two Level approach, the patients who do not have OSA require, on average, more diagnosis steps, and are more likely to need a PSG (since these patients are unlikely to complete the fast track). Therefore, this approach has a shorter time to diagnosis for increased OSA prevalence.

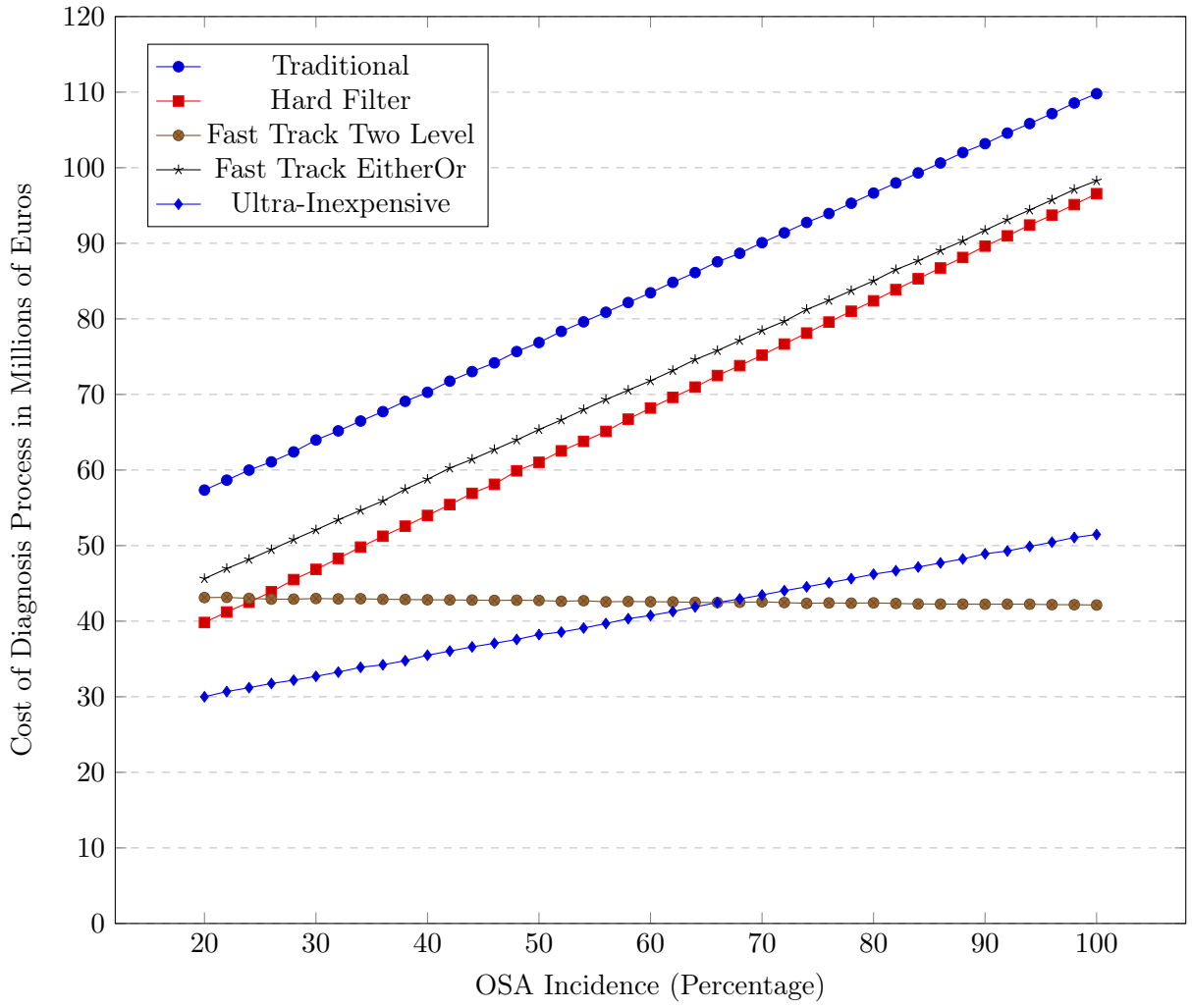

FIGURE 37: Comparison of total OSA Cost for new patients, per year, based on incidence of OSA.

On figure 37, the cost of the diagnosis process is given, compared to the incidence of OSA. It shows that most strategies get more expensive for higher OSA incidences. The Ultra-Inexpensive and Fast Track Two Level strategies are generally the least expensive, with the Fast Track Two Level approach becoming the least expensive for high OSA Incidences.

An intriguing detail is that, while the other methods all become more expensive with increased OSA incidence, the Fast Track Two Level approach becomes less expensive. This is caused by the fact that this methods bypasses the sleep centre if a questionnaire, as well as an ODI measurement yield a positive result. Since this is much more likely for patients *with* OSA, than for patients *without*, this means that, if the OSA incidence is lower, more patients are sent to the sleep centre. Since the tests at the sleep centre are relatively much more expensive than the tests done at the GP, this therefore results in a higher total costs if OSA incidence is lower.

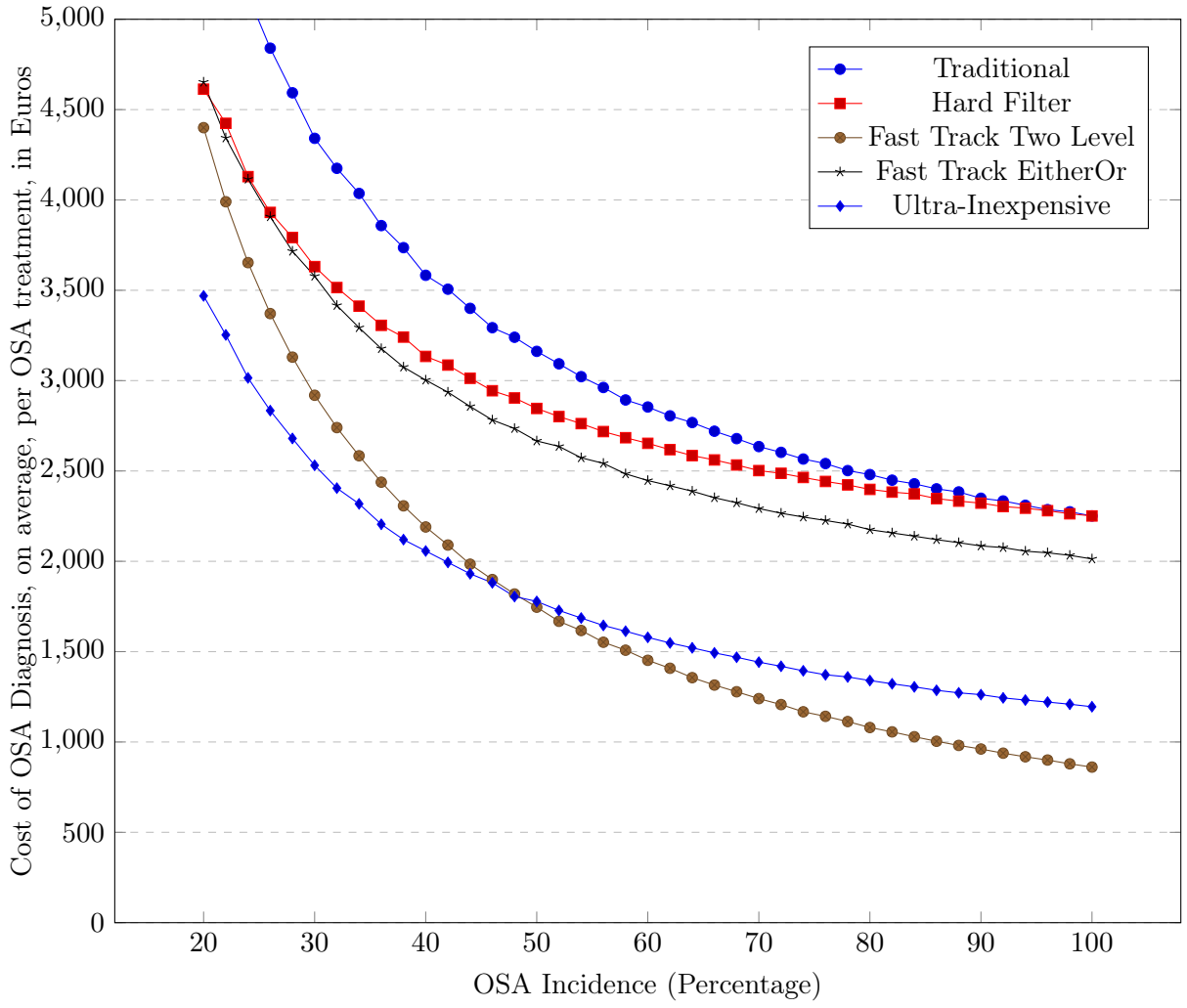

FIGURE 38: Comparison of total OSA Cost per treatment for new patients, per year, based on incidence of OSA.

Figure 38 shows the cost per diagnosis, graphed to OSA incidence. It shows, as expected, that for increased OSA incidence levels the cost per diagnosis goes down. This is caused by the fact that costs for negative diagnoses are divided over the positive diagnoses in this statistic. With higher incidences, more true positive diagnoses can be achieved, and therefore the cost per diagnosis drops.

The graph shows that the Ultra-Inexpensive and Fast Track Two Level methods score the best in this statistic. It also shows that the Fast Track Two Level approach has the lowest cost per diagnosis if the OSA incidence is over 50%. For lower OSA incidences, the Ultra-Inexpensive method becomes less expensive per diagnosis.

From this section, the Ultra-Inexpensive and Fast Track Two Level methods are both good candidates for further research.

10 Conclusions and Discussions

This thesis set out to figure out *how to use UPPAAL to analyse diagnosis alternatives for OSA*.
This problem statement combines two fields; medical and computer science. When discussing the results of this work, this split provides a means of categorising the results of this work.

10.1 Medical Discussion

Recall the first research question for this thesis: *Can UPPAAL modelling be used to explore and compare diagnosis strategies for OSA?*

This question was split up into multiple sub-questions, which are each answered here. After this, the main medical question is answered.

10.1.1 What is OSA?

This question was answered in chapter 4, with an overview of the medical aspects of OSA. Firstly, the physiological aspects, symptoms, and consequences were investigated, to create an idea of what OSA is. This outlined the severity of OSA.

After that, an investigation was done into the prevalence of OSA, since prevalence (or incidence) is an important modelling parameter. If a disease is rare, diagnosis may be very different from if a disease is highly prevalent.

After that, the diagnosis and treatment options were summarised. These are the basis of the model. With these diagnosis and treatment options, also the contemporary diagnosis strategy was described. The contemporary diagnosis strategy for OSA was used as a base-line to compare the new diagnosis strategies to.

10.1.2 What improvements can be made to OSA diagnosis strategies?

This question was answered by showing where improvements could be made to the contemporary strategy. It was shown in chapter 5.6.1 that there are two methods of altering the contemporary diagnosis strategy. Firstly, steps can be replaced by steps with different characteristics. For instance, instead of having a doctor take a Medical History, a questionnaire can be given, or a less complicated test could be given instead of a PSG. As a second method, the order in which the steps are taken could be changed. This can be combined with adding different diagnosis steps, creating a large set of possible diagnosis strategies.

These areas of improvement were used as the basis for the set of diagnosis strategies that were analysed in chapter 8. These strategies combine altering the order of steps with swapping out which specific diagnosis steps are taken.

10.1.3 How can OSA diagnosis be captured in a model?

In chapter 7, a model of OSA diagnosis is given. This model is based on building blocks, which are initialised using statistical properties that were obtained from literature

research, and expert consultation in cases where the required data was not directly available. These building blocks merged as one large model, adaptable to model a wide range of diagnosis strategies. This showed that large parts of the model could be re-used for modelling a multitude of diagnosis strategies, increasing the capabilities for comparing multiple diagnosis strategies in UPPAAL.

10.1.4 What diagnosis strategies for OSA differentiate themselves from the traditional approach?

In chapter 9, nine diagnosis strategies, in five categories, are defined, and are simulated to figure out the characteristics of these models. The goal of this was to select a set of diagnosis strategies that each have unique properties. For diagnosis strategies that utilise a questionnaire, results were obtained for every one of the questionnaires, resulting in a large set of numerical results.

From this set of diagnosis strategies, five were selected as highlighting a direction in which diagnosis strategies can improve over the contemporary strategy.

Strategy	Questionnaire	**Reason for Selection**
Traditional Approach	-	Contemporary option
Hard Filter Approach	Stop-Bang	Inexpensive and easy to implement
Fast Track Two Level Approach	Stop-Bang	Inexpensive, high sensitivity
Fast Track Either Q or ODI Approach	Phillips High	higher specificity
Ultra-Inexpensive Approach	Stop-Bang	Least expensive approach.

Table 22: Strategies chosen for further analysis

Table 22 is a copy of a table also present in chapter 9 (table 18), and illustrates which diagnosis strategies were selected as distinct directions, and why these were chosen. The 'easy to implement' for the Hard Filter Approach is directed towards the changes required to medical protocols to switch to this strategy, not to the modelling of the diagnosis strategies.

10.1.5 How do the results of models of the diagnosis strategies vary, with respect to their parameters?

This question is answered in chapter 9, by analysing the diagnosis strategies selected in chapter 8. Two category of analysis were done: direct comparison and sensitivity analysis.

10.1.5.1 Direct Comparison The five diagnosis strategies were directly compared, to obtain an idea of which alternative has which advantages. In this comparison, it became apparent that the hard filter approach is not a great option, since it gives up on the total number of patients, without getting much of an advantage in costs per treatment.
The other three alternatives showed to each have their advantages, with their differentiation being in the precision of the diagnosis on the one hand, and costs on the other hand. Based on the direct comparison, the Fast Track EitherOr and Ultra-Inexpensive alternatives are especially interesting for further study.

The Ultra-Inexpensive method proved to be the fastest and least expensive option, whereas the Fast Track EitherOr option is neither the least expensive, nor the fastest, but still results in high sensitivity and specificity. Therefore, this indicates that Fast Track EitherOr may be able to replace the traditional approach without lowering the precision of diagnosis.

10.1.5.2 Sensitivity Analysis In the direct comparison of diagnosis strategies, it became clear that some diagnosis strategies outperform the other strategies. To obtain insight into these results, a sensitivity analysis was executed on a set of the model's parameters. The ODI-analysis showed that the sensitivity of ODI measurement is essential for all methods using this test. If ODI measurement sensitivity is lower than around 70%, the traditional approach is a relatively better option. The sensitivity analysis of OSA Incidence shows that, even at a much lower OSA incidence, the alternative approaches maintain their edge over the traditional method. This indicates that the results obtained may also hold for populations in which the incidence of OSA is lower.

10.1.6 Concluding remarks

The medical research question is binary, asking whether UPPAAL modelling can assist the exploration and analysis of OSA diagnosis strategies. In this thesis, UPPAAL modelling was used to model a multitude of diagnosis strategies, and obtain results for some of their key indicators of diagnostic quality. This was used to find a selection of strategies, and analyse them further.

This showcases that altering the diagnosis strategy for OSA may provide benefits, and that analysing this with UPPAAL modelling gives insight into which diagnosis strategies have potential.

10.2 Computer Science Discussion

Consider the second research question: *How to create a modelling infrastructure for modelling medical strategies in UPPAAL?*

This question was split into three questions, which are each answered below, after which the second research question is tackled.

10.2.1 What characterises UPPAAL models?

In chapter 4, a summary is given of UPPAAL's features, giving insight into how UPPAAL works. This shows that UPPAAL models have support for timing, costs and probabilities. Another benefit of UPPAAL is that UPPAAL is graphical, which aids communication between computer scientists that work on the models, and medical experts.

10.2.2 How can a tool chain improve the versatility of UPPAAL models for diagnosis?

In chapter 6, a tool chain for UPPAAL modelling analysis is introduced. This tool chain was built on multiple components: a model, a specification and a query. The specification is where the tool chain allows for new possibilities. Through the specification, multiple experiments could be set up for diagnosis strategies. This allowed for increased flexibility to the analysis. Besides an increase in modelling comfort, it also made it possible to do sensitivity analysis.

10.2.3 What new insights can be obtained by utilising this infrastructure?

In chapter 9, the results of advanced analysis of diagnosis strategies are shown. This analysis shows that the tool chain made for this project allows for the simulation of large sets of data in a structured way, and that this analysis leads to the ability to generate graphical results. These graphical results provide additional insights, through a visual representation of the dependence of the results on the parameters of the model.

10.2.4 Concluding remarks

The UPPAAL model, combined with the tool chain, allows for the simulation of OSA diagnosis strategies in a semi-automated way. This setup generates large amounts of data in a structured way, which can be turned into tables and graphs. Since the tool chain can be set up to execute multiple simulation experiments, this allows for utilising the same model for answering multiple questions about a diagnosis strategy. This versatility allows for greater insights into diagnosis strategy models, while maintaining consistency of modelling through re-use of the UPPAAL model.

10.3 Final Conclusions

The original problem statement that this thesis set out to solve was the following: *how to use UPPAAL to analyse diagnosis alternatives for OSA?*

In this thesis, it was shown that individual steps in the diagnosis process could be modelled separately, and that UPPAAL's composition of templates could be used to combine these building blocks. This UPPAAL model was expanded upon by using a tool chain for analysis of the models, the combination of which was able to analyse diagnosis strategies for OSA.

This showcased at the same time the strength of UPPAAL, especially when combined with an external tool chain, while also showcasing that the traditional OSA diagnosis strategy may not be the best option.

11 For Further Study

In this section, an overview is given for possible improvements on the work of this thesis. This was split up into multiple categories. Suggestions are given on possible further study on the computer science side of this work, followed by some suggestions for how to improve the modelling aspects. Finally, some suggestions are given for using this thesis as a starting point for medical studies.

11.1 Computer Science Future Study

As part of this thesis, a tool-chain was developed for the analysis of UPPAAL-models. This tool-chain highlights that UPPAAL's analysis capabilities can be increased by added tooling. Below here there are some means to extend this work.

11.1.1 Abstract Model

The UPPAAL model used in this research is presently only editable by someone with experience in UPPAAL modelling. An addition to the tool-chain could be to create a simplified model, which is translated into an UPPAAL specification.

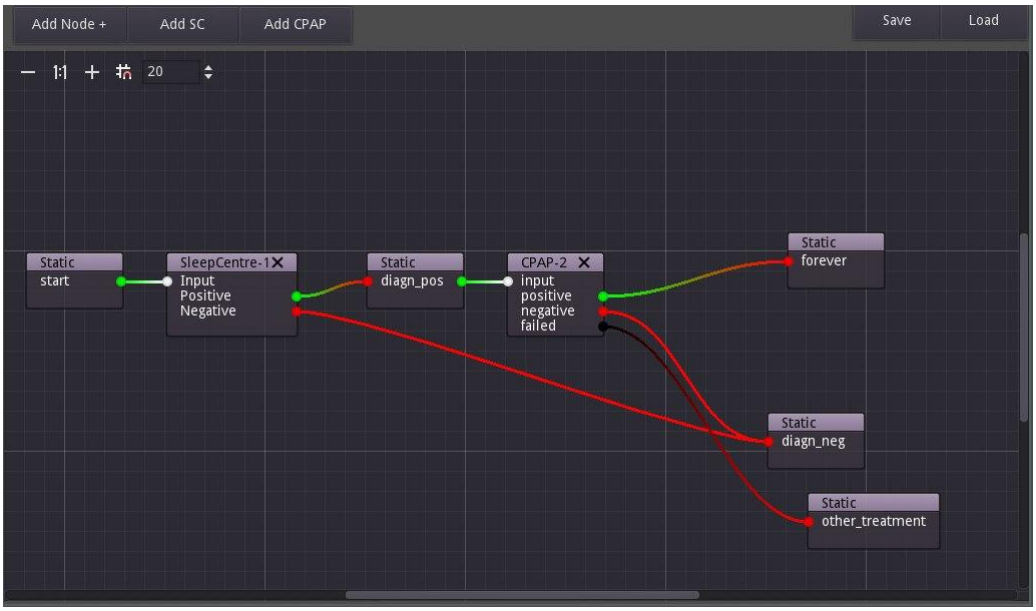

FIGURE 39: Prototype of Future Work.

Figure 39 shows a quickly built visual prototype of the idea of such a tool. This prototype was experimented with early in this thesis, but left out of the final scope of this work.

11.1.2 Integration of Tooling in UPPAAL

This requires collaboration with the UPPAAL project, but would provide large advantages to the UPPAAL community. The tooling as built for this thesis is built as a layer around UPPAAL, fully separated from it. Ideally, this work, or something similar to it, could be integrated in UPPAAL itself, providing the functionality to a larger audience.

11.2 Improved Medical Modelling

As a second area for future study, the model itself can be expanded upon.

11.2.1 Model Treatment

This thesis is involved almost exclusively with the modelling of diagnosis strategies, and no differentiation was made between different treatment strategies.

There are two ways this can be expanded upon. Firstly, treatment could be modelled more precisely, also including the available alternatives, such as Mandibilar Devices, and surgery. Secondly, the negative side of not receiving treatment could be included in the model, as a way of offsetting the costs of diagnosis and treatment, when compared to the societal gains of treating Sleep Apnea.

11.2.2 Model Patient Non-commitment

In the models in this thesis, it was assumed for the most part that the patient is a perfect being that will do whatever they are told, just because they are told so. The patient's imperfections only show up in the statistical distributions of questionnaire results, and failure rates of CPAP, PSG and PG.

This assumption does not hold in practice, and the model can be updated to reflect this.

11.2.2.1 Lowered Waiting Times if lower patient volumes at sleep centre

Logically, the waiting times at the sleep centre depend on the number of OSA patients that get referred there. Therefore, the wait may decrease. This is a point that can be further explored. This is probably true in theory, but, given the fact that sleep centres are organisations that have a financial incentive towards helping patients, a much lowered patient count at the sleep centre's doors may result in a decreasing capacity in sleep centres, and therefore the waiting time may not be changing by as much as a simple calculation may suggest. Nevertheless, future research into this may be a good thing.

11.3 Future Medical Studies

The analysis that was done for this thesis shows that some diagnosis strategies outperform the traditional approach. Of special note are the Fast Track diagnosis strategies, where patients skip the sleep centre if they score highly on relatively simple diagnosis tests. These diagnosis strategies show high potential in the modelling results of this thesis, indicating that these methods have the potential to decrease costs and waiting times of OSA diagnosis, while maintaining the sensitivity of the testing.

These strategies should be verified using more accurate medical data. After that clinical trials may be a good step forward, to verify these strategies in practice.

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Appendices

The appendices are not complete (yet).

A Parameter Setup DSL Specification

Any DSL setup file starts from a single scope, in which some setup is done. Any scope has zero or more children, which may either be commands or other scopes. This DSL was implemented in python, using Lark, a parsing library. An example of the syntax used is below.

```
{
   setLocalIntSensAnal("Patient", "const int PREV",300,700,1000)

   addTemplateChoices("TEST")
   addTemplateChoice("TEST", "TestHSAT(TEST_START)", "HSAT")
   {
       addTemplateChoice("TEST", "TestPSG(TEST_START)", "PSG")
   }
}
```

A.1 Syntax

The syntax of the Domain Specific Language was implemented using Lark, a python parsing library for context-free languages. Below is the full syntax as used in the tool-chain.

```
?start: scope

?statement: scope -> scope
   | COMMENT
   | "import(" [string] ")" -> import
   | "merge(" [string] ")" -> merge
   | "setTemplate(" [string "," string "," string] ")" -> set_template
   | "addTemplateChoices(" [string] ")"          -> add_template_choices
   | "addTemplateChoice(" [string "," value "," string] ")" ->
    add_template_choice
   | "setLocalValue(" [string "," string "," value] ")" -> set_template_value
   | "setGlobalValue(" [string "," value] ")" -> set_global_value
   | "setLocalIntChoices(" [string "," string ] ")" -> local_int_choices
   | "setGlobalIntChoices(" [string ] ")" -> global_int_choices
   | "setLocalIntChoice(" [string "," string "," SIGNED_NUMBER] ")" ->
    local_int_choice
   | "setGlobalIntChoice(" [string "," SIGNED_NUMBER] ")" -> global_int_choice

COMMENT: "#" /(.)+/

scope : "{" statement* "}"

?value: string
   | SIGNED_NUMBER      -> number
   | "true"             -> true
   | "false"            -> false
   | "null"             -> null

?string : ESCAPED_STRING

%import common.ESCAPED_STRING
%import common.SIGNED_NUMBER
%import common.WS
%ignore COMMENT
%ignore WS
```

A.2 Scoping

The DSL is capable of defining the characteristics of multiple runs. This is described adequately in the main-text of the report, in section 6.2.2.

A.3 Commands

In this subsection, a short description is given of all commands supported by the DSL.

A.3.1 Import

The first way of importing another file into a DSL-file is by using the import function. Importing adds the tree of the imported file as a sub-node of the scope that the import

statement is in, essentially adding it as a sub-tree.

A.3.2 Merge

Merging is the second way of importing into a DSL-file.

A.3.3 setTemplate

This overrides the value of a template line in UPPAAL.

A.3.4 Template Choices

This overrides the value of a template line in UPPAAL, but gets a list of options. The runs are set up in such a way that each template choice gets simulated.

A.3.4.1 addTemplateChoices This function is used to set up a set of template choices. Beware that using only this one, without adding options results in the number of runs in this part of the tree will be zero, because the carthesian product of options per direction is used. Using this a second time (for instance, inside a subscope) resets the templatechoices.

A.3.4.2 addTemplateChoice This adds an option to a templatechoices.

A.3.5 setValue family

A.3.5.1 setLocalValue This sets a value in an uppaal template's variable definitions to a specific value.

A.3.5.2 setGlobalValue This sets a value in an uppaal's global variable definitions to a specific value.

A.3.5.3 setLocalIntSweep This sweeps a value in an uppaal template's variable definitions over an integer range.

A.3.5.4 setGlobalIntSweep This sweeps a value in an uppaal's global variable definitions over an integer range.

A.3.5.5 setLocalIntChoices This sets up a local variable (variable within a template) to support multiple integer options.

A.3.5.6 setLocalIntChoice This adds an integer value option to a local variable (as initalised with the command above)

A.3.5.7 setGlobalIntChoices This sets up a global variable to support multiple integer options.

A.3.5.8 setGlobalIntChoice This adds an integer value option to a global variable (as initalised with the command above)

B Description of Tooling

In this appendix, an overview is given of the technical way the tooling works. It gives an overview on the code-structure, and how to use it. The tooling is available on https://github.com/nanderv/uppaalDSL.

To use the toolset, firstly, the path to UPPAAL's verifyta tool needs to be set. This is done in conf.py, a configuration file that only has this variable.

B.1 Simulation setup

The starting point for running UPPAAL models is program.py.

B.2 Results generation

After running the simulations, a file is created in output/results/... This file is named after the name of the simulation setup that was run. The results file starts on a line that describes the names of all values that were set using the DSL. Then, alternatingly, it has a line that describes the parameters, followed by a line of results.

This format can be parsed back into a format that is easier to work with, using the graph_run function in graphDataCreation.py.

C Uppaal Specification

Below are images of the UPPAAL templates used for this project.

The UPPAAL file is distributed on figshare [40]. Url: https://doi.org/10.6084/m9.figshare.19213923.v1.

C.1 Patient Generator

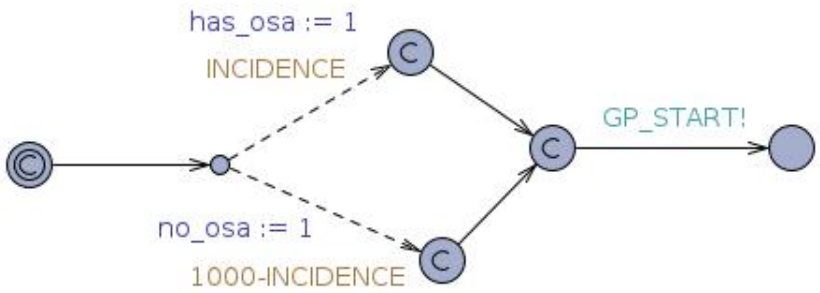

FIGURE 40: Patient Model

```
const int INCIDENCE = 700; //TRANS
```

C.2 GP Models

Multiple models were implemented for different strategies for the GP.

C.2.1 Traditional Model

This is the traditional approach of the GP. Since we only consider patients who are traditionally referred by the GP, this is equivalent to the GP letting through this entire population.

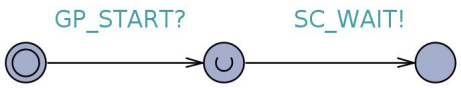

FIGURE 41: Traditional GP Model

C.2.2 Hard Filter Model

In this approach the GP only sends through patients if they test positive on a questionnaire.

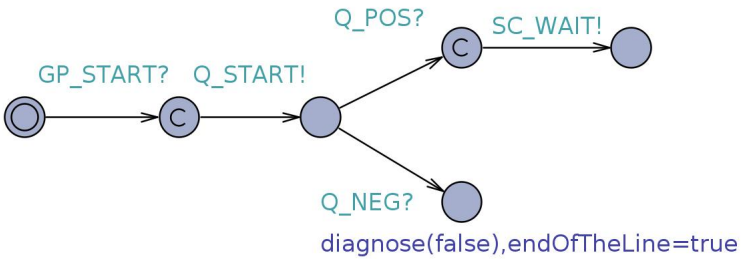

FIGURE 42: Hard Filter Model

C.2.3 EitherOr Model

In this GP strategy, the patients gets referred for further diagnosis if the patient either tests positive on a questionnaire, or tests positive on a diagnosis test (ODI in this research).

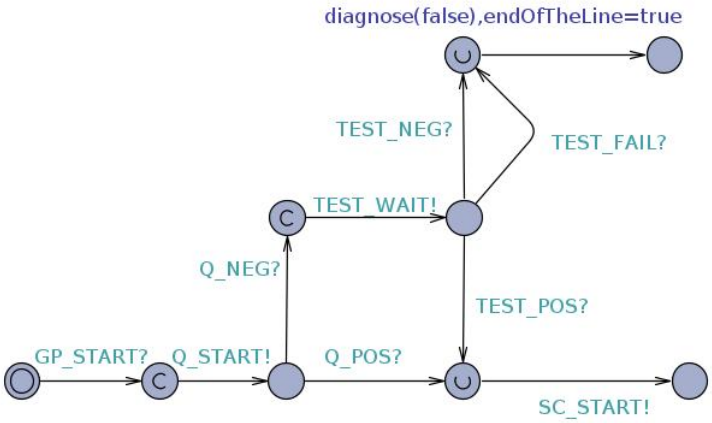

FIGURE 43: Hard Filter Either Or Model

C.2.4 Fast Track Two Level Model

This models a GP strategy which, if both a questionnaire, and a diagnosis test yield a positive result, sends the patient directly to treatment. If either is negative, patient is sent to the Sleep Centre.

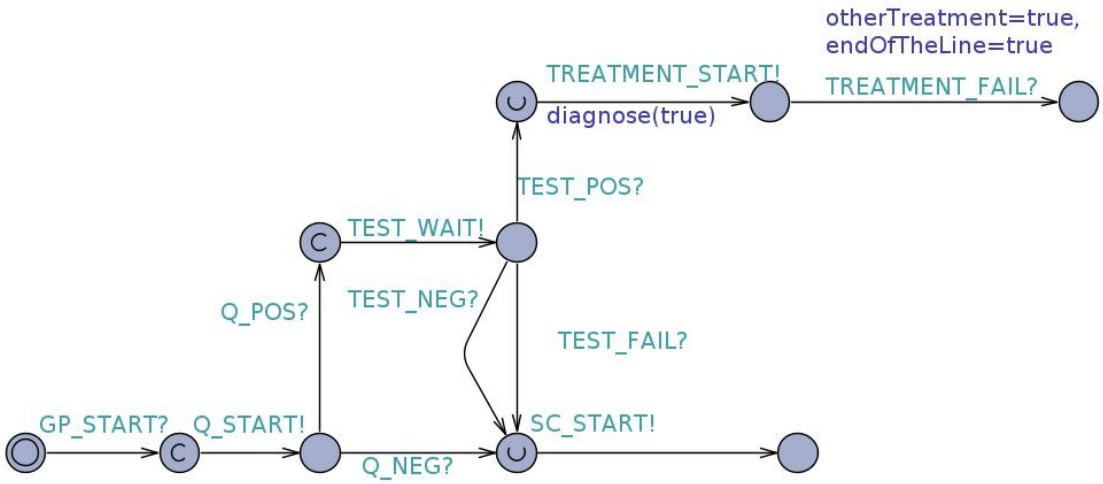

FIGURE 44: Fast Track Two Level Model

C.2.5 Fast Track Three Level Model

Akin to the one above, but uses the three level phillips questionnaire. If the middle result is yielded by the three level phillips questionnaire, then always refer the patient to the sleep centre. In the negative case, give a negative diagnosis directly.

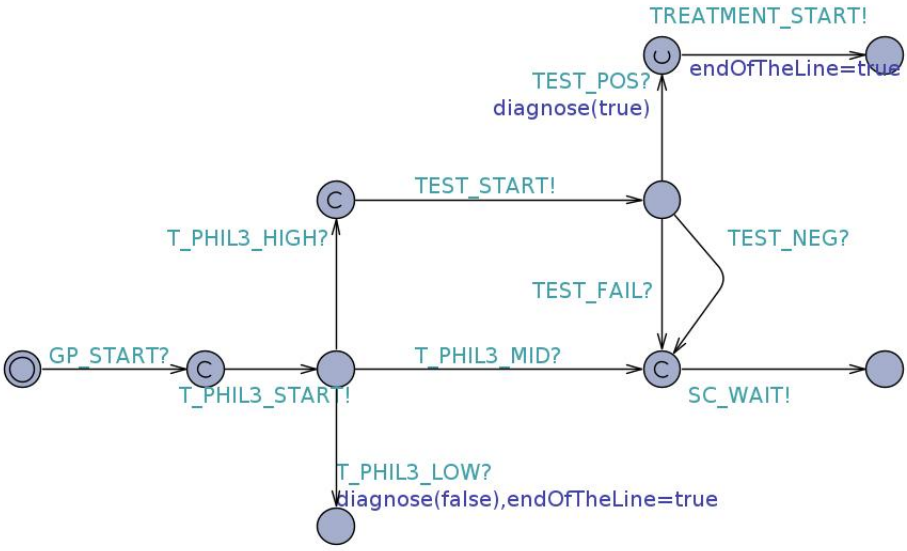

FIGURE 45: Fast Track Three Level Model

C.2.6 Fast Track Either Or Model

If Q and Test: directly treatment If Q xor Test: to sleep centre. If neither Q nor test: negative diagnosis

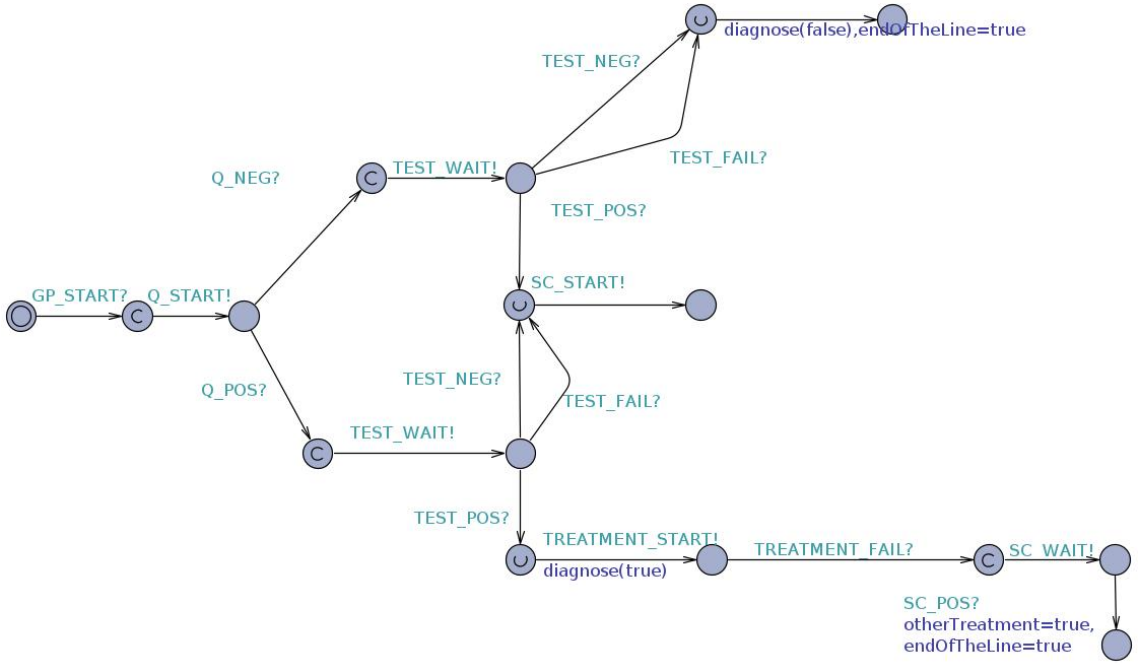

FIGURE 46: FastTrack Either Or Model

C.2.7 Ultra Inexpensive Model

Treatment if Q and test. Otherwise: negative diagnosis. If CPAP fails: refer to sleep centre.

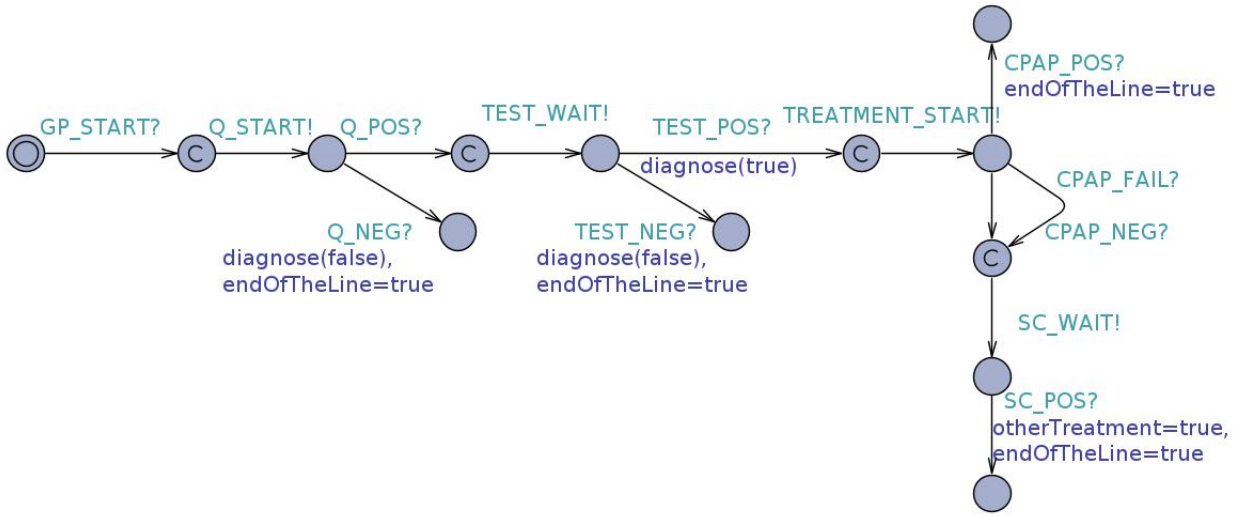

FIGURE 47: UltraInexpensive Model

C.2.8 Cpap First Model

Start patient on CPAP. If that fails, send patient to sleep centre.

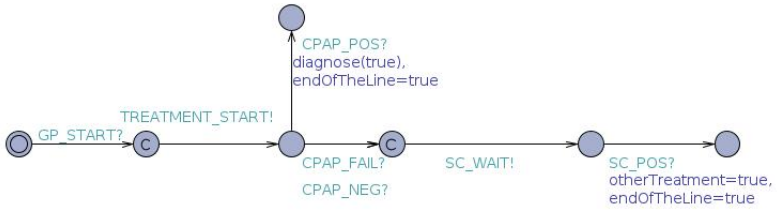

FIGURE 48: CPAP First Model

C.2.9 Q then CPAP Model

Start with a questionnaire. If positive: continue as CPAP First model. If negative, continue as traditional model.

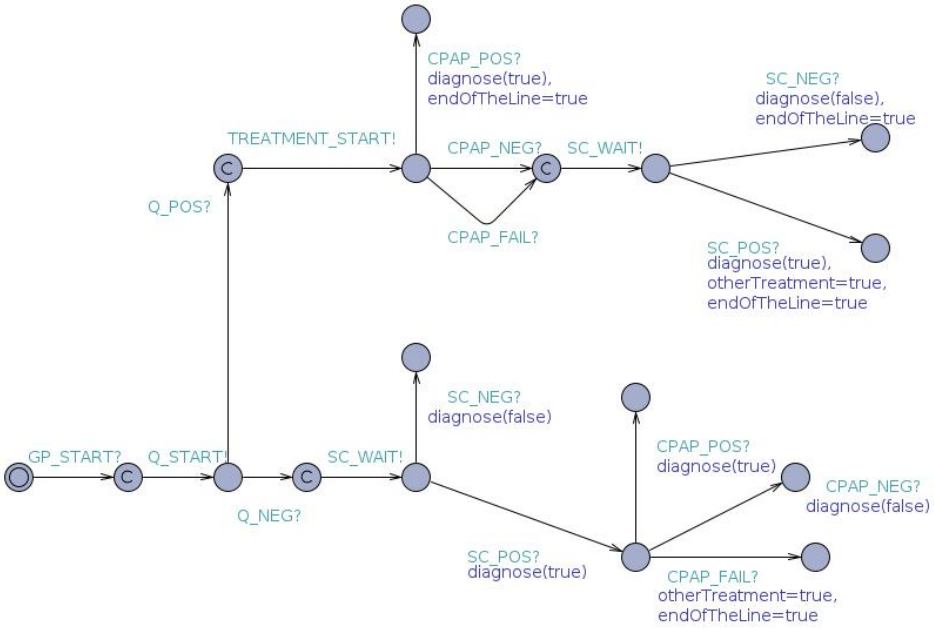

FIGURE 49: Q then CPAP Model

C.3 Sleep Centre

This is the model of the sleep centre. It's described in more detail in the relevant chapter of the main thesis.

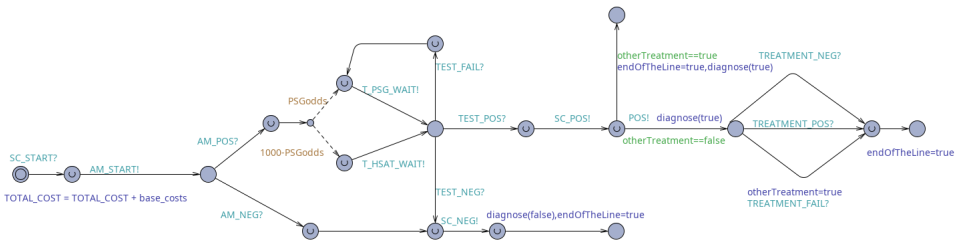

FIGURE 50: Sleep Centre Model

```
int base_costs = 300;

int T[2] = {1000,0};
int F[2] = {700,300};

int NOO = 100;

int PSGodds = 1000; //trans
```

C.4 Tests

In this subsection a printout is given of the uppaal models that were used to model the diagnosis steps.

C.4.1 PSG

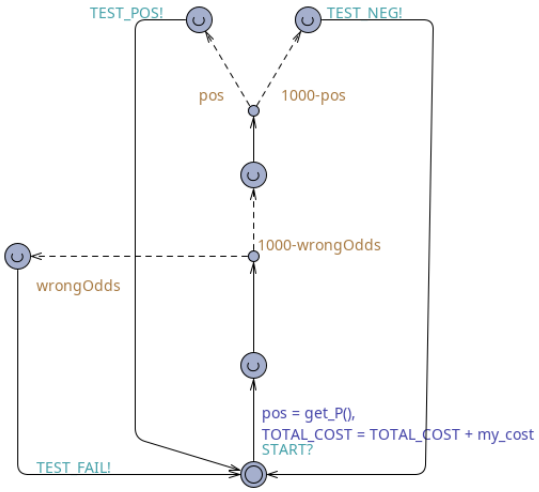

FIGURE 51: PSG Model

```
int tabl[2] = {0, 1000};
int pos = 0;
int my_cost = 1250;
int wrongOdds=50;
int get_P(){
    return tabl[has_osa];
}
```

C.4.2 PG

Same model as PSG, but with the following:

```
int tabl[2] = {0, 1000};
```

C.4.3 ODI

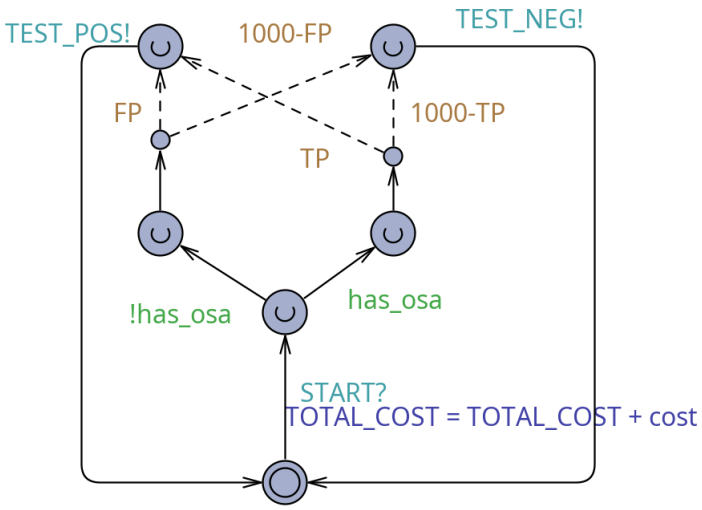

FIGURE 52: ODI Model

```
int FP = 500; //trans
int TP = 1000; //trans
int cost = 120;
```

C.4.4 Anemnesis

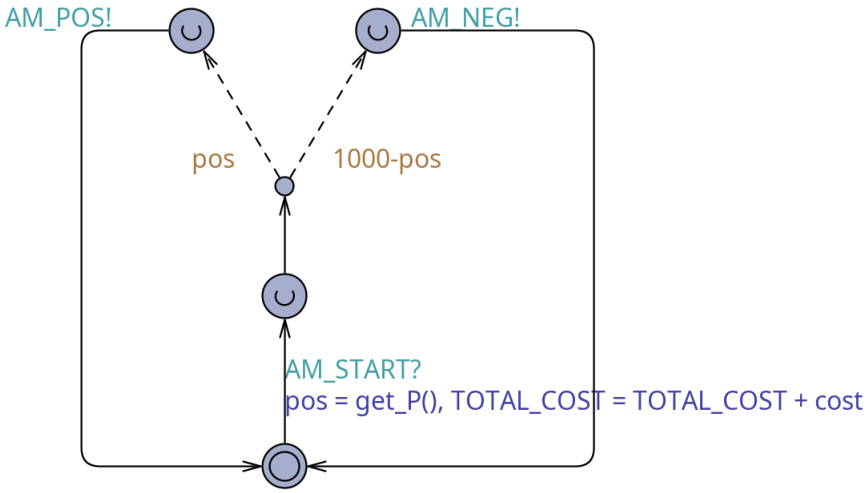

FIGURE 53: Anemnesis Model

```
const int FP = 333; //trans
const int TP = 1000; //trans
int tabl[2] = {FP , TP}; // FP, TP
int cost = 30;
int pos;
int get_P(){    return tabl[has_osa]; }
```

C.4.5 StopBang

Uses the same diagram as the Anemnesis model.

```
const int sens = 880; //TRANS
const int spec = 420; //TRANS
int tabl[2] = {1000-spec, sens}; // FP, TP
int cost = 0;
int pos;
int get_P(){
    return tabl[has_osa];
}
```

C.4.6 BerlinQ

Uses the same diagram as the Anemnesis model.

```
int tabl[2] = {300,460}; // FP, TP
int cost = 30;
int pos;
int get_P(){
    return tabl[has_osa];
}
```

C.4.7 Phillips 3 Value

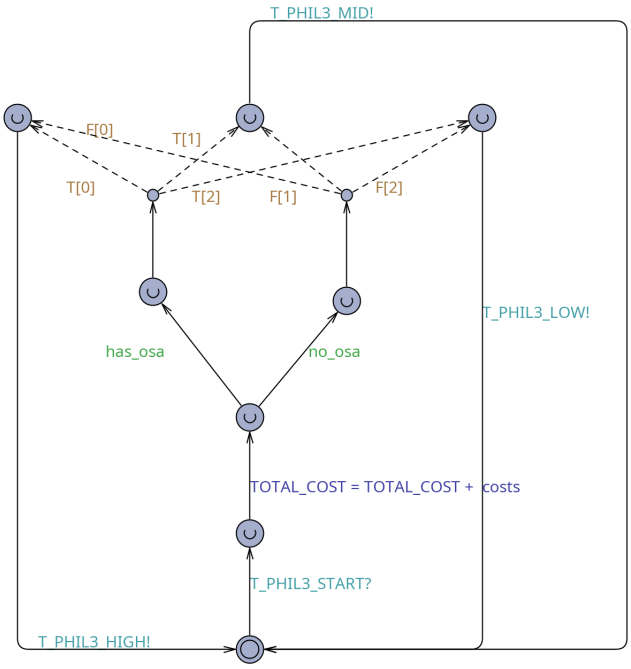

FIGURE 54: Phillips 3 level QModel

```
int costs = 0;

int T[3] =  {333, 444, 222};
int F[3] = {100,300,600};
```

C.4.8 Phillips High

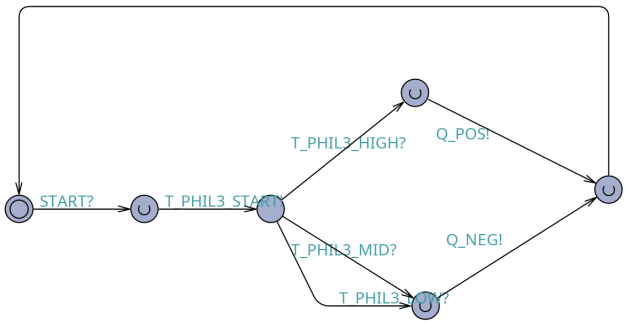

FIGURE 55: Phillips High Model

C.4.9 Phillips Low

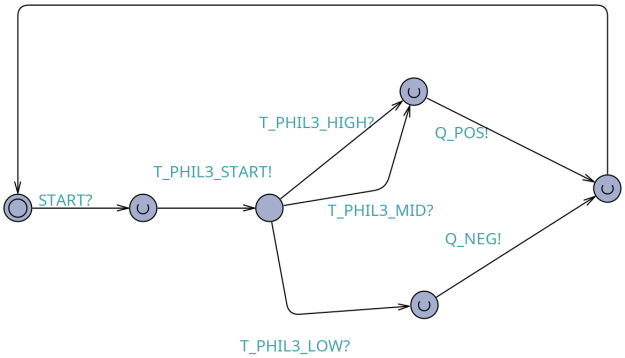

FIGURE 56: Phillips Low Model

C.5 CPAP

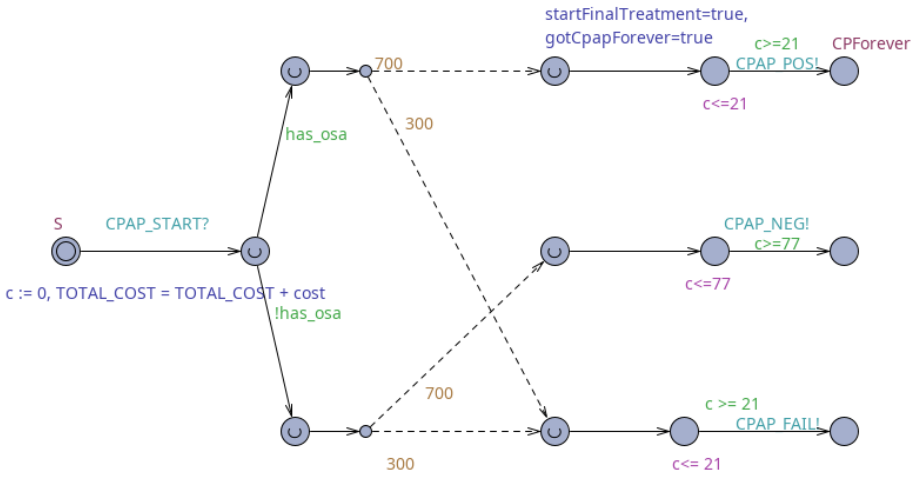

FIGURE 57: CPAP Model

```
clock c;
int cost = 350;
int MT = 21;
```