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Economic Decision Modeling in Dental Care: Towards Making Better Use of Resources in the Context of Pulpal Disease Management

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Table of Contents

List of Tables & Figures

List of Abbreviations

BEMA	*Einheitlicher Bewertungsmaßstab für zahnärztliche Leistungen* (uniform fee scale for dental interventions)
CaOH	Calcium Hydroxide
CBA	Cost Benefit Analysis
CEA	Cost Effectiveness Analysis
CUA	Cost Utility Analysis
DHS	Dentin Hypersensitivity
EE	Economic Evaluation
GOZ	*Gebührenordnung für Zahnärzte* (fee scale for dentists)
IADT	International Association of Dental Traumatology
ICER	Incremental Cost Effectiveness Ratio
IOM	Institute of Medicine
MTA	Mineral Trioxide Aggregate
RCT	Root Canal Treatment
RCT	Randomized Controlled Trial
SA	Sensitivity Analysis
SMD	Standardized Mean Difference Pain Scale
VAS	Visual Analogue Scale for Pain Evaluation
VRS	Verbal Rating Scale for Pain Evaluation
WTP	Willingness To Pay

1 Introduction

1.1 Relevance and Motivation

Dental care within the context of the **German health care system** differs from other types of medical care due to the **high proportion of cost sharing** by patients. Many state-of-the-art dental treatments require high **private cost contributions** from patients (KZBV 2018), but close to **90% of the patient population** have **serious doubts about the benefits** of additional medical services offered to them (Klemperer and Dierks 2011). Hence, there is a strong imperative for **transparent communication of the value for money** of care that is provided to patients (Klingenberger et al. 2006). Beyond the actual call for cost sharing, today's **dental care decision making** increasingly **requires knowledge sharing** and demands **shared decision making** (Frosch and Kaplan 1999). Hence there is a strong need for dentists to provide **patient-centered advice** (Johnsson and Nordgren 2019) and **highly personalized information about the benefits of treatment options to patients** (Elwyn et al. 2010). The **dentist´s role as an advisor** is becoming **increasingly important** beyond the sole role of providing high-grade technical services to patients in clinical processes. **Education and counseling** of patients as well as **informing and explaining** proposed diagnostic and therapeutic measures **takes up an increasingly large portion of the daily work routine** (Klingenberger et al. 2006).

However, **several challenges exist in daily clinical practice** that may have an **impact on the implementation** of the latter **requirements** into **today´s clinical decision making**.

What is special about dental care decision making and why may it be difficult for dentists to transparently communicate value for money to patients? The economic concept of **asymmetric information** (Hillier 1997) **is highly applicable to the dental health decision making context**. In clinical practice, dentists advise patients on which therapeutic option to choose, since dentists have significantly higher knowledge of treatment options and corresponding health outcomes (Darbar 2018). The **knowledge gap** between dentists and patients can create a significant **imbalance of power**, which makes it **difficult for patients to assess the appropriateness of recommended treatment options** (Arrow 1963). It needs to be considered that within this asymmetric information constellation dentists may have an **income interest** since they earn money from executing the recommended treatments. The risk of **supplier-induced demand** is inherent to dental care decision making scenarios (Birch and Listl 2015). This raises the **serious question** of the **extent to which dentists consider only patients' preferences for value for money when giving advice to patients on which treatment option to choose**. As a result, **unbiased evidence about the value for money of recommended treatment options is needed** for clinical decision making in dental care.

Why may it be difficult for dentists to provide personalized health care recommendations to patients? There are several challenges making it difficult for dentists to provide personalized healthcare recommendations to patients. Historically**, providing personalized information** to patients may have been an **underdeveloped area**. The **classic social model of the dentist-patient relationship** (Sondell and Soderfeldt 1997), under which dentists only provide little information about planned treatment and under which patients blindly follow dentists' advice, **is no longer valid** (Klingenberger et al. 2006). Today's preferred model is characterized by **mutual coherence** and **participation in the decision process** (Reissmann et al. 2019) and by **mutual agreement on therapeutic option choices** (Scheibler and Pfaff 2004). This raises the question of **how patients' preferences can be accounted for and how therapies can be tailored around patients' needs**. In many cases, **patients' preferences** in clinical practice are **limited due to budget restrictions** (Varian 2003). Therefore, **dentists must be able to advise which options to choose in a limited resources scenario**. Dealing with **decision making under budgetary constraints** of patients is becoming a **crucial pillar in todays' clinical practice**. However, **evidence for decision making under budgetary constraints is limited** and not readily available in all fields of dentistry (Shariati et al. 2013).

How can health economics contribute to addressing the challenges, i.e. establishing evidence for the transparent communication of the value for money and enabling shared decision-making support to patients under budgetary constraints?

Health economics is the discipline applying economic toolkits to **health care scenarios** (Arrow 1963) and **economic evaluation (EE)** is a concept that is used when **choices need to be made between different alternatives** (see section 2.1). **EE** can be applied to the

oral health context in order to identify, to measure and to **value the inputs and outputs of alternative options (i.e. therapeutic options),** thereby **enabling a comparative analysis of one or more treatment alternatives with the goal of maximizing the health output under a given budget** (Drummond 2001). There are **several benefits** resulting **from applying EE** techniques to the **dental care setting**. When EE is applied to daily clinical decision making contexts, the analysis can **reveal the real value of treatment options for the money without risk of supplier-induced demand** (Birch and Listl 2015). Furthermore, EE can **simulate decision making under consideration of budgetary constraints**, even though budget restrictions might be **a priori unknown** (Elhanan 1988). Hence, EE can be considered as **enabler** of **evidence-based** and **patient-centered decision making in the dental care context**.

The **motivation** of this dissertation is to **explore the extent** to which existing **health economic frameworks can be applied to the oral health context** and to assess how the application can help dentists and patients **to better choose from therapeutic options**. This dissertation aspires to **show the limitations of daily clinical decision making** and attempts **to demonstrate how EE can be applied to overcome these limitations**. Moreover, beyond the technical economic analysis, this dissertation aspires to give an outlook on what **impact EE** can have **beyond the micro-economic level**. It will be discussed to what extent EE can contribute to total welfare improvements and to real world change (i.e. by creating **awareness** that might ultimately **induce willingness of dentists** to embrace new treatment approaches). Since evidence in health economics for dentistry has been a neglected concern (Shariati et al. 2013), especially within the German context (Kirch 2008), **this dissertation claims to be the first comprehensive health economic contribution in the field of endodontics**.

Bringing it all together, **EE can help to make better use of resources in the context of oral disease management**, which is the **key motivation of this dissertation**, with the latest evidence suggesting that up to **34% of expenditures in health care are wasted** or **allocated towards inappropriate health care decisions** (OECD 2017).

Since the focus of this dissertation from a dental medical perspective is on **endodontics**, this area of dentistry will be introduced in the next section first.

1.2 Endodontics – Pulpal Disease Management

Endodontics is a field within **conservative dentistry** that deals with the **anatomy and physiology of the pulp** as well as with the **diagnosis**, **treatment** and **prevention** of **pathologies** of the **dental pulp** and **surrounding tissues** (Weber 2017). The **pulp** is defined as the **soft tissue** inside the tooth that contains **nerves, vessels and lymphatic tissue** (Hargreaves and Louis H. Berman 2015).

Pathologic conditions of the pulp can occur when **bacteria** enter the pulp and cause an inflammation that can **ultimately lead to tissue death**, which is associated with a tooth becoming **de-vital,** or even cause an **inflammation** of the tissue surrounding the root ends of a tooth. There are different ways in which **bacteria enter the pulp**, but most infections occur as a result of the **dental pulp having been exposed**, e.g. by deep carious lesions or trauma (Sivapathasundharam 2016). An **overview** of different **pathologic endodontic conditions** and **possible treatments** can be depicted as follows:

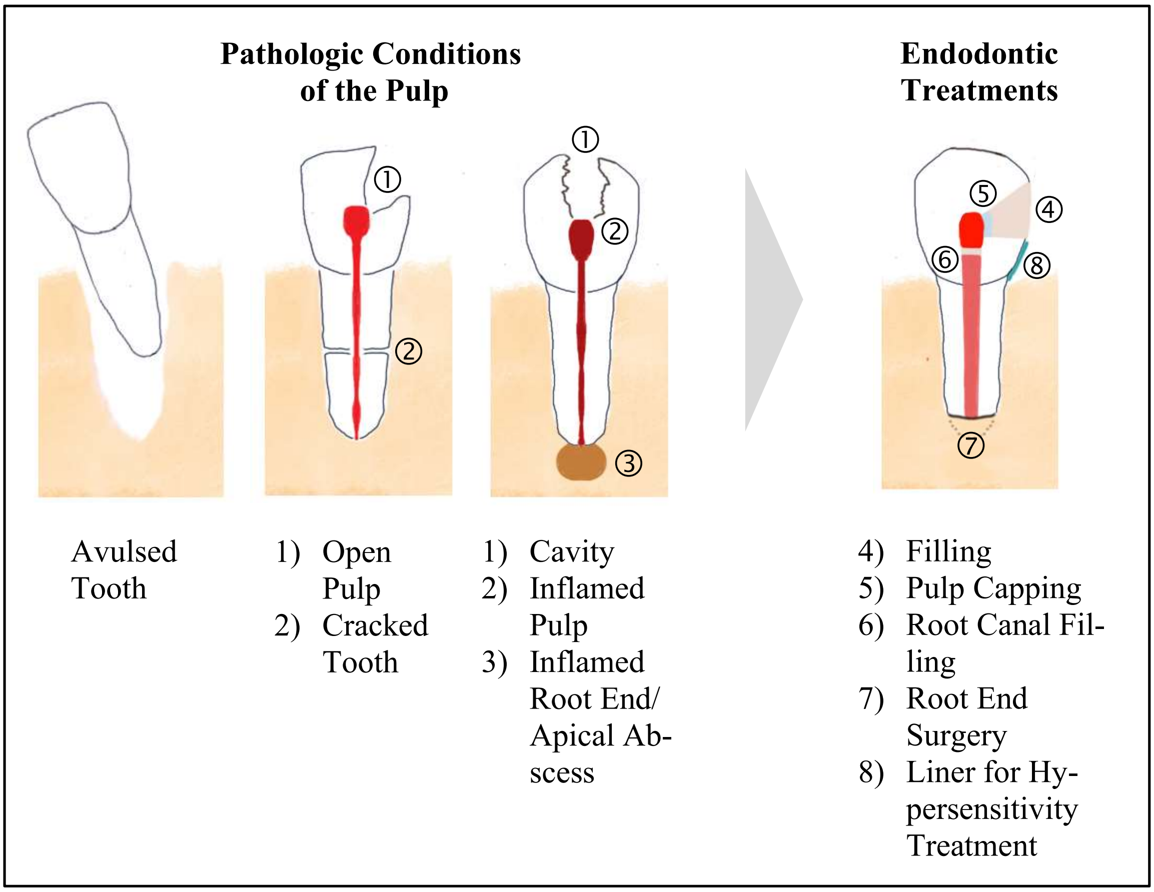


Figure 1: Overview of Pathologic Endodontological Conditions and Treatments (Own - Derived from (Weber 2017) p.71)

Endodontic treatments (Hargreaves and Louis H. Berman 2015) can be mainly **categorized** into **preventive endodontics** (e.g. protection of the pulp), **conservative endodontics** (e.g. root canal treatment and re-treatment in case of failed first line root canal treatment), **endodontic surgery** (e.g. root-end surgery) and **trauma treatment** (e.g. treatment of a cracked tooth).

Different **therapeutic treatment options exist** that can be applied to **prevent or eliminate an inflammation** of the root canal system and result in a **positive long-term prognosis** for a tooth **to remain in the mouth** as an alternative to ultima ratio treatment, i.e. extraction. These include:

- **Treatment of pulpal discomfort** (e.g. pain hypersensitivity treatment – **see chapter 3**)
- **Pulp capping** (applying a "patch" to a small pulp opening in certain cases – **see chapter 4**),
- **Root canal treatment** (removal of pulpal tissue after irreversible infection, disinfection of the root canal system and obturation – **see chapter 4**)
- **Root canal re-treatment** (re-treatment of failed first-line root canal treatment – **see chapter 4**)
- **Root end surgery** (surgical removal of an inflamed root end after root canal treatment)
- **Treatment of trauma** (e.g. re-plantation of a tooth that has been out of the pocket – **see chapter 5**)

Even though **clinical research in endodontics** has experienced strong growth, **especially over the last decade** (Naik et al. 2016), the latest **clinical evidence** has **not** yet **fully translated into the German public health care system** (KometDental 2018). Compared with other fields of conservative dentistry, **endodontics still requires very high cost contributions** from patients since **reimbursement regulations for endodontic treatments are very restricted** (KZBV 2018). **Decision scenarios** in endodontics are **highly applicable for health economic research** due to the vast availability of therapeutic alternatives and due to considerable cost differences and cost contributions involved for patients. For defining the scope of this dissertation, several scenarios will be introduced in the next section.

1.3 Clinical Scenarios for this Dissertation

Three distinct, relevant and clinically meaningful decision making scenarios in endodontics are addressed in this dissertation. The aim here is that these clinical scenarios cover all **major treatment categories** presented in the previous section to ensure a broad-based health economics analysis for the field of endodontics:

1. **Pain Scenario**: a patient is visiting the dentist's office due to a painful tooth when drinking or eating. In many cases, pain is related to **dentin-hypersensitivity** of a tooth, which can be treated by administration of pain-reducing agents. However, there are many different agents that can be applied to a sensitive tooth. Some treatment options are covered by public health insurance, some treatments require co-pay (Lin et al. 2013). The question is then **which agent should be applied and under which conditions it makes sense to invest in more expensive treatments for pain reduction?** For further details see Chapter 3.

2. **Open Pulp Scenario**: when a dentist is treating a deep carious lesion of a tooth, the pulp can be opened, which requires follow-up treatment. One first-line treatment option is treating a tooth with pulp capping (Mente et al. 2014), for which different materials can be used (CaOH or MTA). However, MTA requires co-pay from a patient. Evidence is needed to determine under which conditions it makes sense to invest in MTA as a material for pulp capping. Since both agents have failure rates, cost and clinical effectiveness of follow-up treatment need to be taken into account. The question is then **if and under which conditions does it makes sense to invest in MTA as more expensive material** in case of an open pulp? For further details see Chapter 4.

3. **Trauma Scenario:** a patient is visiting the dentist's office due to an avulsed tooth (tooth out of pocket) caused by trauma. If the tooth has not been out of the pocket for a long time and has been stored properly, a dentist can recommend replantation

of an avulsed tooth (Andreasen et al. 1995). However, the cost of replantation is high and there is a risk of failure. Clinical data is very limited for success rates of replantation of an avulsed tooth and evidence-based decision making is only conditionally possible. The question is then **under which conditions does it makes sense to invest resources into re-planting a tooth? A priori it is not clear if a robust model can be built upon the rudimentary clinical data available. The goal is to assess decision uncertainty within the model.** For further details see Chapter 5.

All together, it can be stated that with **9 million hypersensitivity treatments, 7 million root canal treatments and 0.8 million pulp capping treatments** performed in Germany each year (see section 3.2 and section 4.2), all these scenarios are **highly relevant clinical scenarios for general dental practitioners as well as for dentists specialized in endodontics**.

1.4 Research Questions

Based on the clinical scenarios, three **distinct** and **concise research questions** were formulated, which will provide guidance for the three main chapter of this dissertation and will be profoundly explored and discussed:

1. **Which** of the currently available **treatment options** for **dentin hypersensitivity** is the **most cost-effective**? The hypothesis is that there might be treatment alternatives that are more cost-effective than the gold standard treatment (chemical occlusion).

2. There is evidence that **MTA** has a high clinical effectiveness when treating an **open pulp**. However, MTA is also more expensive than **CaOH** and treatment alternatives outside of pulp capping exist. The question arises **which treatment option is cost-effective in the long run** when cost and effectiveness of follow-up treatments are considered. The hypothesis is that the application of **transition state modeling** enables long-term decision making.

3. Is **replantation** of an **avulsed tooth** a **cost-effective treatment** alternative in case of dental trauma, or are other therapeutic alternatives more cost-effective? The hypothesis is that a robust model can be built from the limited clinical data available and that variance analysis can be applied to **assess the uncertainty of decision making within the model**.

The **goal of this dissertation** is to **identify the most cost-effective therapeutic alternatives for the given scenarios** by modeling clinical decision situations based on 1) currently available **clinical evidence** for the **effectiveness** of treatments of teeth and the periodontal system in case of pulpal disease treatment, and 2) available **cost** information within the context of the public and private **German health care system**.

Since there are various approaches available that can be used to identify cost-effective therapeutic alternatives in endodontics, the **next chapter** will focus on assessing available methodologies in health economics and will provide details about the methodical approach for this dissertation.

2 Methodology

2.1 Background

Three main types of **EE analysis** in health economics can be differentiated. **Cost Effectiveness Analysis (CEA)**, **Cost-Utility Analysis (CUA)** and **Cost-Benefit Analysis (CBA)** are established tools for modeling. With these tools, cost and health outcomes for two or more treatment alternatives can be weighed up and evidence-based recommendations for therapeutic alternatives can be derived (Drummond 2001). The suitability of each tool for the given scenarios in this dissertation will be assessed in the following sections.

2.1.1 Cost Effectiveness Analysis (CEA)

CEA was first introduced in 1977 by Weinstein (Weinstein and Stason 1977). CEA is an evaluation technique in which the clinical outcome of a treatment (effectiveness) and the resources used for treatment (cost) for different treatment alternatives are analyzed **comparatively** by calculating the cost per non-monetary outcome measure for each available alternative:

$$\text{Cost Effectiveness (of Alternative)} = \frac{\text{Cost (of Alternative)}}{\text{Effectiveness (of Alternative)}}$$

In CEA, **cost** is measured in *monetary units*. **Effectiveness** is measured in *non-monetary units*, e.g. life-years gained, pain-free years/days, number of post-treatment complications, patient satisfaction, etc.

After cost and effectiveness of different alternatives have been calculated, rules are described for decisions making based on the relation between the two numbers (Robinson 1993). For instance, when Cost of Alternative 1 < Cost of Alternative 2 and Effectiveness of Alternative 1 > Effectiveness of Alternative 2, it is easy to reject Alternative 2.

In economics, marginal considerations always play an important role and economists prefer to analyze the extra cost that is needed to gain an increment of effectiveness Therefore, the concept of **incremental cost-effectiveness ratios (ICER) is introduced for CEA**:

$$\text{Incremental Cost Effectiveness Ratio} = \frac{\text{Cost of Alternative}_1 - \text{Cost of Alternative}_2}{\text{Effectiveness of Alternative}_1 - \text{Effectiveness of Alternative}_2}$$

ICERs allow analysts to make statements about the incremental cost of one additional unit of health whenever two therapeutic alternatives are compared (Pearson 2018).

2.1.2 Cost-Utility Analysis (CUA)

Cost-utility analysis (CUA) is a derivate of CEA that includes the **time factor** and the **utility**. The first CUA was published in 1968 (Klarman 1968) on renal disease. CUA became the technique of choice when **overall health of a patient is assessed**. It is measured in Quality Adjusted Life Years (QUALY). A QUALY is a “life year gained” multiplied by the “utility ratio” (number ranging from 0=death to 1=perfect health). For example: If a patient is about to die without treatment within one year at 20% of perfect health, his QALY is 0.2*1=0.2 QUALY. If a treatment allows him to live 5 more years at 60% of perfect health, his QUALY with treatment would be 5*0.6=3.0 QUALYs and his net gain for the treatment would be 2.8 QUALYs (Zweifel 2013).

2.1.3 Cost-Benefit Analysis (CBA)

CBA was first used in health care in 1962 (Roberts 1962). CBA differs from CEA in that **monetary units** are **assigned** to **both cost** *and* **clinical effectiveness**. It may be the case that a common unit of measurement is needed for different alternatives, and since money is a very convenient and common unit it is used in CBA for measuring clinical effectiveness. In order to compare alternatives, the benefit-cost ratio is calculated for each alternative.

$$\text{Cost Benefit Ratio} \quad = \frac{\text{Benefit (of an Alternative)}}{\text{Cost (of an Alternative)}}$$

Using monetary measures as a vehicle makes it also possible to integrate qualitative and quantitative measures into a common summary, the cost-benefit ratio. The cost-benefit ratio can be calculated for every single alternative and indicates whether the costs outweigh the benefits. A widely accepted advantage of CBA is that the unit of analysis (monetary units) can be easily and universally understood by decision makers (Leung 2016).

2.2 Applied Methodology of this Dissertation

Historically, **methodology choice has been a matter of dispute in EE** and the analyses at hand have various pros and cons that are evaluated for this dissertation at this point (Drummond et al. 1993).

CBA has the advantages of providing a **common monetary denominator** of inputs and outputs, but there are **several challenges** inherent in the use of this EE tool in the healthcare context. While **various approaches** exist for the **valuation of health benefits in monetary measures** (e.g. **contingent valuation method** (Olsen and Donaldson 1998), **discrete choice experiments** (Ryan 2004) or **conjoint analysis** (Ryan and Farrar 2000)), there are several reasons given in the literature for why **monetary measures of health benefits are difficult to assess in medical and dental care**. It is argued that it is **problematic** for an individual **to attach value to health** (Drummond 2001), while there is also controversy around the idea of **placing a monetary value on human life** (Card and Mooney 1977). Furthermore, **preference revelation** is problematic when health is partly financed indirectly through a health care system and therefore patients do not necessarily reveal their valuation of benefits in health markets (Watson and Ryan 2007). As of today, comparable and **reliable monetary values** are **not available for dental health benefits** as required by the decision making contexts of this dissertation. Therefore, **CBA is not applied in this dissertation**.

As for **CUA**, transferring this concept to dental health economics means that the impact of oral diseases, treatments and the corresponding clinical effectiveness need to be translated into a QUALY (Kay et al. 2018). However, since oral diseases (except e.g. oral cancer) have only a marginal effect on the utility ratio and the overall expected lifetime of a patient, QUALY data as needed for endodontics is as of today not available. An alternative approach to QUALY is to measure "dental utility" analogously to QUALY "life utility", resulting in a Quality Adjusted Tooth life measure – QUATY. However, endodontic treatment QUATYs have not yet been derived (Mohd-Dom 2014). Therefore, **CUA is not applied in this dissertation**.

There are various reasons why CEA is the methodology of choice for this dissertation. The fact that **underlying clinical studies** provide measures of clinical effectiveness that **can directly be used and extended into required cost-effectiveness makes CEA highly applicable and a very pragmatic approach in the context of this dissertation**. Also, CEA is **suitable for research where costing and budgeting is important** – and this is the case as demonstrated in the scenario description and research question. Therefore, **CEA allows to focus on the key question of this dissertation, to evaluate decision making under budgetary restraints and to highlight the use of scarce resources** (Drummond 2001). However, it needs to be admitted at this point that there might be several limitations inherent to CEA that place limitations on the model and on this dissertation itself. Details concerning the limitations of CEA within the context of this dissertation will be explored in the discussion part (see section 6.2)

After the methodical choice in favor of CEA has been made for this dissertation, the last section of this chapter will deal with CEA **modeling** required to explore the research questions and the **process** that will be followed to implement endodontic health care decision models.

2.3 CEA Modeling and Applied Modeling Process

The CEA analysis of this dissertation will be performed by using the software **TreeAge Pro 2019 (TreeageSoftware 2019)**, which offers a **model building tool** and various **analysis tools** as well as **extended functionalities** (i.e. **variance analysis functions**) designed for the **implementation of CEA in health care**. The software will be used to build **decision trees**, which are mathematical structures that include decision nodes, health states and extended logic and can be used to represent and simulate the health and cost outcomes for a tooth or population for the given scenarios (Myles et al. 2004).

The decision trees of each model are enriched with available **clinical data** from the field of dental medicine, for which a systematic literature research is performed to identify highest available evidence levels for the different scenarios; i.e. a secondary use of published clinical data is performed. To enrich the models with **cost data**, the cost of different alternatives is assessed and calculated according to **BEMA** (*Einheitlicher Bewertungsmaßstab für zahnärztliche Leistungen* (uniform fee scale for dental interventions)) and **GOZ** (*Gebührenordnung für Zahnärzte* (fee scale for dentists)) within the **context of the German health care system**. Health states are included with the introduction of **Markov Models (Cassidy et al. 2019)** and **Monte-Carlo Simulations** (Di Paola et al. 2018) are used to populate the models. The data emerging from the different models will reveal information about the cost effectiveness ratios of different therapeutic alternatives. Risk will be incorporated and analyzed under **sensitivity analysis**. A basic concept and process that the CEA models will follow in this dissertation can be depicted as follows:

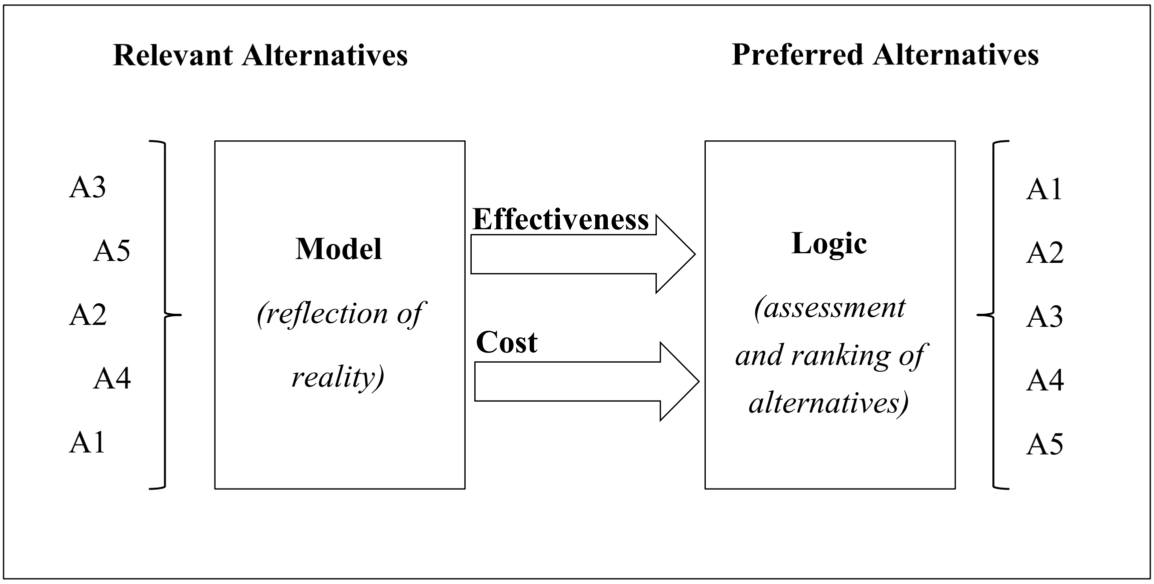


Figure 2: Modeling Process of CEA in this Dissertation (Own – Derived from (Quade 1970), p.236)

Each research question requires its own case-specific model. Therefore, **three different models will be built**, which will result in three main chapters forming the **main part** of this dissertation (**chapters 3-5**).

3 Deciding on the Cost Effectiveness of Therapeutic Alternatives for the Treatment of Algesic Irritation of the Pulp (Dentin Hypersensitivity)

3.1 Background

According to the latest available data from the German Federal Union of Public Dentists (KZVB), treatment for hyper-sensitive teeth within the public German healthcare context occurred **9,346,500** times in 2013 (KZBV 2014). Assuming 302 working days in 2013, a decision in favor of dentin hypersensitivity treatment was made **30,949 times every working day** – only taking into account public dentists. Looking at the data from a different angle, **out of 100 cases** reported to KZBV in which conservative or surgical treatment was needed, **10.2 cases (i.e. 10.2%) included dentin hypersensitivity (DHS) treatment**. Given that 50,264 public dentists were registered in 2014, the conclusion can be drawn that – on average – **every single public dentist decided for, performed and accounted for DHS treatment every second working day**.

The numbers above make it quite obvious that most dentists clearly decide to treat the condition of DHS, and it has become a very common standard treatment in Germany's healthcare system. However, **the best way to treat the condition is still a matter of dispute from a health economics perspective**. There are various ways to treat this condition. Considering the absolute numbers of treatments performed per year in Germany, the need for a health economics analysis is readily apparent.

3.2 Dentin Hypersensitivity (DHS) from a Medical Perspective

Before delving into the effects of how to treat DHS, this dissertation will convey a deeper appreciation of the medical science behind DHS. The question that will be addressed is how DHS is defined from a medical perspective and what conditions and processes that cause this pathologic condition are.

3.2.1 DHS Definition and Overview

The **definition of DHS** is as follows:

> *"A short **sharp pain** arising from exposed tubuli in response to **various stimuli** ... which cannot be ascribed to any other form of dental defect or pathology"(Holland et al. 1997).*

Stimuli causing pain range from thermal, electrical, mechanical (tactile), osmotic and evaporation to chemical stimuli. The **thermal stimulus (cold) is most common** among patients (Shiau 2012). Not every patient suffering from DHS will seek in-office treatment, since the **pain presentation** may only be in the range of a minor inconvenience. But patients may also end up with quality-of-life disturbing pain (Hellwig et al. 2009).

It is important to be clear about the **differential diagnosis of DHS.** Before a diagnosis of DHS can be made, **other defects and pathologies must have been ruled out**. Normally, this is done by asking the patient for pain quality and duration. **Pain** caused by DHS normally **lasts as long as the stimulus**. Other pain-causing defects or pathologies (e.g. cracked tooth syndrome, pulp infection, and pulpal sensitivity) normally feature a different pain presentation. For instance, pulp infection features a long-lasting pain and exaggerated response to a stimulus (Chen and Abbott 2009). The **focus here is strictly limited to DHS**, and other pain-causing dental conditions are not considered.

3.2.2 Macro- and Micro-Anatomy of DHS

It is important to understand what causes the discomfort or even pain when speaking about DHS and what the medical preconditions that may lead to DHS are. An analysis of the tooth anatomy and physiological processes behind DHS is therefore provided here.

Macro-anatomy: DHS can only occur when the **dentine surface is exposed** and **dentinal tubules are open** (Addy et al. 2000). This is the case e.g. when **gingival recession** occurs, **cementum is abraded,** enamel is **attrite,** or an **erosion** is persistent. Therefore, DHS can only persist with a pre-existing pathology.

Micro-anatomy: Dentin is characterized by having **tubules** which **reach from the dentin-enamel junction to the pulp**. Tubules are filled with a serum-like fluid and odontoblast cells, which are located in the pulp chamber. Odontoblasts, in turn, are accompanied by or connected with nerve-endings of neurons, which, when polarized, send signals to the brain. In other words, dentin has tiny “pores”, which connect the tooth’s surface with the pulp. Through this connection, a stimulus can be conducted from the pathologic tooth surface to the pulp, and **stimulation of the pulp is mostly related to pain**.

Physiology: There are currently three main theories in the literature to explain the physiology of DHS and how a stimulus is conducted (Garg and Garg 2010):

- **Neural theory**: Nerve fibers in the dentine tubule are directly excited by a stimulus and afferent neurons forward the stimulus to the brain, resulting in pain.
- **Odontoblastic transduction theory**: Odontoblasts receive the stimulus and transmit the stimulus to sensory nerve endings via a synapse.
- **Hydrodynamic fluid shift theory (Brannestrom 1963)**: Fluids in the dentin tubule are deviated inbound and outbound and the fluid shift stimulates nerve endings in the pulp.

The **hydrodynamic fluid shift theory is the most widely accepted**. However, there is as yet no final agreement on the mechanisms to fully elucidate DHS (Lin et al. 2013).

3.2.3 Epidemiology

A systematic review by Splieth (Splieth and Tachou 2013) on the **prevalence of DHS** revealed that reliable longitudinal studies hardly exist. The prevalence in existing studies ranges from 3% to 98% in adults, whereas most studies conclude that the prevalence ranges from 3 to 57%, depending on the study sample. However, there are many reasons why existing studies are not representative (e.g. selection bias, diagnostic criteria, etc.). Therefore, Splieth and Tachou estimated that the life-time prevalence is supposedly 100% and 1-3 month prevalence “**will range from 10 – 30% in adults** with very little variation for gender or age in a population sample” (Garg and Garg 2010).

3.2.4 Treatment Alternatives (Strategies) and Desensitizing Agents

There are **various options for the treatment of DHS**, but being aware of the fact that the pre-conditions for DHS are exposed and open tubules, the main strategy behind treatment quickly becomes clear – **occlusion of open tubules**:

- **Physical occlusion** of the dentin tubule to prevent the flow of fluids
- **Chemical occlusion** of the dentin tubule to prevent the flow of fluids

Furthermore, interruption of stimuli is also a legitimate option:

- **Nerve desensitization** with potassium nitrate
- **Laser treatment**

The table below shows that different treatment "**agents**" are available for every category mentioned above.

Treatment Strategy:	Physical Occlusion	Chemical Occlusion	Nerve Desensitization	Laser Therapy
Treatment Agents:	Pumice Paste Sodium Bicarbonate Hydroxyapatites Bioglasses Glassionomers Dentin Bonding Agents* Resin Adhaesive*	Fluorides** Oxalates Glutaraldehyde Agents Calcium compounds	Potassium nitrates (NK) Guanethidine	XGY:Laser
	** Mostly used in this category*	*** Brand e.g. Duraphat*		

Figure 3: DHS Treatment Options and Agents (Lin et al. 2013)

At this point, it may be noted that the table above does not include treatment agents like desensitizing toothpastes or desensitizing mouth wash and the like. This is because this dissertation is **limited to in-office treatment alternatives and agents**, and toothpastes etc. are **non-prescription home-care products** and therefore are **not considered in this model**. But it is highly recommended to apply home-use desensitizing agents in case of light DHS as a first step before looking for in-office treatment (Garg and Garg 2010).

3.3 Health Outcomes and Clinical Effectiveness of DHS Treatment

3.3.1 Underlying Meta-Analysis for CEA Modeling

For an economic evaluation model in DHS treatment, recent and reliable data on clinical effectiveness is needed. Systematic review of the literature was conducted, using the PubMed-Database. The Query „Dentin Hypersensitivity“ & „Meta Analysis“ (01.11.2018) specified a result-set of 5 publications from within the last 10 years. Search Criteria were:

- ("dentin sensitivity"[MeSH Terms] OR ("dentin"[All Fields] AND "sensitivity"[All Fields]) OR "dentin sensitivity"[All Fields] OR ("dentin"[All Fields] AND "hypersensitivity"[All Fields]) OR "dentin hypersensitivity"[All Fields]) AND (Meta-Analysis[ptyp] AND "2005/01/11"[PDat] : "2014/01/11"[PDat])

Out of the 5 Meta-analyses, **4 publication** were **excluded** according to the following reasons:

- (Sgolastra et al. 2013) was restricted to laser treatment
- (De Munck et al. 2012) was restricted to dentin bonding
- (Cunha-Cruz et al. 2011) was restricted to oxalates
- (Poulsen et al. 2006) was restricted to potassium

The data for clinical effectiveness of DHS treatment is taken from:

Lin, et al (2013): In-office treatment for dentin hypersensitivity: a systematic review and network meta-analysis

It was found that Lin´s meta-analysis comprises all treatment options that can be chosen by dental health decision makers as of today for the treatment of DHS. Furthermore, an evaluation of the meta-analysis using the PRISMA Checklist (PRISMA 2015) was positive, thus ensuring the transparency and completeness of the meta-analysis at hand.

3.3.2 Clinical Parameters used for CEA Modeling

The clinical effects in Lin's network meta-analysis that will be used for decision modeling are shown below:

	Clinical Effect SMD Pain Scale Reduction	(95% CI)
Physical Occlusion vs. Placebo Treatment	**-2,57**	**(-4,24 ; -0,94)**
Chemical Occlusion vs. Placebo Treatment	**-2,33**	**(-3,65 ; -1,04)**
Nerve Desensitization vs. Placebo Treatment	**-1,72**	**(-4,0 ; 0,52)**
Laser vs. Placebo Treatment	**-2,81**	**(-4,41 ; -1,24)**
Combination Therapy	**-3,47**	

Figure 4: Pair-wise Meta-Analysis of Clinical Effectiveness for Different In-office Treatments of DHS (Lin et al. 2013)

3.3.3 Meta-Study Pain Scale: Standardized Mean Difference (SMD)

The pain scale for measuring the clinical effectiveness of DHS treatment that was used in Lin's meta-analysis needs some further explanation to ensure sure that results are correctly interpreted. Basically, a meta-analysis is a statistical evaluation aiming at the aggregation of results of different independent single studies (e.g. clinical trials) for further analysis and interpretation. In many cases however, different clinical studies may use different clinical measurement (i.e. scales in the field of pain) as well as clinical end points. Aggregating clinical data and results therefore presents a challenge, and a common "denominator" needs to be defined that allows aggregating the data.

In Lin's meta-analysis, two different pain scales were used in the underlying clinical trials:

- **Verbal Rating Scale** (**VRS**): Uses **verbal descriptions** (None, Mild, Moderate, Severe Pain) according to (Holland et al. 1997).
- **Visual Analogue Scale** (**VAS**): Uses a **line of 10 cm;** patients mark the pain presentation on the line (Scott and Huskisson 1976)

The **Standardized Mean Difference (SMD) pain scale** was introduced by Lin as a way to aggregate the data at the meta-level. The standardized mean difference "can be viewed as the mean difference that would have been obtained if all data were transformed into a scale where the standard deviation within-group was 1.0" (Lin et al. 2013).

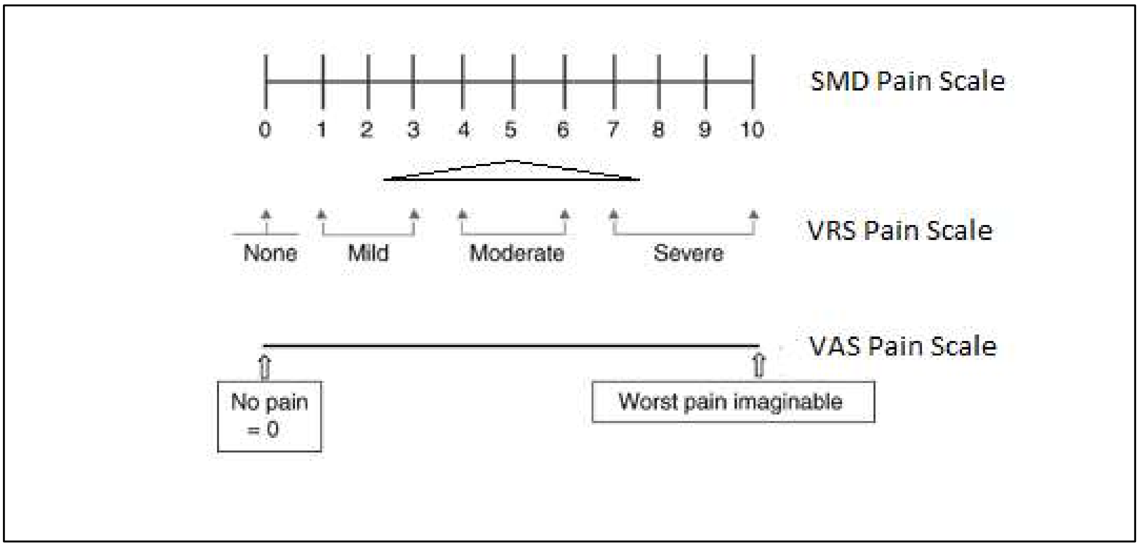


Figure *5: SMD, VRS and VAS Pain Scales – taken from (Lin et al. 2013) p.5)*

As a result, calculated effects and standardized mean differences that are used in the model have to be considered as "numbers", which are not necessarily related anymore to the original measurement scale. As can be seen in Figure 5, a pain reduction of e.g. 3.0 on the SMD Pain Scale could have enough impact on the VRS Pain to reduce "medium moderate" pain to "medium mild" pain.

3.4 Cost Modeling in the Context of the German Health Care System

This dissertation accounts for DHS treatment as listed in the German fee schedule for dentists GOZ and BEMA (KZBV 2018). **"*GOZ*** *is uniformly valid throughout Germany and constitutes the medical fee schedule for* ***privately insured patients***" (Listl and Faggion 2010). It rules that basically all dental treatments are to be accounted for according to GOZ, unless there is another federal law that constitutes "something different", which is the case for BEMA. **BEMA** is an agreement between the Federal Union of Public Dentists and the Union of Public Health Insurances and defines medical fees **for publicly insured patients**. GOZ and BEMA use an **activity-based costing system**, which means that activities that can be charged to patients are defined in GOZ and BEMA and total costs arising from a treatment are defined by adding up the activities that were performed.

In general, treatment for privately insured patients is more costly, since e.g. treatment is performed by chief dentists and more time can be allocated to the patient by the dentist, which allows for an increased time factor that results in higher costs. Furthermore, it should be stated that every publicly insured patient can request privately insured treatment standards according to GOZ, However, the difference between GOZ and BEMA needs to be covered by the patient privately.

The cost arising from DHS treatment depends on the insurance type of the patient (publicly or privately insured) and on whether special treatment agents (e.g. laser) are requested by the patient or not. To take these differences into account, two different scenarios are created in order to show a simplified monetary reflection of reality for DHS treatment:

Scenario A: In the **publicly insured patient** scenario, basic treatment and basic treatment agents are accounted for according to BEMA. Laser treatment is not covered by public health insurance and must be paid for privately according to GOZ.

Scenario B: In the **privately insured patient** scenario, basic treatment, basic treatment agents and laser treatment are accounted for according to GOZ.

Cost of activities during DHS treatment is calculated according to GOZ and BEMA on the basis of the following formula (Bundesgesetzblatt 2001):

$$\text{Cost (GOZ, BEMA)} = p\text{ (GOZ, BEMA)} * \mu * \pi$$

- p (GOZ / BEMA) is the chargeable item points for a certain activity according to GOZ/BEMA
- μ is the monetary conversion factor (€ 0.0562421 per GOZ item point and € 0.95 according to BEMA)

- π is the treatment time factor, dependent on the complexity of the individual case" (π=1 with GOZ, π = 2.3 or 3.5 with BEMA)

The standard treatment process is modeled by adding up **activities** i.e. cost drivers:

- Anamnesis and consulting (BEMA: Ä1, GOZ: 0010)
- Dentist performs symptom-specific intra-oral inspection (BEMA: Ä5, GOZ: 0010)
- Vitality testing for differential diagnosis (GOZ: 0070, BEMA: ViPr)
- Treatment of hypersensitive teeth (BEMA: ÜZ, GOZ: 2010)

3.5 Assumptions for Modeling of DHS Treatment

The following **further assumptions for cost modeling** are made:

- Hypersensitive teeth are present in both the **maxilla and mandible** (upper and lower jaw).
- **4+ teeth** are hypersensitive, which allows an increased treatment time factor of π = 3.5.
- **One treatment - one effect** assumes that there is no follow-up treatment needed in the model and the clinical effect is reached by one in-office-treatment session.
- **Cost modeling of laser treatment**: according to current GOZ and GEMA regulations, the inclusion of laser for DHS treatment must not be accounted for as a separate item and cannot be charged to the patient. However, laser treatment for DHS is a fairly new field and GOZ and GEMA regulations do not yet fully take write-off of laser equipment into account at the time when this model was created. Therefore, accounting of laser treatment in the field of DHS is considered to be **understated in GOZ and BEMA**. This is further backed by the fact that the German Society for Dental Treatment with Laser in 2014 petitioned for an update of GOZ accounting standards and for the inclusion of laser treatment in areas where clinical effectiveness of later treatment has already been proved. As a result of this petition, 9 treatment items were included in GOZ which allow to account for laser equipment (Esser 2014). Economic analysis requires a cost model that allows

encoding reality in a formal model. Therefore, this thesis will use the average cost of 9 treatment items for which laser usage has been included in 2014. **The cost that will be used in this model is € 16.19** for laser treatment.

3.6 Cost Modeling of DHS Treatment

Taking all previous assumptions into account, a DHS treatment session would be accounted for as follows:

DHS treatment without laser:	**Privately insured – GOZ**	**π = 2.3**	**π = 3.5**
	anamnesis & consulting	€ 10.72	€ 10.72
	intra-oral inspection	€ 10.72	€ 10.72
	vitality testing	€ 6.47	€ 6.47
	DHS treatment (1x per jaw)	€ 6.47	€ 19.68
		€ 34.38	**€ 47.59**

DHS treatment with laser:	**Privately insured – GOZ**	**π = 2.3**	**π = 3.5**
	anamnesis & consulting	€ 10.72	€ 10.72
	intra-oral inspection	10,72 €	10,72 €
	vitality testing	6,47 €	6,47 €
	DHS treatment (1x per jaw)	6,47 €	19,68 €
	Laser treatment	16,19 €	16,19 €
		50,57 €	**63,78 €**

DHS treatment without laser:	**Publicly insured – BEMA**	
	anamnesis & consulting	8,55 €
	intra-oral inspection	5,70 €
	vitality testing	1,92 €
	DHS treatment	5,70 €
		19,95 €

DHS treatment with laser:	**Publicly insured – BEMA**	
	anamnesis & consulting	8,55 €
	intra-oral inspection	5,70 €
	vitality testing	1,92 €
	DHS treatment	5,70 €
	Laser treatment	16,19 €
		36,14 €

Figure 6*: DHS Treatment Cost According to GOZ and BEMA*

3.7 Deciding on Cost Effectiveness

In this section, the cost effectiveness of Scenarios A and B is discussed and the ratio of cost to effectiveness of different treatment alternatives is calculated according to the following formula:

$$\text{Cost Effectiveness Ratio} = \frac{\text{Cost}}{\text{Clinical Effectiveness}}$$

In the model, cost is measured in "EUR" and effectiveness by the "SMD Pain Scale Reduction". The decision tree that is used is very simple and includes only one decision, which is which treatment alternative to take.

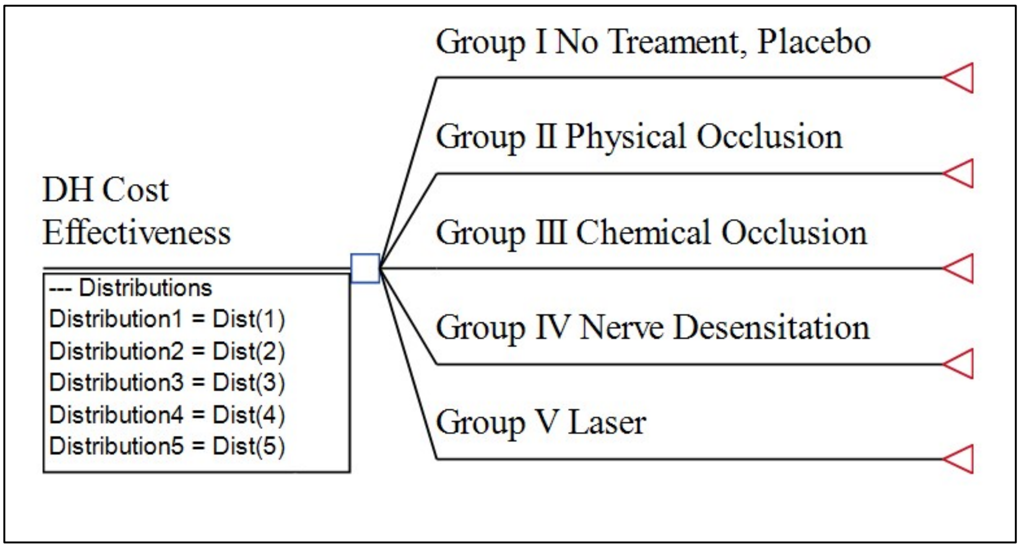


Figure 7: DHS Decision Tree

To incorporate uncertainties regarding the effect of SMD pain reduction, a triangular distribution function was included for each health outcome. The upper and lower bounds equate to the 95% confidence intervals and the most likely point within each distribution is defined by the point estimate for the reduction of standardized mean derived from the

VAS and VRS scale as reported in section 2.3.3. Furthermore, a Monte Carlo simulation with 10,000 repetitions is conducted.

3.8 Scenario A: Cost Effectiveness Plane for a Publicly Insured Patient and ICER Analysis

The cost effectiveness plane shows the cost effectiveness frontier for Scenario A (publicly insured patient). In general, it can be said that the more to the right and the more to the bottom an alternative is, the better is the respective cost effectiveness.

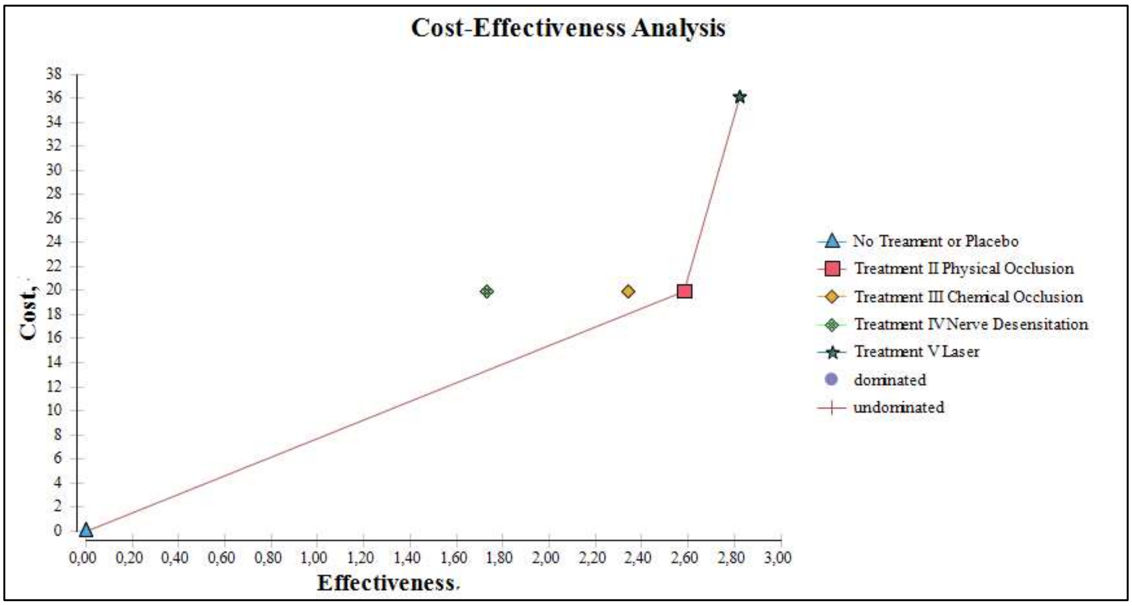


Figure 8: Cost Effectiveness Plane DHS Treatment (Scenario A)

It can be concluded that treatment options **III & IV** (chemical occlusion and nerve desensitization) **are dominated** by treatment options **II & V** (**physical occlusion and laser treatment**). In other words, nerve desensitizing, chemical occlusion and physical occlusion all cost the same, but **physical occlusion "works the best"**. Furthermore, a second treatment alternative that dominates chemical occlusion and nerve desensitization is **laser treatment**. However, laser treatment is not only better than physical occlusion but also significantly more expensive. As a first indicator, the slope between physical occlusion and laser treatment can be used: the steeper the slope between two treatment alternatives, the more expensive it is to get from one treatment option to the other.

If a decision maker has to decide between two different cost-effective alternatives, in this case physical occlusion and laser treatment, the concept of **Incremental Cost Effectiveness Ratio (ICER)** can be consulted to gain further insights. The **ICER** is defined as the **ratio of incremental cost** arising from moving from one treatment alternative to the next, **set in relation to the effectiveness gain** arising from moving from one treatment alternative to the next alternative (see section 2.1.1):

$$\text{ICER} = \frac{\text{Cost(Alternative2)} - \text{Cost(Alternative1)}}{\text{Effect(Alternative2)} - \text{Effect(Alternative1)}}$$

The **ICER of physical occlusion vs. placebo** in this model is calculated at **7.76 EUR/1.0 SMD Pain Scale unit reduction**.

The **ICER of laser treatment vs. physical occlusion** in this model is calculated as **6.4 EUR/0.1 SMD Pain Scale unit reduction**, which is represented by the steep slope between the two alternatives in the graph. Transposing this result to a **percentage view** for a better understanding, the following conclusion can be drawn: **If patients wants to further reduce the pain by 10 percentage points (%), the cost increases by 87 percentage points (%).**

3.9 Scenario A: Sensitivity Analysis (Hypothetical WTP)

The concept hypothetical **Willingness to Pay (WTP)** will be introduced for **further analysis** and for **inclusion of budgetary constraints into the model.**. WTP **is the maximum price at which a consumer is willing to "buy" a product/service** (Varian 2003). **Whenever a good/service is exchanged between a buyer and a seller, the buyer's willingness to pay meets the seller's willingness to sell.** WTP can be used in CEA to analyze decisions under budget restrictions (Gafni 1998).

The following figure depicts **the cost acceptability curve along WTP**. Put in other words, the graph shows us which treatment alternative should be preferred under a given Willingness to Pay. Furthermore, the graph assigns a probability to a treatment option being cost-effective given a certain WTP.

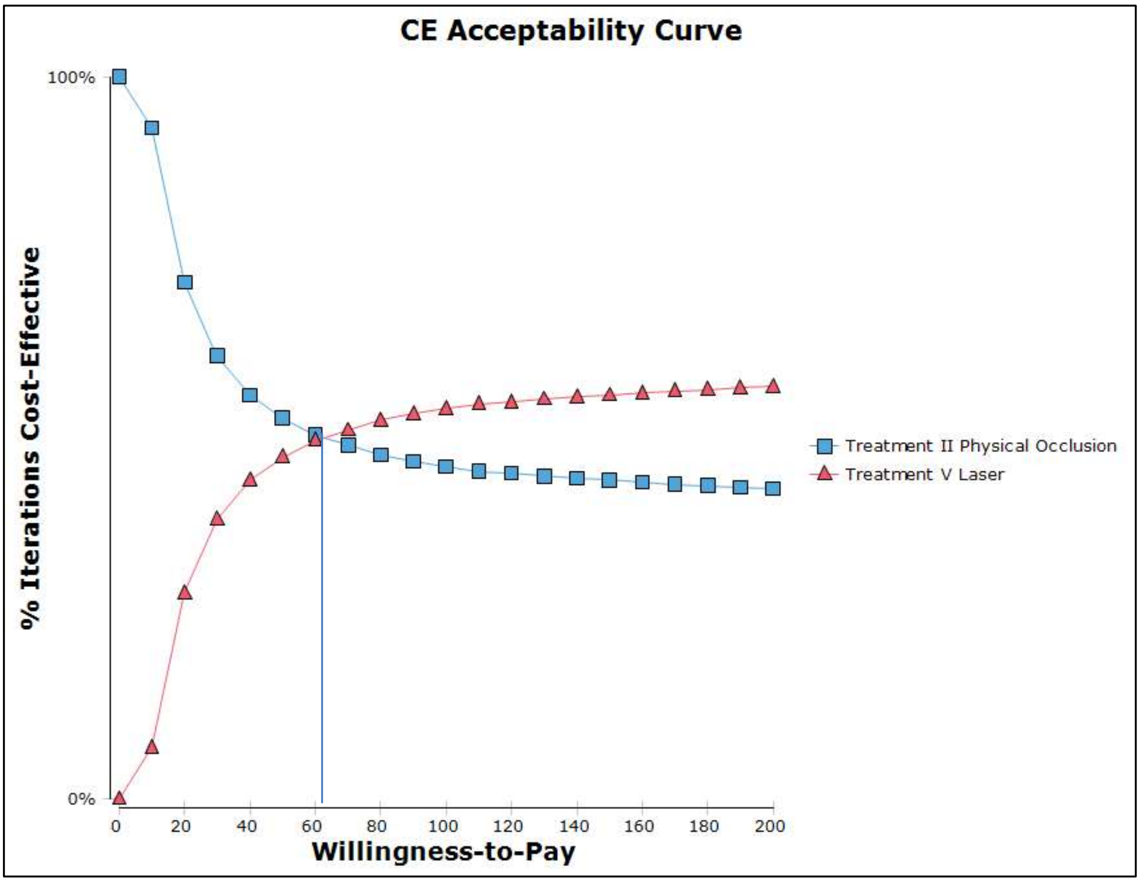


Figure 9: Cost Effectiveness Acceptability Frontier for Scenario A

- **Laser treatment is the most cost-effective therapeutic choice** if the patient is **willing to pay more than 63 EUR** for the incremental SMD Pain reduction (reduction increment on the SMD Pain Scale = 1.0)
- **Physical occlusion is the most cost-effective therapeutic choice** given that the patient is **willing to pay less than 63 EUR** for the incremental SMD pain reduction (reduction increment on the SMD Pain Scale = 1.0)

However, it has to be noted that this analysis is based on the fact that pain reduction can be continuously reduced by multiplying or adding treatment sessions. In reality, pain reduction is limited, with the ultimate pain reduction attainable lying at a reduction of 2.81, which can be achieved through laser treatment.

The maximum increment that can be reached is 0.24. Transposing the results from the graph above to the DHS treatment scenario, it makes sense to shift from pain reduction increments of 1.0 to 0.1.

The transposed statements would be as follows:

- **Laser treatment is the most cost-effective therapeutic choice** if the patient is **willing to pay more than 6.4 EUR** for the incremental SMD pain reduction (reduction increment on the SMD Pain Scale =**0.1**)
- **Physical occlusion is the most cost-effective therapeutic choice** if the patient is **willing to pay less 6.4 EUR** for the incremental SMD pain reduction (reduction increment on the SMD Pain Scale = **0.1**).

3.10 Scenarios B: Cost Effectiveness Plane for a Privately Insured Patient

The cost effectiveness plane shows the cost effectiveness frontier for a Scenario A (privately insured patient). In general, it can be said that the more to the right and the more to the bottom an alternative is, the better is the respective cost effectiveness.

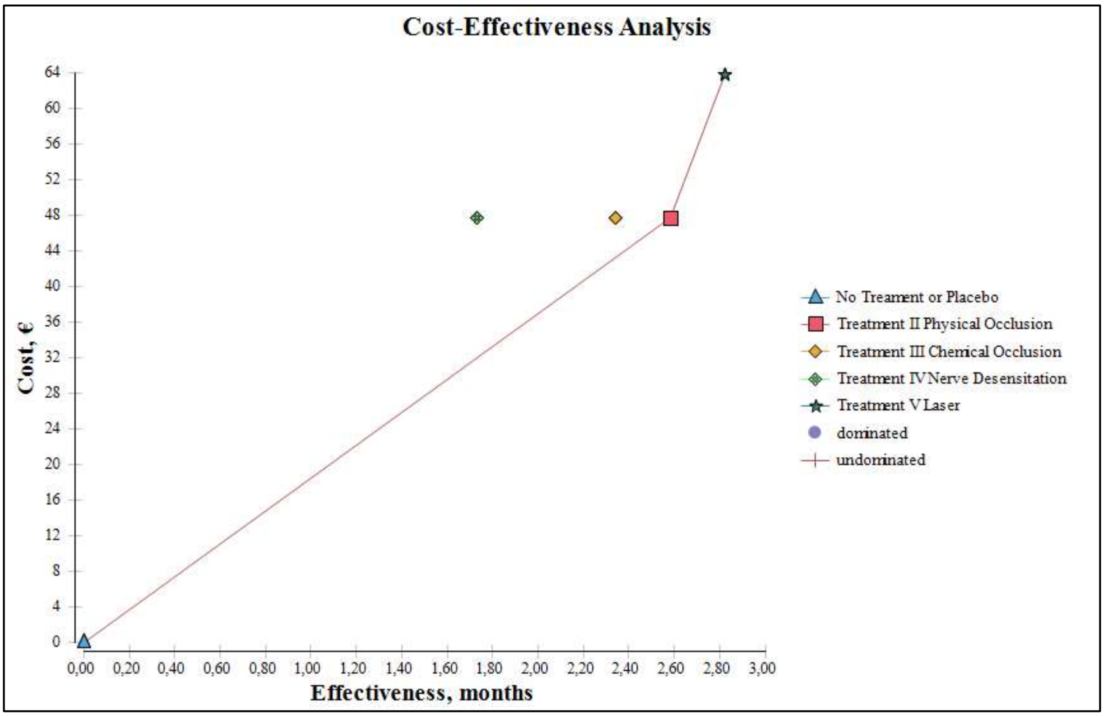


Figure 10: Cost Effectiveness Plane DHS Treatment (Scenario B)

The results of the cost effectiveness analysis for a privately insured patient are the same as for a publicly insured patient, but **at a higher cost level.** It can be concluded that Treatment Options **III & IV** (chemical occlusion and nerve desensitization) **are dominated** by treatment options **II & V** (**physical occlusion and laser treatment**). Put in other words, nerve desensitizing, chemical occlusion and physical occlusion all cost the same, but **physical occlusion “works the best”**. Furthermore, a second treatment alternative that dominates chemical occlusion and nerve desensitization is **laser treatment**. However, laser treatment is not only better than physical occlusion but also significantly more expensive.

Since ICER is not significantly different for a publicly insured patient, please refer to the ICER analysis in section 2.8.

3.11 Scenario B: Sensitivity Analysis (Hypothetical WTP)

Analogously to Scenario A, Willingness to Pay is analyzed and the cost acceptability frontier along WTP is depicted:

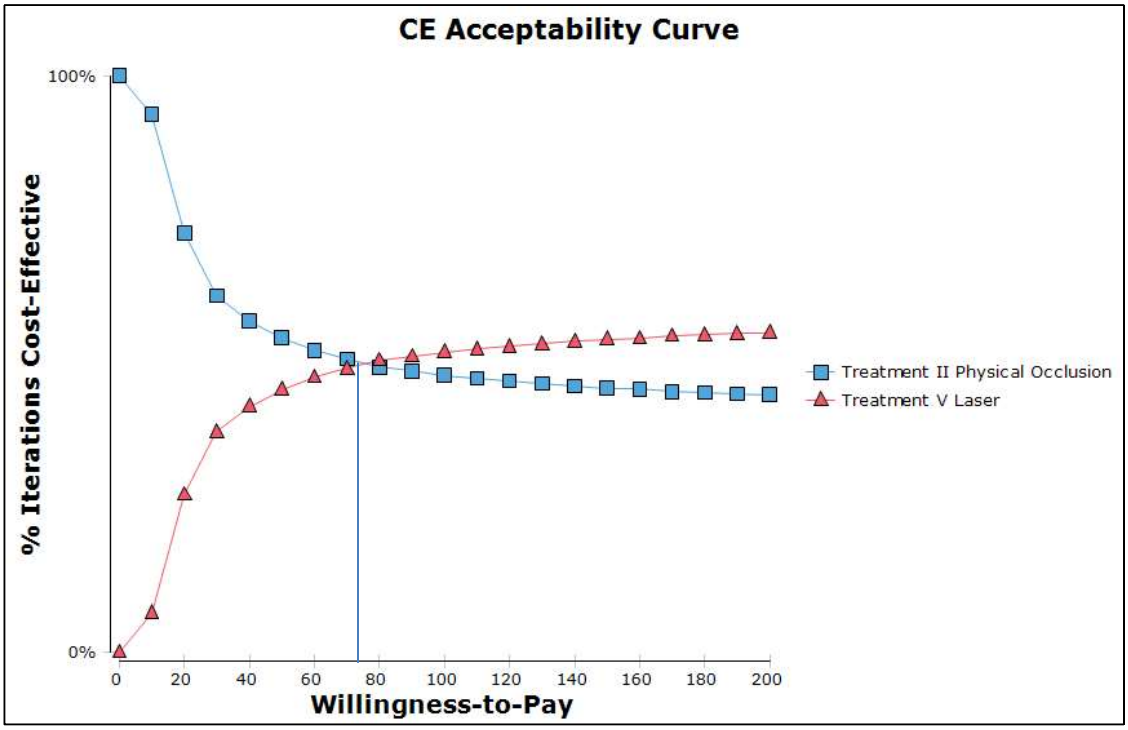


Figure 11: Cost Effectiveness Acceptability Frontier (Scenario B)

In general, it can be said that shifting from a publicly insured to a privately insured cost scenario does not make a difference regarding the cost effectiveness of treatment choices. Equivalent to Scenario A, laser treatment and physical occlusion are the dominant treatment alternatives. **The only difference between Scenario A and Scenario B is that the absolute cost level is higher**.

The following conclusions can be drawn for the privately insured patient scenario:

- **Laser treatment is the most cost-effective therapeutic choice** given that the patient is **willing to pay more than 7.4 EUR** for the incremental SMD pain reduction (reduction increment on the SMD Pain Scale =0.1)

- **Physical occlusion is the most cost-effective therapeutic choice** given that the patient is **willing to pay less than 7.4 EUR** for the incremental SMD pain reduction (reduction increment on the SMD pain Scale = 0.1).

To sum up the results for a privately insured patient, besides minor differences in the Willingness to Pay analysis the results of the overall cost effectiveness do not change in a privately insured patient scenario when treating DHS.

3.12 Overall Summary

The model clearly shows that within this model, **nerve desensitization** and **chemical occlusion** are **dominated** and ineffective compared with physical occlusion and laser treatment as alternatives for DHS treatment. Physical occlusion and laser treatment are cost-effective choices. The technical analysis can be summed up as follows:

- **Under a restricted budget, a choice between physical occlusion and laser treatment is recommended**.
- **ICER analysis publicly insured patient: The ICER for physical occlusion compared with placebo is 7.76 EUR / 1.0 SMD pain reduction**
- **ICER analysis publicly insured patient: if a patient wants to further reduce the pain by 9.3 percentage points (%) by choosing laser treatment over physical occlusion, the cost increases by 81.1 percentage points (%).**
- **Publicly insured patient decision under budget restrictions**: for a **Willingness to Pay < 6.3 EUR** for the improvement of an additional 0.1 of SMD pain reduction, the patient should choose **physical occlusion**.
- **Publicly insured patient under budget restrictions:** for a **Willingness to Pay > 6.3 EUR** for the improvement of an additional 0.1 of SMD pain reduction, the patient should choose **laser treatment**.
- **Privately insured patient under budget restrictions:** for a **Willingness to Pay < 7.4 EUR** for the improvement of an additional 0.1 of SMD pain reduction, the patient should choose physical occlusion.
- **Privately insured patient under budget restrictions:** for a **Willingness to Pay > 7.4 EUR** for the improvement of an additional 0.1 of SMD pain reduction, the patient should choose laser treatment.

- **Under an unrestricted budget**, the patient should choose laser treatment.
- **It was shown that the effectiveness scenarios for privately and publicly insured patients are the same; however the cost level for a privately insured patient is higher**.

Key Findings: Based on the model, cost effectiveness analysis shows that in a scenario where DHS is treated, **physical occlusion and laser treatment should be preferred treatment alternatives**. From an ICER perspective, a clinical decision maker treating for DHS should always opt for physical occlusion. The most commonly used agent for physical occlusion is a dentin-bonding agent. **However, clinical practice shows that chemical occlusion is the standard treatment options**. **Physical occlusion should be the standard treatment of choice when treating DHS**. However, in extreme cases of hypersensitivity, laser treatment is always an additional option (second best), but the steep ICER should be considered by a decision maker.

3.13 Model Evaluation

Based on latest available clinical evidence and a cost model based on GOZ and BEMA, a cost effectiveness analysis of DHS treatment alternatives was performed. The question is whether all factors, that are key characteristics of good cost effectiveness analysis were fulfilled (Tonmukayakul et al. 2015)**:**

Factor 1 transparency of cost calculations: cost calculation was provided for in detail (see section 2.6).

Factor 2 cost discounting: discounting was not required. No information was given about whether the effects last one or more years. In general, clinical practice shows that the effects of hypersensitivity treatment are rather short-term effects, lasting less than one year. The model was based on the assumption “one treatment - one effect”, therefore, no discounting is applicable and needed.

Factor 3 quality of underlying clinical endpoints: Lin’s meta-analysis was checked thoroughly by investigating clinical endpoints in underlying studies. Additionally, the introduction of a meta-level pain scale properly aggregated clinical endpoints on the meta-level.

However, **CEA models can only be as good as their underlying data**. It is possible that the lack of evidence in certain areas might have limited this cost effectiveness analysis. To further reduce uncertainty in the model and to improve cost effectiveness analysis, enhanced clinical trials are needed and their data needs to be implemented into the models. However, as of today, and until further clinical studies are available, physical occlusion has the highest probability of being cost-effective and should therefore be chosen. Certain **limitations** to this model need to be discussed:

First, a limitation of this analysis is that **categories** were used for effectiveness, e.g. physical occlusion category. **Each category summed up different treatment agents** into a category, and confidence intervals for a category were quite large. If analysis could be performed on the treatment agent level, variances could be reduced and further insight could be gained.

Second, using GOZ and BEMA for cost calculations "ignores" the fact that different treatment alternatives can have different "price tags". If cost information was available on the treatment agent level, e.g. through micro-costing analysis, this could have an impact to the result of this model. But as micro-costing is not available at the treatment level, the best available information as of today was used for this model.

Third, it can be argued that cost effectiveness was not measured accurately in appropriate physical units, but on a more abstract meta-level (standardized meta-level pain scale). Since this model was based on a meta-analysis, a common denominator was needed for heterogeneous underlying pain scales. But even though an "abstract" scale was used, the impact on health outcomes could still be analyzed.

Fourth, the model assumed "one treatment - one effect", which means that there is no follow-up treatment included in the model (e.g. 2nd application of an agent after 6 months). As a result, **the decision tree and the model were designed for analyzing a "one-off" decision**. No data on how long the treatment effect persists over time was included in the model. **To further enhance the model, clinical data is required on how long the clinical effects of DHS treatment last**. There are currently no reliable longitudinal studies on the long-term effects of DHS treatment available. Longitudinal studies of the clinical effectiveness and reliable recommendations on follow-up treatments could have a significant impact on the cost and effectiveness of the model. With this information, an extended cost effectiveness analysis could be implemented and extended research could further support the finding of this study that physical occlusion and laser treatment are not only cost-effective choices in a one-off scenario, but also in the long run.

The conclusion can be drawn that at the current state and without knowledge about how long the effects last, the results of **this study can only support short-term decision making**. In order to **provide proper guidelines to clinical decision makers**, a **model is needed that includes the information on how long the effects of the treatments last (long term)**. An extended long-term model that supports the findings of this short-term model could improve decision making for dentin hypersensitivity treatments, with 9 million treatments being performed every year in Germany alone. **A long-term model could support a paradigm shifts towards using physical occlusion as the standard treatment option for dentin hypersensitivity**, which could help gain 10% more effectiveness, everything else being equal, by shifting the treatment decision from chemical to physical occlusion.

How the results of this dissertation can be implemented in clinical practice will be discussed in the concluding section (chapter 6) of this dissertation.

From a modelling perspective, this chapter found that the long-term impact was not assessed with the model due to data limitations. How a model can be developed when appropriate long-term clinical data is available will be shown in the next chapter.

4 Deciding on Cost Effectiveness of Therapeutic Alternatives in Direct Pulp Capping (Open Pulp Treatment): Mineral Trioxide Aggregate vs. Calcium Hydroxide (Transition State Modeling)

4.1 Background

In the clinical situation of an open pulp, **pulp capping** and **root canal treatment are** different **treatment alternatives** that can be selected by clinical decision makers. According to the latest available data from the German Federal Union of Public Dentists (KZVB), about **7 million root canal treatments** are performed and accounted for every year (KZBV 2018). In contrast, **pulp capping treatments** were performed and accounted **for 775,600 times** within the public German healthcare context in 2013 (KZBV 2014).

Pulp capping itself is significantly less expensive than root canal treatment, but risk of failure can vary, depending on the material used for pulp capping. A recent long-term study has shown that **the material** used in direct pulp capping treatment has a **significant effect on the clinical performance** of the treatment of an open pulp (Mente et al. 2014).

In addition to differences in clinical effectiveness, **different capping materials** also have **different price tags**. Modern materials that can be used for direct pulp capping have a higher price tag. The question is whether this additional spending is allocated towards the right material?

Also, the overall costs and benefits of an overall treatment strategy are highly dependent on the sequence of the first chosen treatment option in the clinical situation of treatment an open pulp. It is not trivial to take all these interdependencies into account without a proper decision rationale.

Therefore**, an economic evaluation model will be established** to support **decision making** for direct pulp capping. It will help to clarify if and under which budget restriction it makes sense for a decision maker to invest in a more expensive material. The focus of this analysis lies on the implementation of long-term data and the highest evidence level that is available for clinical effectiveness for direct pulp capping as of today.

4.2 Open Pulp and Direct Pulp Capping as a Treatment Option from a Medical Perspective

This section describes what direct pulp capping is from a medical perspective and in which clinical situation is it needed. The clinical situation where pulp capping is needed is described by the term **open pulp, or *pulpa aperta* (latin)**. This describes the state when the **pulp of a tooth is exposed (opened)** due to e.g. deep caries treatment (*caries profunda*), dental trauma, or other causes. If **no treatment is performed**, **harmful germs (bacteria, viruses)** from the oral flora will be able to enter the pulp. As a consequence, the pulpal tissue will be attacked by these germs, which will ultimately lead to an infection and in most cases also to destruction of the pulpal tissue (Hargreaves and Louis H. Berman 2015).

Direct pulp capping is one therapeutic treatment option, and a frequently **performed treatment alternative to more invasive root canal treatment** (Mente et al. 2014). It should be clearly stated that pulp capping treatment is not only an alternative to the above mentioned treatments, but is also **an attempt to preserve and maintain the vitality of the tooth** with an open pulp (Hargreaves and Louis H. Berman 2015). Root canal treatment or further clinical procedures might be ultimately necessary if pulp capping fails and are important next-step treatment options – under certain conditions.

There are several **clinical prerequisites** that must be fulfilled for the indication of direct pulp capping, the most important of which include (EuropeanSocietyOfEndodontology 2006):

- No caries remaining in the cavity
- Vitality & ability of the pulp to regenerate
- No pre-existing endodontic pre-condition (e.g. pulpitis)
- Possibility to keep treatment sterile (e.g. by placing rubber dam)

How pulp capping works will be briefly explained. As per the clinical definition, the **pulp capping treatment itself** is described as “a procedure in which the pulp is covered with a **protective dressing** placed **directly over the pulp at the site of exposure**” (EuropeanSocietyOfEndodontology 2006). A **second layer** is then placed on top of the protective dressing, covering the surrounding dentin and the first layer. The second layer serves as a “bandage” and is ideally made of an **adhesive permanent restoration** (e.g. dental composite material). It needs to be placed on the same day if the highest available clinical survival rate is aspired to (Welbury 2003).

Bringing all pre-requisites together, **pulp capping treatment involves applying a seal to an open pulp** and leaving the pulp in a condition **with limited to no bacterial infection**, so **that it can heal**. This principle is supported by the very early findings of Kakehashi et al. in 1965 (Kakehashi et al. 1965), which showed that opened pulps of germ-free rats (gnotobiotic rats) can heal under sterile conditions due to the regenerative power of dentine, but that in contrast if the exposed pulp is exposed to micro-organisms, necrosis is an inevitable result (Trohorsch et al. 2012).

4.2.1 Alternative Treatment Options – Indirect Pulp Capping

For reasons of completeness, it should be mentioned that in the dental medical literature the clinical procedure **of indirect pulp capping** is often mentioned as a treatment option for *pulpa aperta* situations. However, this treatment is not considered a valid treatment option, as a study (Mente 2014) showed bad prognosis for teeth that were indirectly pulp capped. Indirectly pulp capped teeth have an approximately 3.2 times higher risk of failure than directly pulp capped teeth. This **clinical procedure is obsolete today** and should not be performed anymore. Therefore, **indirect pulp capping will be excluded from the model**.

4.3 Health Outcomes and Clinical Effectiveness of Open Pulp Treatment

4.3.1 Material Selection for Clinical Outcomes of Direct Pulp Capping – Introduction

The most widely accepted material currently used by dentist for direct pulp capping as a protective dressing material is **calcium hydroxide (CaOH)**. **Mineral trioxide aggregate (MTA)** is also being increasingly used as a popular alternative to CaOH. There are several other pulp capping materials being used as of today, but this thesis will **focus** only **on the most commonly used materials** in an everyday dental clinic environment.

The treatment outcomes of CaOH vs. MTA has long been a matter of dispute amongst dental practitioners and scientists. The first long-term studies and clinical data on treatment outcome have been published by J. Mente, providing an important insight into this matter of dispute (Mente et al. 2014). Mente analyzed clinical data from 2001 to 2011. The study, as of today, represents the largest controlled clinical trial comparing CaOH vs. MTA in pulp capping with follow-up periods from 2 years up to 10 years.

4.3.2 MTA and Calcium Hydroxide: Clinical Outcome and Reasons for Different Clinical Performance

Mente's long-term research shows the following clinical outcome, indicating that MTA materials achieve better long-term results for direct pulp capping than CaOH:

	Clinical Success Rate (10 years)	**95% Confidence Interval [CI]**
Mineral Trioxide Aggregate	80.5%	*74.5–86.5*
Calcium Hydroxide	59%	*46.5–71.5*

Figure 12: Clinical Success Rate MTA vs CaOH in Direct Pulp Capping

An examination of this study and several other studies dealing with the material properties of MTA and CaOH allows us to infer that CaOH must have several disadvantages that lead to a weaker clinical performance (Bakland and Andreasen 2012). The most important ones should be mentioned at this point for a deeper understanding of how CaOH and MTA work as a material:

- **Ability to form dentin bridge**: CaOH's pH of 12.5 leads to a liquefaction and coagulation necrosis zone in the area where CaOH meets the pulp. This initiates wound healing through growth factors resulting in a calcification reaction and the formation of a hard tissue bridge. The hard tissue bridge is the biological seal of the pulp. The dentin bridge is formed faster when MTA is used.
- **Antibacterial effect (due to pH)** leaves a bacterial-free environment of the pulpal amputation site. MTA tends to last longer than CaOH, and therefore the antibacterial effect of MTA also lasts longer.
- **Micro-leakage and tunnel defects**: CaOH materials tend to dissolve over time. Micro-leakage and tunnel defects are pathways for bacteria into the pulp, which can ultimately result in pulpitis. Furthermore, the antibacterial effect is weakened once CaOH dissolves. MTA in contrast forms a tighter seal with dentin and the MTA seal minimizes the risk of bacterial penetration to the pulp through micro-leakage and tunnel defects.
- **Dentin softening effect of CaOH** (Yoldas et al. 2004) means a higher risk of fracture. In contrast, no softening effect of MTA is known.

4.3.3 Alternative or Consecutive Treatment Options in Case of Failure of Pulp Capping

As mentioned above, pulp capping treatment can fail. Remaining treatment options and follow-up treatments are as follows (Salehrabi and Rotstein 2004):

1. **Root canal treatment – description and clinical effectiveness**

   Root canal treatment is a therapy option for an inflamed pulp and describes the process of carefully removing the pulp inside the tooth. Tooth canals are cleaned, disinfected and shaped, and a filling is placed to finally seal the root canal space to avoid further invasion of bacteria (AmericanAsscociationOfEndodontists 2018)

The latest meta-analysis of the clinical effectiveness shows an **85.8% estimated success rate** (Ng et al. 2007) with 95% CI [81,8 ; 89,9] based on clinical and “loose” radiographic outcome measures. This aggregated number is most representative for a **4-year follow-up** period after treatment.

2. Root canal revision – description and clinical effectiveness

If **root canal treatment fails**, further treatment options are **root canal revision and endodontic re-treatment.** The pooled estimated survival rate of **endodontic revision is 77.2%** (Ng et al. 2008) [95% CI: 61.1%, 88.1%] based on loose criteria. In this meta-analysis, follow-up was between 6 months and 20 years. Due to the underlying data, attempts to pool data by follow-up period were not possible. However, 8 out of 17 included clinical trials with a follow-up period of at least 4 years and therefore it will be **assumed for further economic modeling** that the given 77.2% survival rate is **represented at a 4 year follow-up** after treatment.

3. Extraction – description and clinical effectiveness

Extraction of a tooth is always the last resort in dental medicine for the survival of a single tooth. The extraction of a tooth has an assumed clinical effectiveness of 0.0% in this model.

4.3.4 Clinical Decision Tree: Direct Pulp Capping and Post-Direct Pulp Capping Treatments

A clinical decision tree is drawn that will be used in this model. It starts with the clinical condition of an open pulp and follows the different treatment options resulting in different health states.

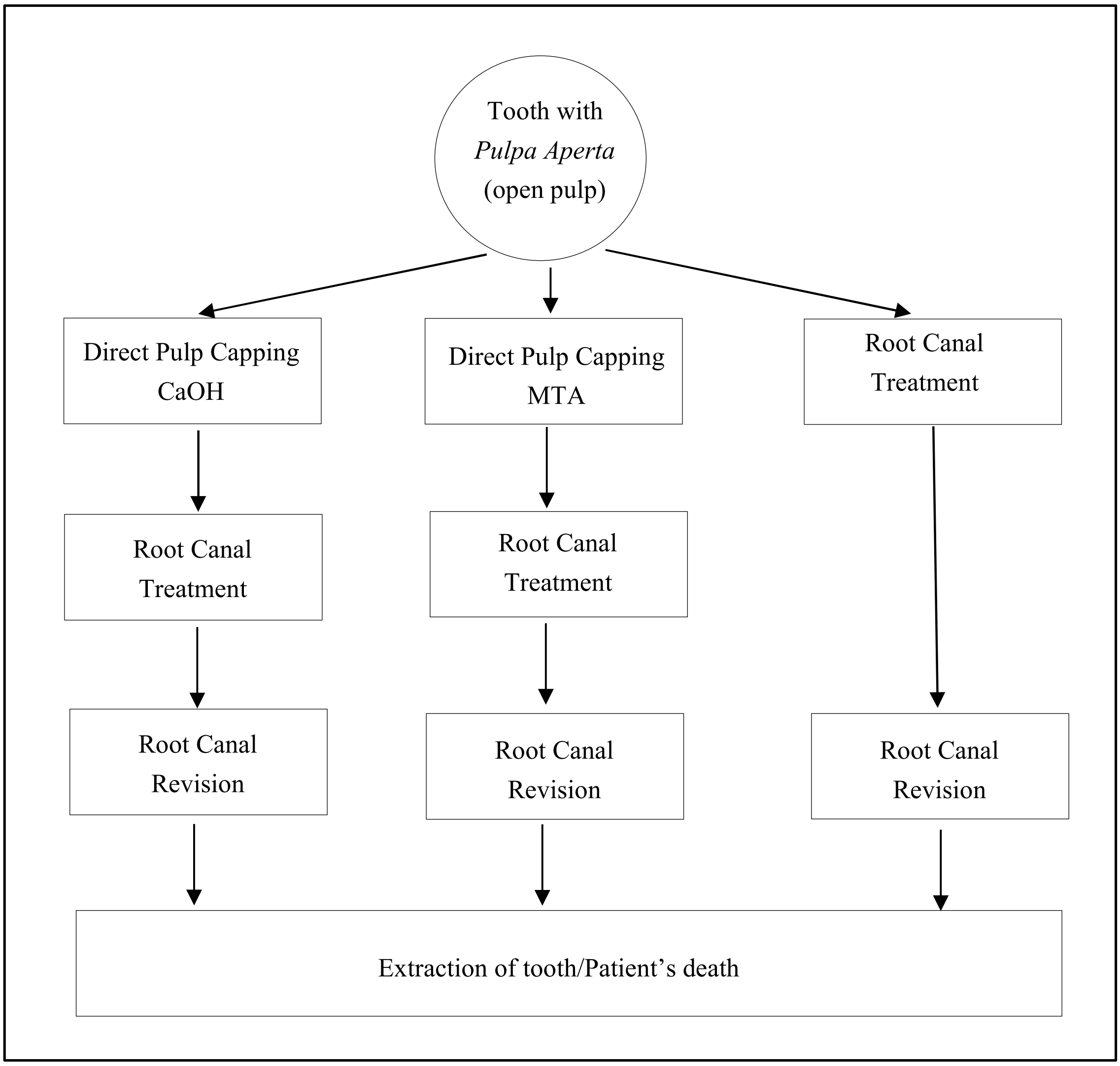


Figure *13: Clinical Decision Making for Treatment in Case of Pulpa Aptera (Open Pulp)*

The model ends with the extraction of a tooth or the patient's death (everything else being equal).

4.4 Cost Modeling Direct Pulp Capping

The model accounts for direct pulp capping and post-direct pulp capping treatment as listed in the GOZ and BEMA Costs will be modeled analogously to the previous chapter; for further cost modeling details please refer to section 2.4.

For this cost effectiveness analysis, a GOZ-only scenario will be developed due to the fact that most activities used in the model are not accounted for in BEMA. It was shown in Chapter 2 that shifting from a publicly insured patient scenario to a privately insured patient scenario only impacts a cost shift of all costs but does not change overall cost effectiveness. Therefore, **cost of activities** is calculated according to GOZ on the basis of the following formula (Bundesgesetzblatt 2001):

$$\text{Cost (GOZ)} = p\ (\text{GOZ}) * \mu * \pi$$

- p (GOZ) is the chargeable item points for a certain activity according to the GOZ
- μ is the monetary conversion factor (€ 0.51 per GOZ item point)
- π is the treatment time factor, dependent on the complexity of the individual case (π=2.3 or 3.5).

4.4.1 Assumptions for Modeling

The following assumptions were used for the modeling:

- All treatment happens within the context of the German healthcare system
- Male patient, 30 years old
- Remaining life expectancy of patient is 48.55 years (StatistischesBundesamt 2015)
- Open pulp of a lower jaw molar with 3 root canals
- Direct pulp capping treatment is conducted in compliance with latest findings to achieve highest clinical outcome of treatment – i.e. capping treatment in first session
- Root canal treatment is conducted in 2 sessions and 3 root canals are treated
- **Cost Estimate for MTA**: 2 factors driving MTA cost in this model, 1) increased material cost directly charged to the patient and 2) excess time needed for MTA handling. Increased material cost was estimated to be 36.50 EUR, which corresponds to the average sales price of 0.5 g MTA (Pro Root MTA – own Micro

Costing Analysis). To account for the additional time for MTA placement, the treatment time factor was shifted from 2.3 to 3.5 according to the fee scale for dentists (GOZ). Both factors result in an additional cost of **50 EUR** for MTA charged to the patient in the model.

4.4.2 Standard Treatment Process for Modeling

A standard treatment process is modeled by adding up **activities,** i.e. cost drivers for the different treatments:

1. **Treatment 1: Direct Pulp Capping**

- Anamnesis and consulting (GOZ 0010, 100 points)
- Symptom-specific intra-oral inspection (GOZ 0010, 100 points)
- Vitality testing for differential diagnosis (GOZ 0070, 50 points)
- Local anesthesia lower jaw (GOZ 0100, 70 points)
- Placement of rubber dam (GOZ 2040, 65 points)
- Treatment of an open vital pulp (GOZ 2340, 200 points)
- MTA capping expense (**50 EUR**)
- Adhesive restoration (GOZ 2100, 642 points)

Treatment 2: Root Canal Treatment

- Anamnesis and consulting (GOZ 0010, 100 points)
- Symptom-specific intra-oral inspection (GOZ 0010, 100 points)
- Vitality testing for differential diagnosis (GOZ 0070, 50 points)
- Local anesthesia lower jaw (GOZ 0100, 70 points)
- Placement of rubber dam (GOZ 2040, 65 points)
- Trepanation (GOZ 2390, 65 points)
- VitE 3x (GOZ 2360, 110 points per canal)
- Root canal treatment incl. rinsing 3x (GOZ 2410, 392 points per canal)
- Electromagnetic length determination 3x (GOZ 2400, 70 points per canal)
- Ultrasonic activated rinsing 3x (GOZ 2420, 70 points per canal)
- Med treatment (CaOH & CHX) (GOZ 2430, 204 points)
- Temporary filling (GOZ 2020, 98 points)

- X-ray for diagnosis, length check & Master Point Check, 3x (GOZ 5000, 50 points per X-ray)
- Application of a microscope (GOZ 0110, 400 points)
- Root canal filling 3x (Guttapercha) (GOZ 2440, 258 points per filling)
- Adhesive restoration (GOZ 2100, 642 points)

3. **Treatment 3: Root Canal Revision**

- Anamnesis and consulting (GOZ 0010, 100 points)
- Symptom-specific intra-oral inspection (GOZ 0010, 100 points)
- Vitality testing for differential diagnosis (GOZ 0070, 50 points)
- Placement of rubber dam (GOZ 2040, 65 points)
- Trepanation (GOZ 2390, 65 points)
- Root canal treatment incl. rinsing 3x (GOZ 2410, 392 points per canal)
- Electromagnetic length determination 3x (GOZ 2400, 70 points per canal)
- Ultrasonic activated rinsing 3x (GOZ 2420, 70 points per canal)
- Med treatment (CaOH & CHX) (GOZ 2430, 204 points)
- Temporary filling (GOZ 2020, 98 points)
- X-ray for diagnosis, length check & master point check, 3x (GOZ 5000, 50 points per X-ray)
- Application of a microscope (GOZ 0110, 400 points)
- Root canal filling 3x (Guttapercha) (GOZ 2440, 258 points per filling)
- Adhesive restoration (GOZ 2100, 642 points)

4. **Treatment 5: Extraction**

- Anamnesis and consulting (GOZ 0010, 100 points)
- Dentist performs symptom-specific intra-oral inspection (GOZ 0010, 100 points)
- Vitality testing for differential diagnosis (GOZ 0070, 50 points)
- X-ray (GOZ 5000, 50 points)
- Local anesthesia lower jaw (GOZ 0100, 70 points)
- Extraction & wound suture (GOZ 3010, 110 points)

Taking all previous assumptions into account, an open pulp capping treatment session would be accounted for as follows:

Direct Pulp Capping - CaOH	Privately insured – GOZ	GOZ	Points	Amount	Multiplier	Cost
	Anamnesis & Consulting	Ä1	100		2,3	12,94 €
	Symptomspecific Diagnosis	Ä5	100		2,3	12,94 €
	Vitality Testing	70	50		2,3	6,47 €
	Local Anästhesia Lower jaw	100	70		2,3	9,05 €
	Rubber Dam	2040	65		2,3	8,41 €
	Open Pulp Treatment	2340	200		2,3	25,87 €
	Adhesive Restoration	2100	642		2,3	83,05 €
	Total					**158,72 €**

Direct Pulp Capping - MTA	Privately insured – GOZ	GOZ	Points	Amount	Multiplier	Cost
	Anamnesis & Consulting	Ä1	100		2,3	12,94 €
	Symptomspecific Diagnosis	Ä5	100		2,3	12,94 €
	Vitality Testing	70	50		2,3	6,47 €
	Local Anästhesia Lower jaw	100	70		2,3	9,05 €
	Rubber Dam	2040	65		2,3	8,41 €
	Open Pulp Treatment	2340	200		3,5	39,37 €
	Adhesive Restoration	2100	642		2,3	83,05 €
	MTA - Direct Cost for Material (0.5g)					36,50 €
	Total					**208,73 €**

Root Canal Treatment	Privately insured – GOZ	GOZ	Points	Amount	Multiplier	Cost
	Anamnesis & Consulting	Ä1	100		2,3	12,94 €
	Symptomspecific Diagnosis	Ä5	100		2,3	12,94 €
	Vitality Testing	70	50		2,3	6,47 €
	Local Anästhesia Lower jaw	100	70		2,3	9,05 €
	Rubber Dam	2040	65		2,3	8,41 €
	Trepanation	2390	65		2,3	8,41 €
	VitEx (per canal)	2360	110	3	2,3	42,69 €
	Root Canal Treatment (3x)	2410	392	3	2,3	152,12 €
	Electromagnetic Legth Determination	2400	70	6	2,3	54,33 €
	Ultrasonic Rinsing (per canal)	2420	70	3	2,3	27,16 €
	Med	2430	204		2,3	26,39 €
	Temporary Filling	2020	98		2,3	12,68 €
	X-Ray (3x)	5000	50	3	2,3	19,40 €
	Microscope	110	400		2,3	51,74 €
	Root Canal Filling	2440	258	3	2,3	100,12 €
	Adhesive Restoration	2100	642		2,3	83,05 €
	Total					**627,90 €**

Root Canal Re-Treatment	Privately insured – GOZ	GOZ	Points	Amount	Multiplier	Cost
	Anamnesis & Consulting	10	100		2,3	12,94 €
	Symptomspecific Diagnosis	Ä5	100		2,3	12,94 €
	Vitality Testing	70	50		2,3	6,47 €
	Rubber Dam	2040	65		2,3	8,41 €
	Trepanation	2390	65		2,3	8,41 €
	Root Canal Treatment (3x)	2410	392	3	2,3	50,71 €
	Electromagnetic Legth Determination	2400	70	3	2,3	9,05 €
	Ultrasonic Rinsing	2420	70	3	2,3	9,05 €
	Med	2430	204		2,3	26,39 €
	Temporary Filling	2020	98		2,3	12,68 €
	X-Ray (3x)	5000	50		2,3	6,47 €
	Microscope	110	400		2,3	51,74 €
	Root Canal Filling	2440	258		2,3	33,37 €
	Adhesive Restoration	2100	642		2,3	83,05 €
	Total					**331,67 €**

Extraction	Privately insured – GOZ	GOZ	Points	Amount	Multiplier	Cost
	Anamnesis & Consulting	10	100		2,3	12,94 €
	Symptomspecific Diagnosis	Ä5	100		2,3	12,94 €
	Vitality Testing	70	50		2,3	6,47 €
	X-Ray	5000	50		2,3	6,47 €
	Local Anästhesia Lower jaw	100	70		2,3	9,05 €
	Extraction of Tooth with +1 Roots	3010	110		2,3	14,23 €
	Total					**62,09 €**

Figure *14: Pulp-Capping and Post-Pulp Capping Treatment Cost According to GOZ*

4.5 Markov Model (Transition State Model)

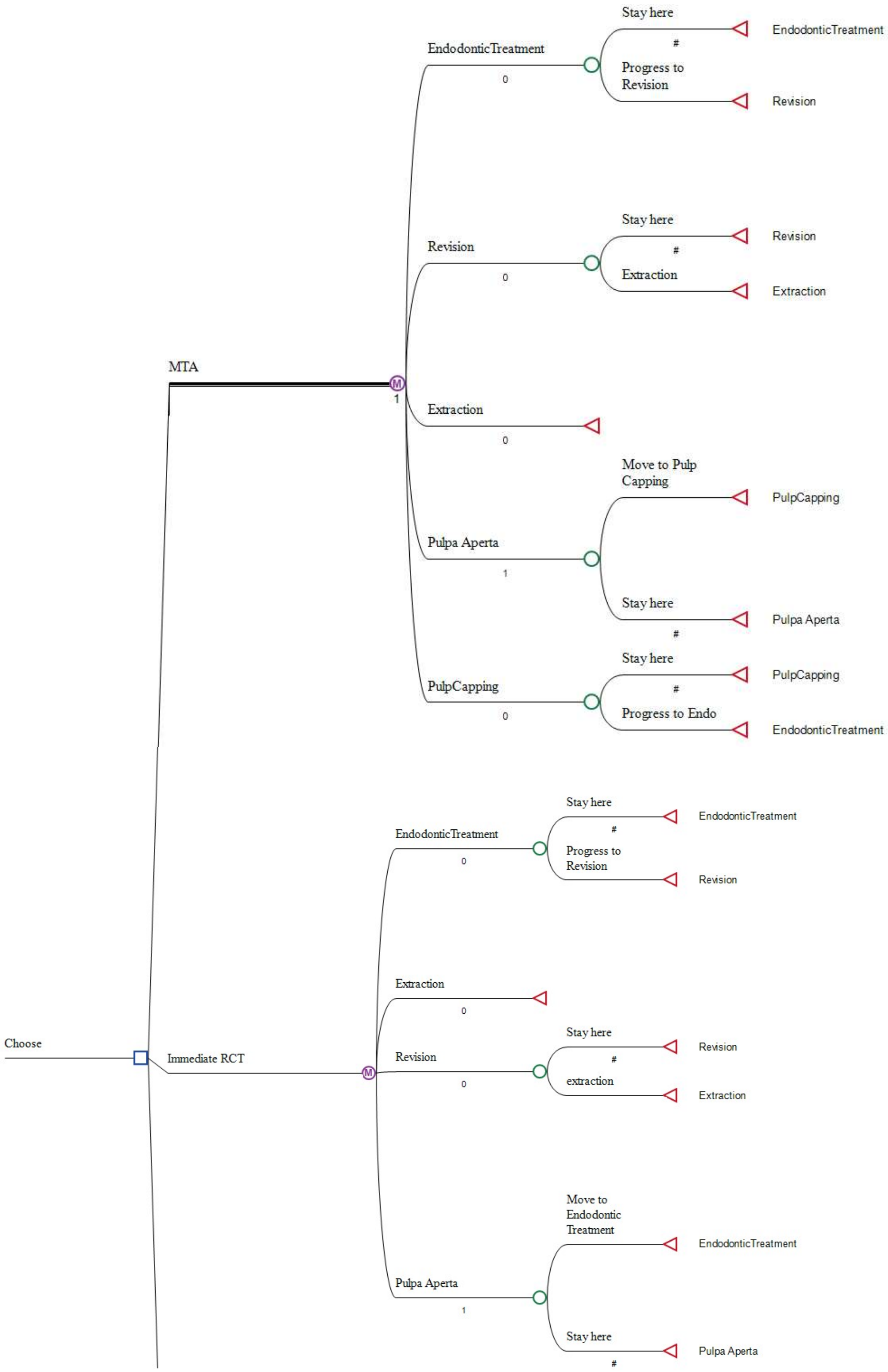
A Markov **transition state model** (Sonnenberg and Beck 1993) was created using TreeAge Pro 2019. The model is based on the clinical decision tree in section 3.3.4.

The model starts with the **clinical situation of a tooth with an open pulp**. In this situation, the clinical decision maker has the choice to **1)** pulp cap the tooth with MTA; **2)** pulp cap with CaOH; or **3)** perform immediate root canal treatment. From these states, the tooth can then transition into the post-pulp capping or post-root canal treatment states (revision, extraction). **Each transition of a health state is associated with a cost and effectiveness** (it is assumed that when a transition happens, treatment is performed that has an associated cost and effectiveness). Transition probabilities to different states were defined **using time-dependent survival functions**, which were implemented into the model. For clinical effectiveness, **triangular distributions** were implemented into the model according to the **95% confidence interval**. Cost was implemented according to GOZ calculations without any variance, but will later be analyzed under variance analysis. One cycle in the state transition model equals one calendar year. **48.55 cycles** were implemented according to the expected remaining tooth life in the model **based on the life expectancy of a 30-year-old male patient**.

The Markov model was populated via a **Monte Carlo simulation** (sample + trial function of TreeAge 2019) and a population of 10,000 teeth was created.

Future cost was discounted (2% p.a.), but effectiveness was not discounted (see section 1.3.6).

The state transition model was implemented in Treeage Pro as follows and additional analyses were run on the model:



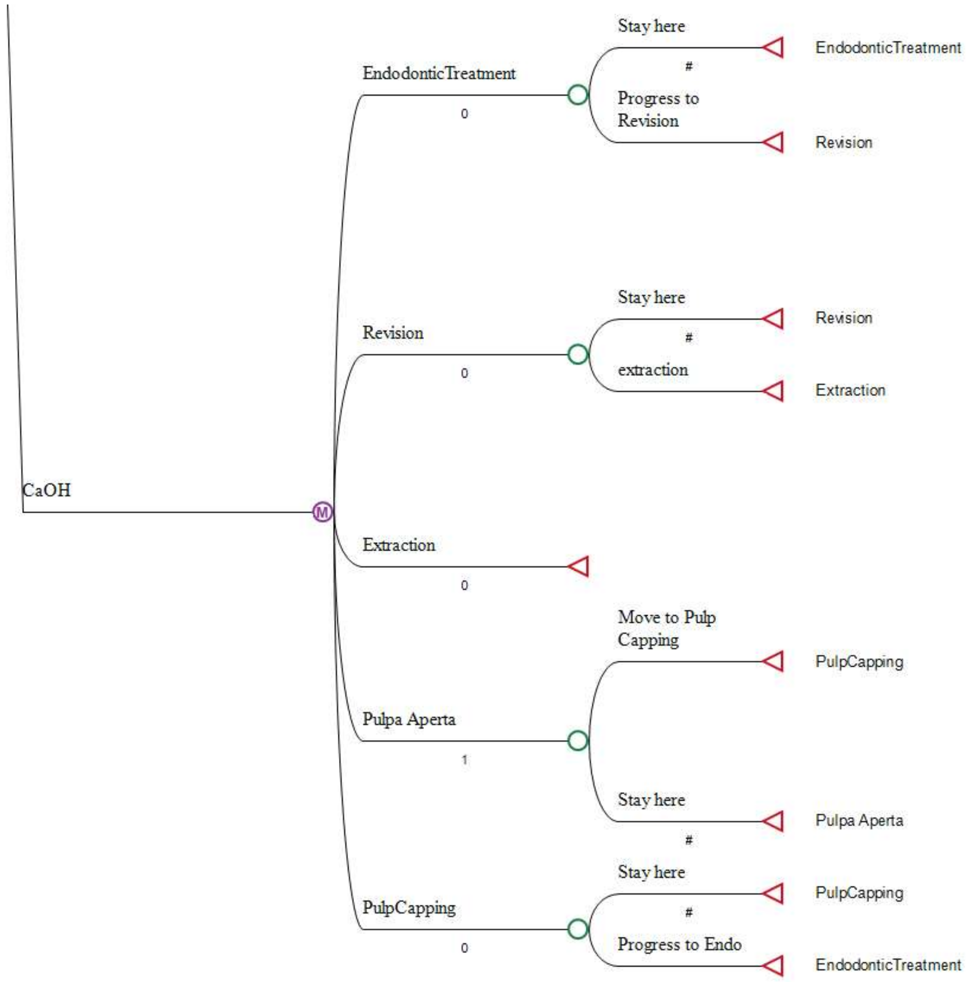


Figure 15: Markov State Transition Model in TreeAge Pro 2019

4.6 Deciding on Cost Effectiveness

4.6.1 Cost Effectiveness Plane

The cost effectiveness plane shows the cost effectiveness frontier for the state transition model. In general, it can be said that the more to the right and the lower an alternative is, the better is the respective cost effectiveness.

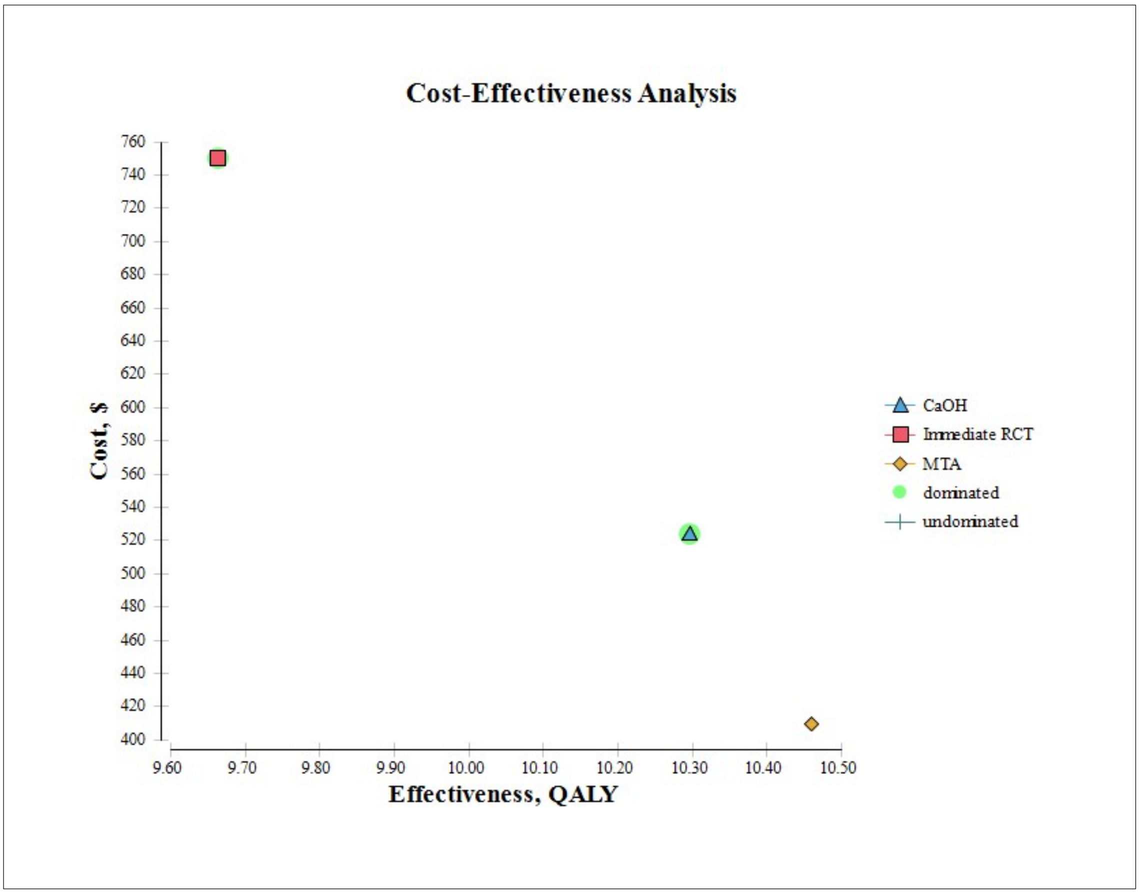


Figure 16: Cost Effectiveness Plane Direct Pulp Capping MTA vs. CaOH vs. Immediate Root Canal Treatment

The depicted cost effectiveness plane can be analyzed as follows:

- In a long-term model of an MTA pulp-capped molar tooth with remaining life expectancy of 48.55 years, **10.3 tooth life years** on average can be gained for the average cost of **402 EUR**. The effectiveness is gained by and cost is accrued for pulp capping and post-pulp capping treatment options. It should be noted that these numbers are based on averages resulting from the Monte Carlo simulation of a sample population of 10.000.

- **MTA pulp capping dominates all other treatment options**

The cost effectiveness plane clearly shows that **MTA pulp capping treatment dominates** both CaOH pulp capping and immediate root canal treatment. Therefore, MTA **pulp capping has the highest likelihood to be the most cost-effective treatment alternative in this model**.

Results for dominated treatment options can be analyzed as follows:

Immediate RCT: comes with a very high price tag. In the short run, immediate RCT might have a slightly higher clinical effectiveness than MTA treatment, but due to lower cost and higher effectiveness on first post-capping treatment, RCT is dominated by MTA treatment in the long run.

CaOH: the result for CaOH in the state transition model can be explained as follows: Due to high failure rates (41%) in the first 10 years post-capping, many simulated teeth end up requiring root canal treatment. Even though substantial effectiveness is gained through root canal treatment, the cost for root canal treatment is high. Therefore, compared to MTA pulp capping, CaOH pulp capping ends up with a higher cost on average. With regard to effectiveness, the MTA pulp-capped tooth population has a serious head start in effectiveness that CaOH cannot catch up to, even if some teeth in the CaOH-capped population gain substantial effectiveness through root canal treatment.

Analysis of the Cost Effectiveness Plane: In a lifecycle model, MTA pulp capping is more likely to give a comparative advantage for effectiveness than CaOH. The model shows that the initially higher cost of MTA treatment is offset by the lower post-MTA pulp capping cost.

The following **conclusions** can be drawn:

- **According to this model, MTA pulp capping treatment** should be the **first treatment choice** in the clinical situation of an open pulp if long-term-survival of a tooth is pursued.

4.6.2 Sensitivity Analysis (Hypothetical WTP)

Decision uncertainty was analyzed by using cost-effectiveness acceptability curves. The figure below depicts **the cost acceptability frontier along hypothetical WTP**. The graph shows us which treatment alternative should be preferred under a given Willingness to Pay. Furthermore, the graph assigns a probability to a treatment option for being cost-effective by using the variances that are included in the model from section 4.3 (clinical variances).

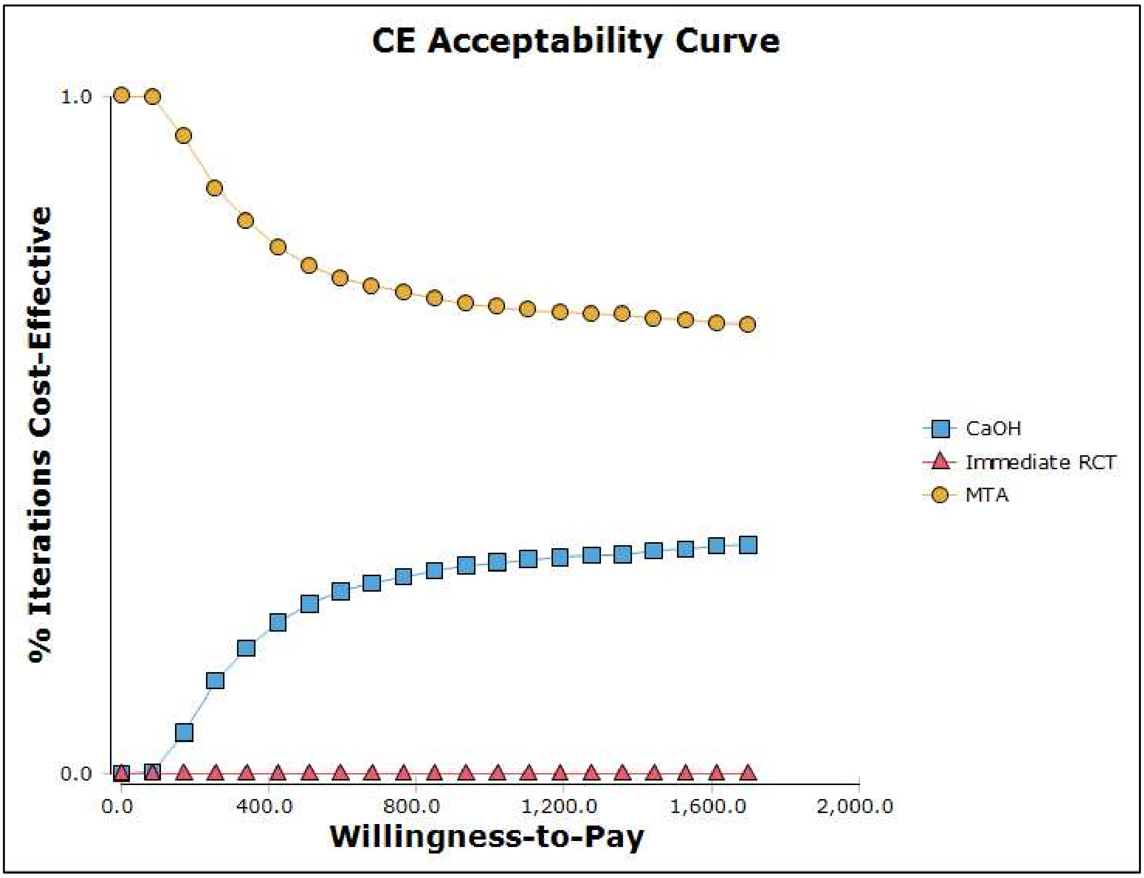


Figure 17: Willingness To Pay: MTA Pulp Capping is Cost-Effective Under All Given Budgets

When the treatment options are analyzed in a long-term scenario with an estimated survival of 48.8 years, along any given WTP, the **strategy** that is most likely cost-effective according to this model is **MTA treatment**. MTA had the highest likelihood of being cost-effective under any given WTP. Regardless of the assumed Willingness-to-Pay ceiling value, MTA pulp capping has the highest probability of being cost-effective in this model.

4.6.3 Extended Sensitivity Analysis (Probabilistic Sensitivity Analysis)

Decisions are always based on imperfect information. One way of dealing with uncertainty regarding cost and effectiveness is probabilistic sensitivity analysis (Robinson 1993). Probabilistic SA allows testing the robustness of a model by varying the values and key variables to a certain extent and by checking the impact on the overall results. With probabilistic SA, the level of confidence in a model can be increased and areas where further research is needed can be identified (Weinstein and Stason 1977). Ranges and distributions are assigned to variables and a statistical tool is then used to select random values for each range. Hereby, a large number of variables can be dealt with and a confidence interval can be calculated for each alternative.

For this dissertation, probabilistic sensitivity analysis is intrinsic to the model for clinical effectiveness, since 95% confidence intervals were used for effectiveness values. Furthermore, the costs for MTA, CaOH and RCT were varied (10%); however, there was no impact on the outcome of the model. The probabilistic sensitivity analysis is depicted below.

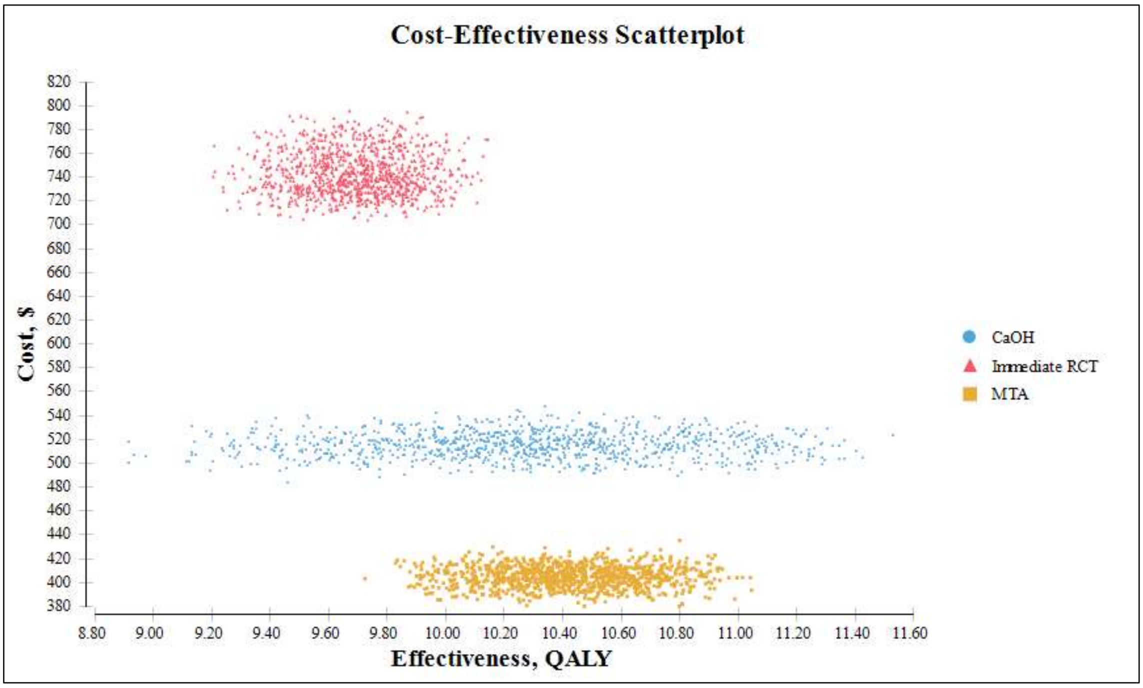


Figure 18: Monte Carlo Sampling of Variances (Effectiveness & Cost)

4.6.3.1 Extended CEA: Time-Dependent Analysis (Lifecycle Variation)

As was shown above, MTA is effective in the long run. However, CaOH is less expensive than MTA and only slightly less effective in the short run. An in-depth analysis is added here, where **time-horizon (lifecycle) is varied** to see if cost effectiveness changes in a model for a tooth that has a shorter life span than the previous model of 48.8 years.

It was necessary to find the life span of a tooth at which the **choice between MTA and CaOH becomes indifferent**. Why is this relevant for a decision maker? If a tooth has other conditions (that could influence its survival) in addition to open pulp, a life span can be defined at which it makes more sense to apply CaOH for cost saving. The model can thus inform a clinical decision maker until which estimated survival time it makes sense to apply CaOH and when it makes sense to apply the more expensive MTA, only taking health economics into account.

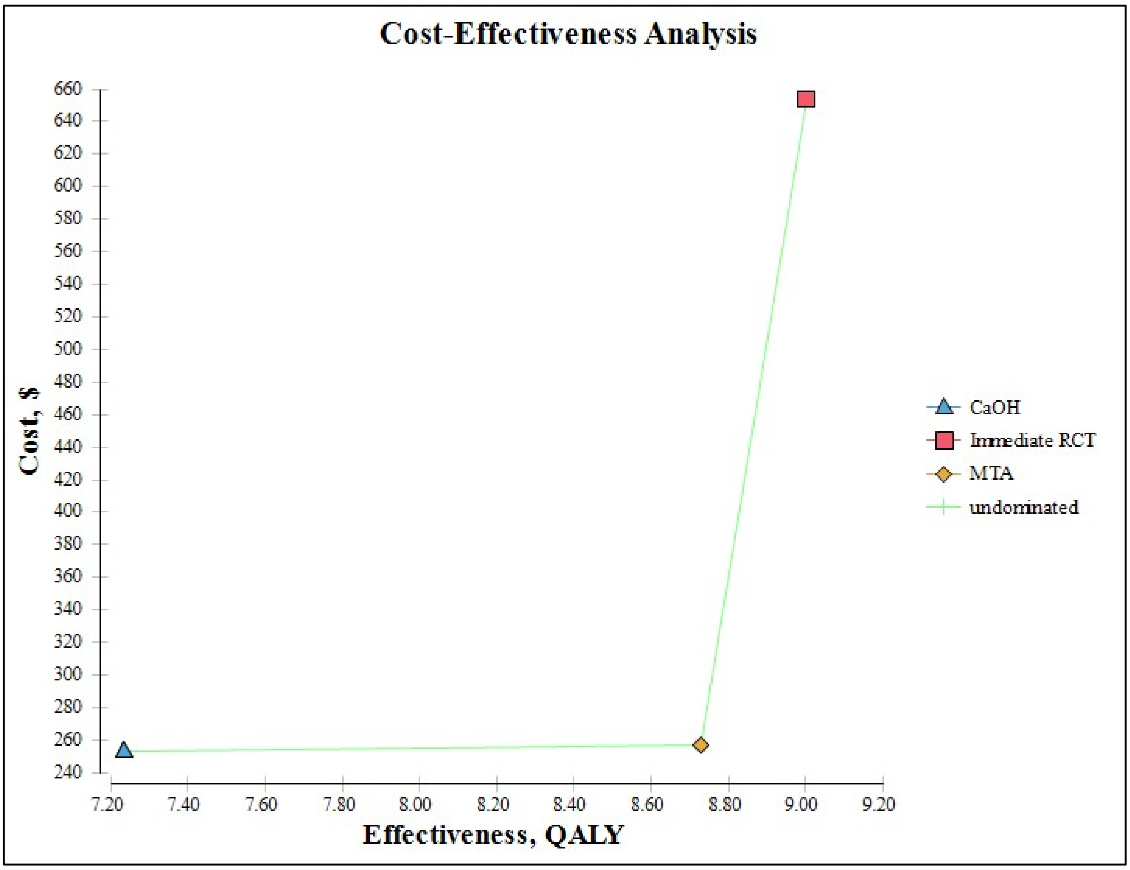


Figure 19: Cost Effectiveness of Open Pulp Capping in a 5-Year Scenario

The graph above shows the cost effectiveness plane of a 5-year scenario. In this case, all treatment options are undominated. The analysis shows that MTA is slightly more expensive but achieves a significantly higher effectiveness than CaOH. It should also be noted that while MTA is only 2% more expensive than CaOH in this scenario, it is still 21% more clinically effective. Furthermore, immediate RCT is also still a cost-effective treatment alternative in this model. However, while immediate RCT is 153% more expensive than MTA treatment, it is only 3% more clinically effective in this model. Finally, a cost-aware decision maker should choose CaOH as treatment alternative, and a clinical effectiveness-aware decision maker should choose immediate RCT as a treatment alternative in this scenario. MTA should be chosen by an indifferent decision maker.

In the next step, the cost effectiveness plane of a 6-year scenario is shown:

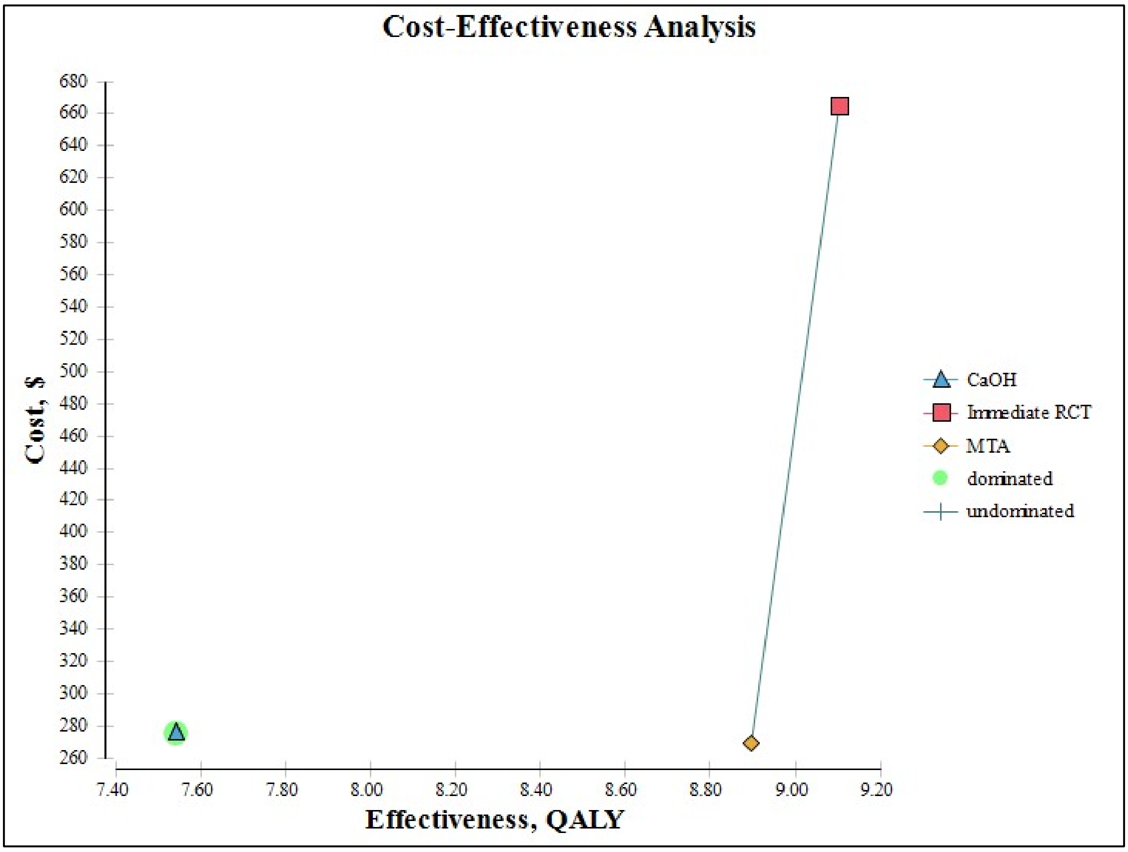


Figure 20: Cost Effectiveness of Open Pulp Capping in a 6-Year Scenario

When the model is shifted from 5 to 6 years, MTA and RCT both dominate CaOH. CaoH is dominated in this model because it is more expensive and less clinically effective in this scenario. RCT is significantly more expensive and only slightly less clinically effective. When a decision maker should choose between MTA and RCT, the steep ICER should be considered.

Therefore, the conclusion can be drawn from the previous two models that if remaining tooth life of a treated tooth is expected to be less than 6 years, CaOH treatment should be preferred by a cost-sensitive decision maker, since 6 years is the point in a time-dependent analysis at which CaOH becomes relatively more expensive than MTA and should therefore be avoided since resources could be used for something else.

To conclude the extended time-dependent analysis, it can be stated from the models that for a tooth life expectancy of more than 6 years, a decision maker should opt for MTA as a treatment strategy. For a lifetime expectancy of 5 years or less, a decision maker should opt for CaOH as a treatment strategy for pulp capping.

4.6.4 Overall Summary

In a long-term lifecycle model, MTA pulp capping always has a head start in effectiveness compared to CaOH. The initially higher cost of MTA treatment is offset by the lower post-MTA cost for follow-up treatments.

The following conclusions can be drawn as recommendations to a clinical decision maker based on the results of the models and extended analyses:

- **MTA pulp capping treatment** should be the **first treatment choice** in the clinical situation of an open pulp with a molar tooth when long-term survival of a tooth is pursued (48.55 years).
- In a long-term model, under all budget conditions, MTA treatment should be the treatment of choice.
- If expected life expectancy is varied, **CaOH treatment is cost-efficient and should be preferred** by a cost-sensitive decision maker from a **0 to 5-year scenario**.
- If expected life expectancy is varied, MTA treatment is cost-efficient and should be preferred by a cost-sensitive decision maker **in a 6-year scenario and above**.

Modeling the cost and clinical outcome suggests that MTA pulp capping is more likely to be cost-effective in a lifetime scenario of 48.55 years in a German healthcare system setting. Therefore, the use of MTA as a pulp-capping material is clinically relevant and represents a cost-saving treatment strategy for treating an open pulp and when considering long-term economic consequences.

The modeling results appear to be robust. The variance analysis shows that under different budget restrictions, MTA is cost-effective.

4.7 Model Discussion

A cost effectiveness analysis of open pulp treatment alternatives was performed based on latest available clinical evidence and a cost model based on GOZ and BEMA. One must now ask if all factors required for a good cost effectiveness analysis were fulfilled (Tonmukayakul et al. 2015).

Factor 1 transparency of cost calculations: cost calculations were provided in detail (see section 3.4). Thorough and transparent accounting for MTA treatment and alternative treatment options was demonstrated.
Factor 2 cost discounting: 2% discounting was implemented into the model by using the discounting function in TreeAge Pro 2019.

Factor 3 quality of underlying clinical endpoints: Mente's underlying study declared clinical endpoints. Full transparency was provided for clinical endpoints. However, for alternative treatment solutions, clinical endpoints were not researched in detail. Further research of these clinical endpoints could improve the results of this study.

It should be noted that the **clinical data quality** for this model was **very high** (e.g., time-dependents phasing of survival curves was available). Therefore, high standards for cost-effectiveness modeling and consecutive analysis were fulfilled.

There might be certain **limitations** to this model that need to be discussed. **CEA models can only be as good as their underlying data.** It is possible that the lack of evidence in certain areas might have limited this cost effectiveness analysis. Some limitations of the models will be addressed.

First, it can be argued that **cost-effectiveness information, i.e. information on cost and health** resulting from the model, is a **median average per individual for respective treatment options within the Markov cohort.** Within the TreeAge Pro 2019 software, the **individual treatment cost and health outcome for a treatment/state is calculated by multiplying the health-gain/cost of a state with the likelihood that the state is reached.** Therefore, **decisions** within this model are **based on likelihood-adjusted medians** – which is sufficient for decision making. However, outside of the model, the cost for a patient in the long run is never a likelihood-adjusted median cost. Until the software provides functionality for Markov cohorts to calculate cost on an individual level, this is the best information available as of today.

Second, it can be argued from a clinical viewpoint that the clinical decision tree is missing **root end surgery** as a follow-up treatment option to root canal treatment. However, in practical dentistry root end surgery is mostly performed on single-rooted teeth and is barely performed on molar teeth due to the impeded accessibility of multiple roots in the maxilla bone (Ioannides and Borstlap 1983). Since the model is based on a molar tooth scenario, root end surgery was not included in the model.

Third, it can be argued that the model and analysis were **based on a single trial**. However, a systematic review or meta-analysis of the clinical effectiveness of treatments of an open pulp does not currently exist. Mente's trial is a **university setting trial** and data was retrieved in only **one country** in one university setting. It is currently not known whether the treatment efficacy can be generalized across all patient and dentist populations. To further reduce uncertainty in the model and improve cost effectiveness analysis, enhanced clinical trials are needed and their data needs to be implemented into the models. However, as of today, and until further clinical studies are available, MTA as a therapeutic option for the treatment of an open pulp has the highest probability of being cost-effective in a long-term model and should therefore be chosen.

The conclusion can be drawn that the model at hand, based on a single RCT for the clinical effectiveness of MTA vs. CaOH, indicated that **decision making in favor of MTA in an open pulp scenario can be supported**. However, in order to provide treatment guidance (e.g. *Leitlinie der Kassenzahnärztlichen Bundesvereinigung*, the guidelines of the German Public Dentists’ Association) to clinical decision makers, **higher quality of evidence** needs to be included in the model, e.g. systematic reviews or meta-analyses. Until further clinical studies are available, MTA has the highest likelihood of being cost-effective and should therefore be chosen in an open pulp treatment scenario.

How the results of this dissertation can be implemented in clinical practice will be discussed in the overall discussion (see section 6.2) of this dissertation.

The model presented here showed that high-quality clinical data can improve a model and enable sophisticated decision analysis. The next chapter will explore whether robust models can be built even if the underlying data is very limited.

5 Deciding on Cost-Effectiveness of Therapeutic Alternatives in the Emergency Situation of an Avulsed Tooth (Pulpal Trauma): Re-plantation vs. Implant-Supported Crown vs. Adhesive Bridge (Dry-time-dependent Comparative Scenario Analysis)

5.1 Background Dental Trauma and Avulsed Tooth

A **dental trauma** is defined as “an injury to the teeth and/or periodontium (gums, periodontal ligament, alveolar bone), and nearby soft tissues such as the lips, tongue, etc.” (DentalTraumaGuide 2017). Most dental traumas happen to children with primary teeth within the age bracket of 2-3 years (Flores 2002) when children fall due to the movement system not being fully developed. In permanent teeth, most dental traumas occur due to falls/accidents, violence, sports or eating hard foods (Rocha and Cardoso 2001). 33% of adults have experienced trauma to their permanent dentition. Avulsions of permanent teeth happen in 0.5-3% of all dental injuries (Glendor et al. 1996).

Within dental trauma, tooth avulsion is a category of trauma that is defined as **the complete displacement of a tooth from its socket in alveolar bone owing to trauma** (Weber 2017). If avulsion occurs to a permanent tooth, immediate action is required by the dentist; the reaction time is of utmost importance. Avulsion is very painful and represents the most serious injury of all dental injuries (Andersson et al. 2012). The following section will explore which treatment options are available for a decision maker faced with an avulsed tooth.

5.1.1 Avulsed Tooth and Re-plantation as a Treatment Option – a Medical Perspective

If a patient is suffering from an avulsed tooth, different treatment options are available for a clinical decision maker in this model: **re-plantation, implant with crown, and**

adhesive bridge (for why conventional bridges are ruled out in this model, see section 5.2.4). Whenever possible, re-plantation should be the first choice from a purely dental medical perspective and from a conservative dentistry perspective.

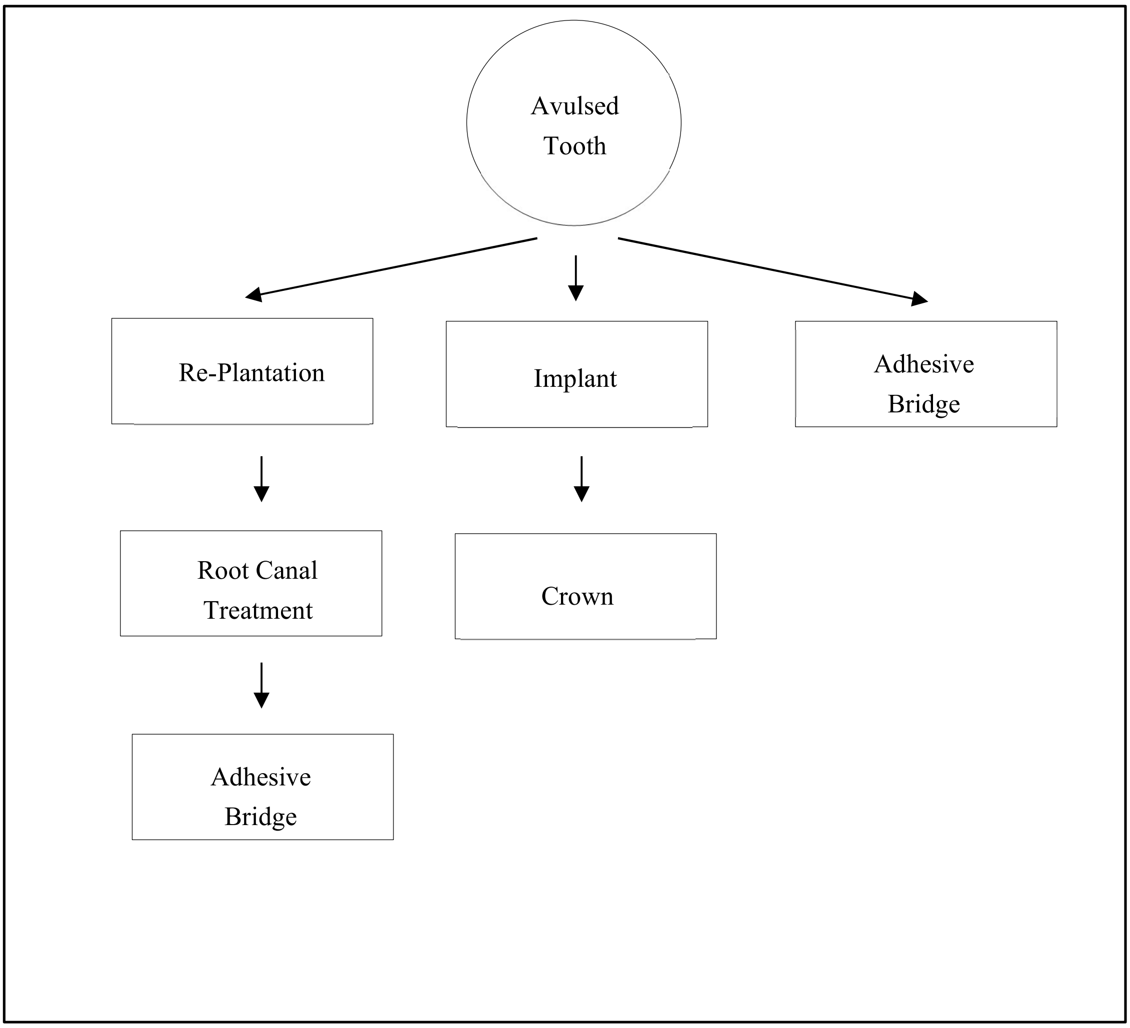


Figure 21: Decision Tree Avulsed Tooth Treatment

Since the focus of this dissertation is on pulpal disease/endodontics, special attention will be given to the re-plantation of an avulsed tooth. The remaining treatment options (implant/crown, adhesive bridge) will only be briefly explained and assessed. Detailed evaluations of these approaches would be of interest in dissertations focusing on surgical or prosthetic aspects of dentistry.

5.1.2 Re-plantation Process and Guidelines

When certain clinical requirements are met, **re-plantation** is the first treatment choice from a purely medical perspective in case of an avulsed permanent tooth. Guidelines for how the treatment should be performed by the dentist are issued by the **International Association of Dental Traumatology (Keels and Section on Oral Health 2014)**:

- **Pre-clinical measures to be taken by patient or helpers:**
    a. Pick tooth up by the crown; the root should not be touched
    b. Rinse tooth (10 sec); touching the root can result in cell crushing
    c. If replacement of the tooth is not possible, place the tooth in a storage medium, preferably "Dento Safe Box"
    d. Seek emergency dental treatment
- **Clinical measures to be taken by dentist:**
    a. Inspect root surface carefully. Clean (rinse) root surface and carefully remove dead cells from root surface. Keep root surface moist. Avoid touching the root surface too much (avoid cell crushing)
    b. Pain management (local anesthesia)
    c. Examination of bone structure/alveolar socket (probing/X-ray)
    d. Prepare the socket for re-plantation
    e. Re-plant the tooth with slight pressure
    f. Verify normal position clinically and radiographically
    g. Apply a flexible splint
    h. Give patient instructions (soft food, etc.)
    i. Root canal treatment 7-10 days after re-plantation

5.1.3 Anatomy of Re-plantation

The medical principle underlying re-plantation is that the **periodontal ligament** that connects the tooth to the bone **is still healthy and can heal** even though it has been severely damaged through avulsion. On the cell level, the periodontal ligament consists of **connective tissue cells (fibroblasts)** that are located on the root's surface. If a critical number of these cells remain vital and the cells are still attached to the tooth surface after avulsion, the avulsed tooth can be placed back in the alveolar pocket and re-generate. It is therefore crucial to keep the metabolism of fibroblasts going, so it must be ensured that the physiological requirements are met while the tooth is outside the pocket in order to prevent the fibroblasts from dying. The cells start dying 15 minutes after avulsion. The cells can be kept vital not only by keeping them wet, but also by providing them with a socket-like environment with regard to pH, osmolality and nutritional metabolites (e.g. glucose). There are special storage media (e.g. tooth safe boxes) that can significantly increase the success rate of a re-planted tooth. The halves of the torn periodontal ligament fibers will re-connect when the tooth is re-planted. Touching the surface of an avulsed tooth therefore diminishes the clinical survival rate (Hargreaves and Louis H. Berman 2015). The main criterion that is used in a clinical situation for decision making in an avulsed tooth scenario is **the dry-time of the tooth**, which will be explained in the next section.

5.2 Health Outcomes and Clinical Effectiveness of Avulsed Tooth Treatments

5.2.1 Clinical Effectiveness of Re-Plantation

It should be noted that the available data concerning the **clinical effectiveness** of **re-plantation** of an avulsed tooth is limited. In 1995, Jens Andreasen published a **prospective study on 400 human re-planted teeth** (Andreasen et al. 1995) with follow-up periods of up to 20 years. In this clinical study, the significant **correlation of dry time and healing complications** was established. This study represents the highest available clinical evidence for survival of re-planted tooth as of today. The study is a **clinical non-randomized controlled trial (non-RCT)**. This represents a **low level in the evidence pyramid**. However, Andreasen is an expert in dental trauma and is an active clinical researcher and publisher in this field (Andreasen et al. 2018).

Even though the evidence level for clinical effectiveness is limited, the **data will still be used for health economics modeling in this dissertation**. Andreasen's data is the best data available today. The latest **systematic review** on clinical effectiveness of re-plantation, conducted by Nene and Bendgude in 2018, came to the conclusion (Nene and Bendgude 2018) that no publications contributing evidence to this field have been made since Andreasen's study in 1995. Andreasen's data is deemed to be appropriate for this chapter and for the research question of how a model can improve decision making in a situation where only limited clinical data is available.

5.2.2 Dry-time-dependent Scenarios for Clinical Effectiveness of Re-Plantation

The clinical success of re-plantation **depends heavily on dry time (co-factor-dependent clinical effectiveness)**. There are **3 scenarios** for the **clinical effectiveness** of re-plantation of an avulsed tooth (Andreasen et al. 1995):

1) Tooth out of alveolar pocket **< 60 minutes and dry**
2) Tooth out of alveolar pocket **20-60 minutes and dry**
3) Tooth out of alveolar pocket **> 60 minutes and dry**

The longer the tooth has been out of the pocket and dry, the more PDL cells have died, and survival is severely limited with increasing dry time (see section 4.2.2).

The clinical data that will be used for the health economics modeling is:

Co-factor: dry-time after tooth loss	Failure rate (10 years)	95% Confidence interval [CI]
0-20 min dry time	21.5%	*6.5 – 36.5*
20-60 min dry time	44.4%	*32.0 – 56.0*
>60 min dry time	70%	*52.6 –87.6*

Figure 22: Dry-time-dependent Clinical Effectiveness of Re-Plantation (Andreasen, Borum et al. 1995)

Since the clinical success of re-plantation of an avulsed tooth is highly dry-time-dependent, the question arises whether the cost effectiveness changes depending on the dry-time of the avulsed tooth. Therefore, a **comparative cost-effectiveness analysis** will be performed.

5.2.3 Alternative Treatments to Re-plantation

5.2.3.1 Implant and Crown (Surgical Treatment Alternative)

Whenever re-plantation of an avulsed tooth is not possible, an alternative treatment is placing an **implant that will be provided with a prosthodontic crown** as a supra-construction after the alveolar socket is perfectly healed. Placing an implant with a prosthodontic crown is a well-accepted surgical/prosthodontic approach to replace a missing tooth. However, this approach is much more time-intensive than a conservative approach, more invasive, more stressful for the patient, and also significantly more expensive.

5.2.3.2 Clinical Effectiveness of Implant and Crown

A systematic review shows a 97% survival rate after 4 years (Creugers et al. 2000). Pjetursson (Pjetursson and Lang 2008), an acknowledged implant researcher, published a median clinical survival rate of **94.5%, 95% CI: [91,8, 96.3] after 5 years for implant-supported reconstructions**. 10-year survival rates are not available on a meta-analysis basis. However, a systematic review by Tomasi (Tomasi et al. 2008) shows that most studies also **tend towards a 95% survival rate after 10 years**. For modeling, 5-year survival rates will be extrapolated to 10-year survival rates with a slight discount, since most dental pathologies are progressive and not regressive.

5.2.3.3 Adhesive Bridge (Prosthodontic Treatment Alternative)

The second alternative approach to replace a missing tooth is an **adhesive bridge.** An adhesive bridge is a resin-bonded fixed partial denture that can be used to close a gap in the anterior region of the dental arch for permanent tooth replacement. The replaced prosthetic tooth is fixed with “wings” to the neighboring teeth and only minimal preparation of the posterior side of the neighboring teeth is required (Prathyusha et al. 2011).

5.2.3.4 Clinical Effectiveness of Adhesive Bridge

A systematic review of the survival of adhesive bridges has been performed by Balasubramaniam (Balasubramaniam 2017). Since survival is heavily dependent on retentive preparation, the study that will be used for adhesive bridge survival is that conducted by Peter Rammelsberg (Pospiech et al. 1996; Rammelsberg et al. 1993). A survival rate of 95% for 10 years was found in the study; no variance was given. For modeling, a 3% standard variance will be assumed, which results in a **10-year median clinical survival rate of 95% with 95% CI of [92.15%, 97.85%].**

Another aspect that needs to be considered for modeling is that the most common complication is de-bonding, which happens in 19.2% of cases over 5 years. Therefore, the model adds **100 EUR for re-bonding in 19.2% of the cases** after 5 years.

5.2.4 Discarded Treatment Alternatives

It needs to be mentioned here that a **conventional bridge** is also a treatment alternative for an avulsed tooth. However, in this case and model, it will be assumed that the neighboring teeth of the avulsed tooth are still in perfect condition. Treating a patient with a bridge requires invasive treatment of the neighboring teeth. Since the adhesive bridge is the superior prosthodontic treatment option when neighboring teeth are in good condition, the bridge as an alternative treatment approach is not a viable option here.

Finally, it should be mentioned that the missing tooth could also be replaced with **removable partial dentures**. However, it can be argued that removable treatment solutions are not a comparable treatment alternative, since they are mostly used as temporary solutions before the permanent replacement of the missing tooth.

5.3 Assumptions for Cost Effectiveness Modeling

- All treatment happens within the context of the German healthcare system
- Front tooth is fully avulsed
- Tooth has one root canal
- Male/female adult > 20 years
- Apex of tooth is fully closed
- Trauma guidelines of the International Association of Dental Traumatology are followed
- **Re-plantation**: 2 weeks after re-plantation, RCT is successfully performed. Follow-up treatment if re-plantation fails is adhesive bridge.

- **Implant**: Bone-grafting is not needed, enough bone available for implant. Immediate prosthesis is made for adequate medical treatment after tooth loss and during implant process.
- **Adhesive bridge**: 100 EUR added for re-attachment after 5 years (section 4.3.3.4)

5.4 Cost Modeling of Avulsed Tooth Treatment

Avulsed tooth treatment is accounted for as listed in the German fee scale for dentists (GOZ, see Bundesgesetzblatt 2001) and the German uniform fee scale for dental interventions (BEMA, see Bundesgesetzblatt 2001). Cost will be modeled analogously to the previous chapters; for further cost modeling details please refer to section 2.4.

For this cost effectiveness analysis, a GOZ-only scenario will be drawn up because activities used in the model are not accounted for in BEMA. It was shown in Chapter 2 that shifting from a publicly insured patient scenario to a privately insured patient scenario only impacts a cost shift of all cost but does not change overall cost effectiveness. Therefore, **costs of activities** for the avulsed tooth treatment alternatives are calculated according to GOZ on the basis of the following formula (Bundesgesetzblatt 2001):

$$\text{Cost (GOZ, BEMA)} = \text{p (GOZ, BEMA)}*\mu*\pi$$

- p (GOZ / BEMA) is the chargeable item points for a certain activity according to the GOZ / GEMA
- μ is the monetary conversion factor (€ 051 per GOZ item point and € 0.95 according to BEMA)
- π is the treatment time factor, dependent on the complexity of the individual case" (π=1 in case of GOZ, π = 2.3 or 3.5 in case of BEMA)
  (Listl and Faggion 2010).
- Cost evaluation of "Implant and crown" cost at 1,808.67 EUR was taken from (Schwendicke et al. 2014). Multiplier 2.3 was used for this calculation to assure comparability of treatment options, i.e. all treatment alternatives have been calculated using Multiplier 2.3 and GOZ accounting.

Taking all previous assumptions into account as well as the standard treatment process of an avulsed tooth explained in section 4.2.1, avulsed tooth treatment would be accounted for as shown in the following table by adding up the cost drivers for the different treatment:

Avulsed Tooth Treatment	**Privately insured – GOZ**	**GOZ**	**Points**	**Amount**	**Multiplier**	**Cost**
Re-Plantation	Anamnesis & Consulting	Ä1	100	1	2,3	12,94 €
	Symptomspecific Diagnosis	Ä5	100	1	2,3	12,94 €
	X-Ray	5000	50	2	2,3	12,94 €
	Local Anästhesia Upper jaw	90	60	1	2,3	7,76 €
	Re-Plantation	3140	550	1	2,3	71,17 €
	Stabilization	7070	90	2	2,3	23,29 €
	Adhesive for Stabilization (per tooth)	2197	130	3	2,3	50,47 €
	Extensive Post-OP Consulting	6190	140	1	2,3	18,12 €
Root Canal Treatment	Trepanation	2390	65	1	2,3	8,41 €
	VitEx (per canal)	2360	110	1	2,3	14,23 €
	Root Canal Treatment 1x	2410	392	1	2,3	50,72 €
	Electromagnetic Legth Determination (p	2400	70	1	2,3	9,06 €
	Ultrasonic Rinsing (per canal)	2420	70	1	2,3	9,06 €
	X-Ray	5000	50	3	2,3	19,41 €
	Microscope	110	400	1	2,3	51,76 €
	Root Canal Filling	2440	258	1	2,3	33,39 €
	Adhesive Restoration F1	206	520	1	2,3	67,29 €
	Removing adhesive stabilization	2702	300	1	2,3	38,82 €
	Total					**511,78 €**
Adhesive Bridge	**Privately insured – GOZ**	**GOZ**	**Points**	**Amount**	**Multiplier**	**Cost**
	Impregum	98a	-	1	2,3	29,00 €
	Adhesive Bridge Placement (NEM)	93b	-	1	2,3	335,00 €
	Abformung Lower Jaw	5170	250	1	2,3	32,34 €
	Registration	8010	180	2	2,3	46,45 €
	Arbitrary Scharnierachsenbestimmung	8020	300	1	2,3	38,80 €
	Face Bow	8050	500	1	2,3	64,68 €
	Dental Lab (Material & Time)					665,47 €
	Total					**1.211,74 €**
Implant & Crown	**Privately insured – GOZ**	**GOZ**	**Points**	**Amount**	**Multiplier**	**Cost**
	Total Implant/Crown cost according to Schwendicke (2014)				2,3	1.806,67 €
	Total					**1.806,67 €**

Figure 23: Avulsed Tooth Treatment Cost according to GOZ

5.5 Markov Model (Transition State Model)

A Markov s**tate transition model** (Sonnenberg and Beck 1993) was created using TreeAge Pro 2019 in order to enable CEA. The model was based on the clinical decision tree in **section 4.2.**

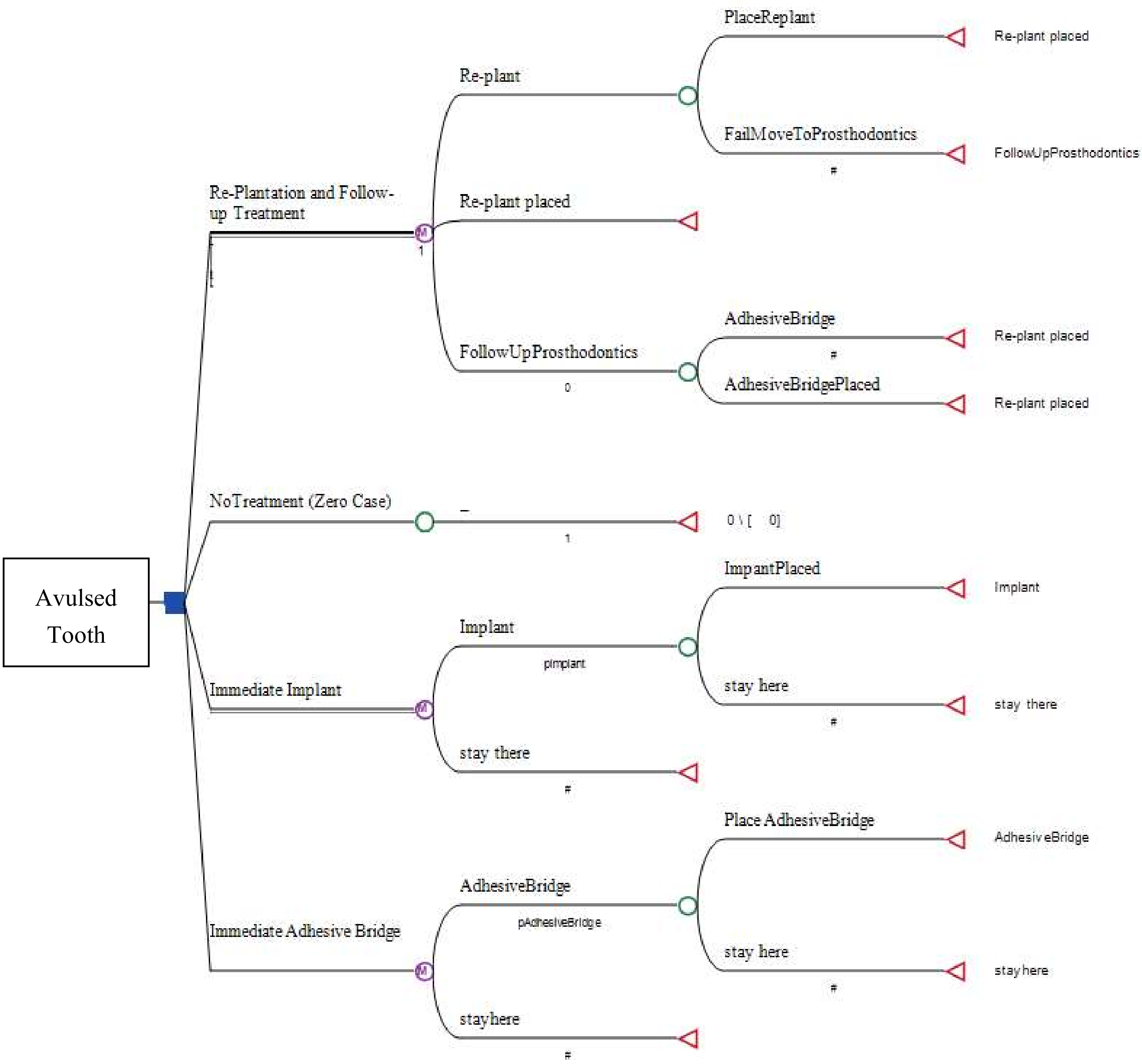


Figure 24: State Transition Markov Model Re-plantation in TreeAge Pro 2019

The model starts with the clinical situation of an avulsed tooth. In this situation, the clinical decision maker has the choice of 1) re-planting the tooth and continuing with root canal treatment; 2) skipping re-plantation and moving directly to placing an implant with an implant-supported crown; 3) skipping re-plantation and moving directly to placing an adhesive bridge. From the state of an avulsed tooth, the re-planted tooth can transition into the post-re-plantation state, which occurs when re-plantation fails.

Transition probabilities for a re-planted tooth were implemented into the model. For clinical effectiveness, **triangular distributions** were implemented according to the **95% confidence interval**. Cost was implemented according to GOZ calculations without any variance but will later be analyzed under variance analysis. The cycles in the transition state model represent a 10-year survival for all treatment alternatives, since reliable data for the 10-year horizon was available for all treatment options of an avulsed tooth.

The Markov model was populated via Monte Carlo simulations (sample + trial) and a population of 10,000 teeth was created. The state transition model was implemented in TreeAge Pro 2019 as follows and additional analyses were run on the model.

5.6 Deciding on Cost Effectiveness

5.6.1 Cost Effectiveness Plane

The cost effectiveness plane shows the cost effectiveness frontier for the state transition model based on cost and on 10-year survival of treatment alternatives for avulsed tooth treatment options. In general, it can be said that the more to the right and the lower an alternative is, the better is the respective cost-effectiveness. A **comparative analysis** was performed to analyze how cost effectiveness changes with different pre-requisites/external factors (dry-time).

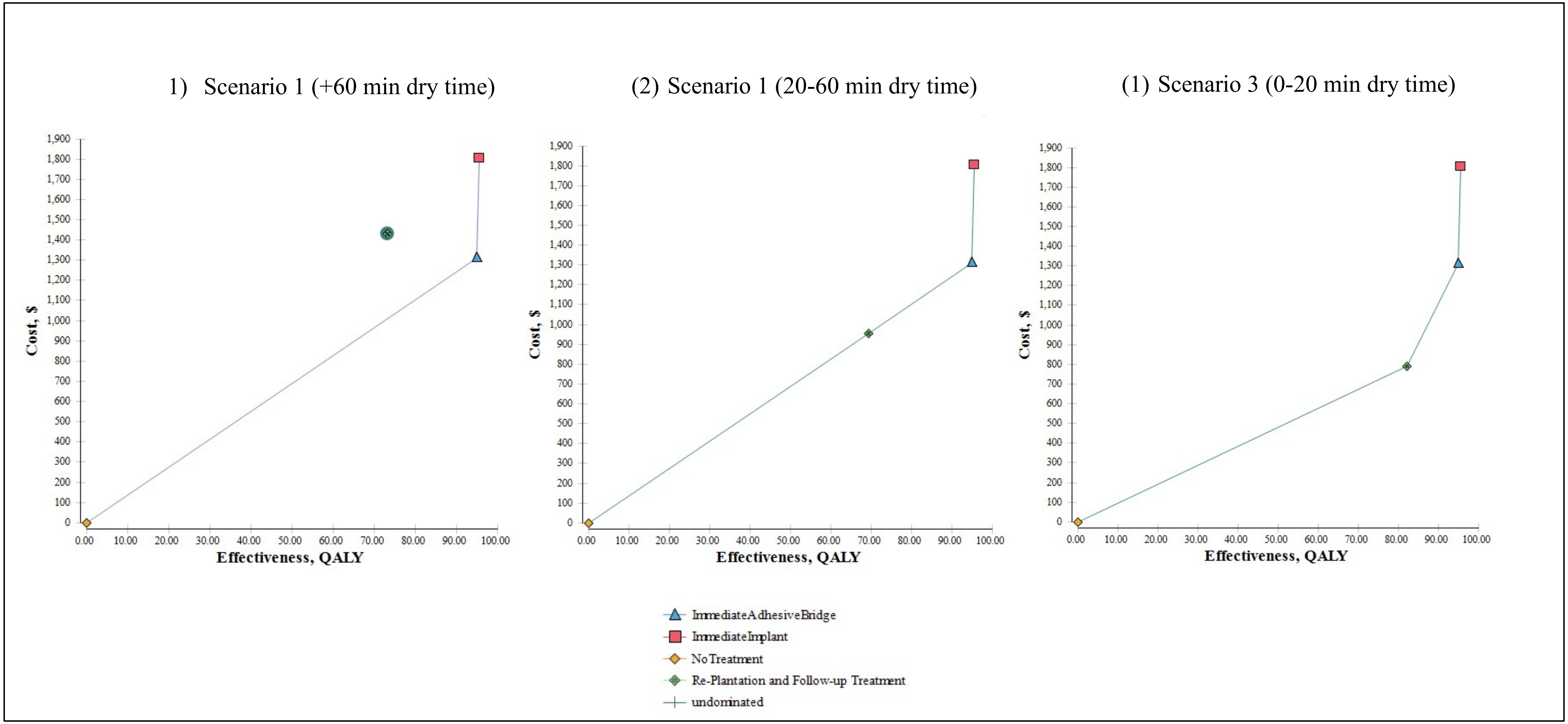


Figure 25: (1) Scenario 1: Cost Effectiveness Plane +60 min dry time scenario; (2) Scenario 2: Cost Effectiveness Plane 20-60 min dry time scenario; (3) Scenario 3: Cost Effectiveness Plane 0-20 min dry time scenario

The cost effectiveness plane for the different dry time scenarios can be analyzed as follows (**comparative analysis**):

- **Scenario (1) +60 min dry time**: Treatment option re-plantation is dominated by immediate adhesive bridge and by implant
- **Scenario (2) 20-60 min dry time**: Re-plantation, immediate implant and immediate adhesive bridge are all cost-effective treatment solutions within this scenario. Extended variance analysis is recommended for the decision maker.
- **Scenario (3) 0-20 min dry time**: Re-plantation, immediate implant and immediate adhesive bridge are all cost-effective treatment solutions within this scenario. Extended variance analysis is recommended for the decision maker.

The following conclusions can be drawn from the comparative analysis as a recommendation for the decision maker based on the 10-year model:

- **If an avulsed tooth has been out of the alveolar pocket for +60 minutes** and stored dry, re-plantation as a first-time treatment option is dominated by implantation and adhesive bridge in a 10-year scenario. Therefore, re-plantation is not cost-effective in this model. From a cost effectiveness perspective, immediate bridge or implant should be preferred.
- **If an avulsed tooth has been out of the alveolar pocket for 20-60 minutes** and stored dry, re-plantation, immediate implant and adhesive bridge are all cost-effective treatment alternatives. However, re-plantation only slightly meets cost effectiveness criteria. If re-plantation was only slightly less effective or slightly more expensive, it would lose out on cost-effectiveness.
  Under variance analysis, re-plantation cost has a high standard deviation in the model, whereas implant and adhesive bridge do not have a deviation. Therefore, if the clinical advisor is risk-averse (or if there are other factors that could have a negative impact on the tooth) he should directly recommend implantation or adhesive bridge. Since re-plantation and adhesive bridge have the same ICER, but adhesive bridge has a lower standard deviation with regard to cost and effectiveness, adhesive bridge should be preferred from a health economics perspective in this model.

- **If an avulsed tooth has been out of the alveolar pocket for 0-20 minutes and stored dry:** re-plantation, immediate implant and immediate adhesive bridge are all cost-effective treatment solutions within this scenario. Comparing re-plantation to adhesive bridge, the ICER of re-plantation is significantly less steep compared with the ICER of immediate adhesive bridge and the ICER of the 20-60 min dry time scenario.

  The depicted cost effectiveness plane can be analyzed as follows (for details see appendix section 7.2):

    - In the 10-year model of an avulsed tooth, **8.3 life years** can be gained for an average cost of **792.60 EUR** with **re-plantation and follow-up treatment**. Effectiveness and cost both increase for re-plantation and post-re-plantation treatments in the state transition model. It should be noted that these numbers are probability-adjusted medians. Variance analysis calculated with the Monte Carlo simulations shows that 97.5% of the values lie within the range of **7.3 years to 9.1 years**.
    - In the **10-year model** of an avulsed tooth, **9.5 life years** can be gained for an average cost of **1311 EUR** by placing an **adhesive bridge**. The calculated ICER for adhesive bridge compared to re-plantation is 432 EUR per additional life year. In percentages: a 14.5% gain in clinical effectiveness can be gained for 65.4% more cost).
    - In the 10-year model of an avulsed tooth, **9.6 life years** can be gained for an average cost of **1808 EUR** by placing an **implant**. The calculated ICER for adhesive bridge compared to re-plantation is 781 EUR per additional life year. In percentages: 16.3% more clinical effectiveness can be gained for a 128.1% increase in cost).

Looking at the variances and ICER, one can draw the conclusion that re-plantation of an avulsed tooth is preferable. If the decision maker has no budgetary constraints, more effective but more expensive treatment alternatives like immediate implant or immediate adhesive bridge should be considered. However, from a purely medical perspective, the latter treatments have additional aspects that are not considered in the model (e.g. invasiveness of surgery) and should therefore be second choices. From a **health economics perspective it makes sense for a decision maker to try re-plantation as a first-time treatment alternative**.

5.6.2 Sensitivity Analysis (Hypothetical WTP)

Decision uncertainty was analyzed by using cost effectiveness acceptability curves. The figure below depicts **the cost acceptability frontier along hypothetical WTP**. The graph shows us which treatment alternative should be preferred under a given Willingness to Pay. Furthermore, the graph assigns a probability to a treatment option for being cost-effective by using the variances that are included in the model from section 4.3.2 (clinical variances).

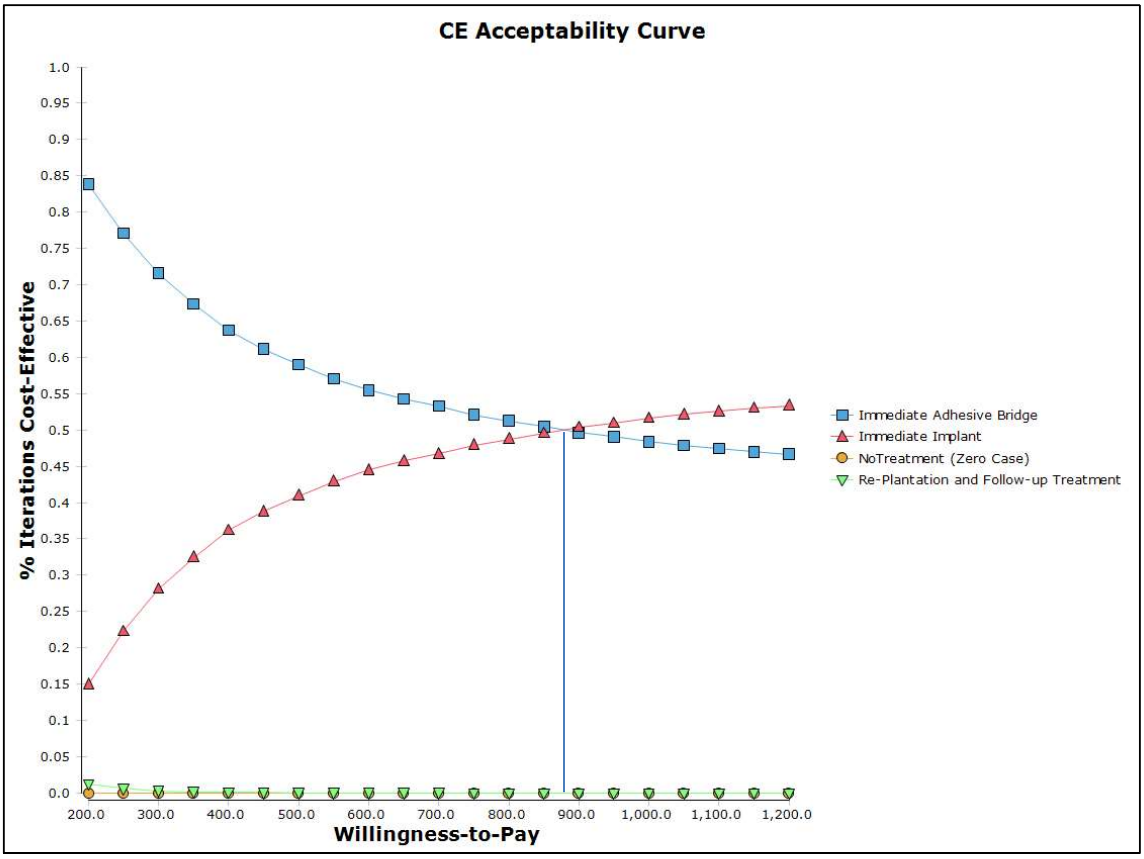


Figure 26: Willingness to Pay Analysis of Avulsed Tooth Treatment Options

- **An implant is the most cost-effective therapeutic choice** given that the patient is willing to pay more than 880 EUR for the treatment of an avulsed tooth.
- **An adhesive bridge is the most cost-effective therapeutic choice** given that the patient is willing to pay less than 880 EUR for the treatment of an avulsed tooth.

5.6.3 Extended Sensitivity Analysis

Probabilistic sensitivity analysis is intrinsic to the model for clinical effectiveness, since 95% confidence intervals were used for effectiveness values. Furthermore, costs for treatment alternatives were varied (10%); however, there was no impact on the outcome of the model. The probabilistic sensitivity analysis is depicted below.

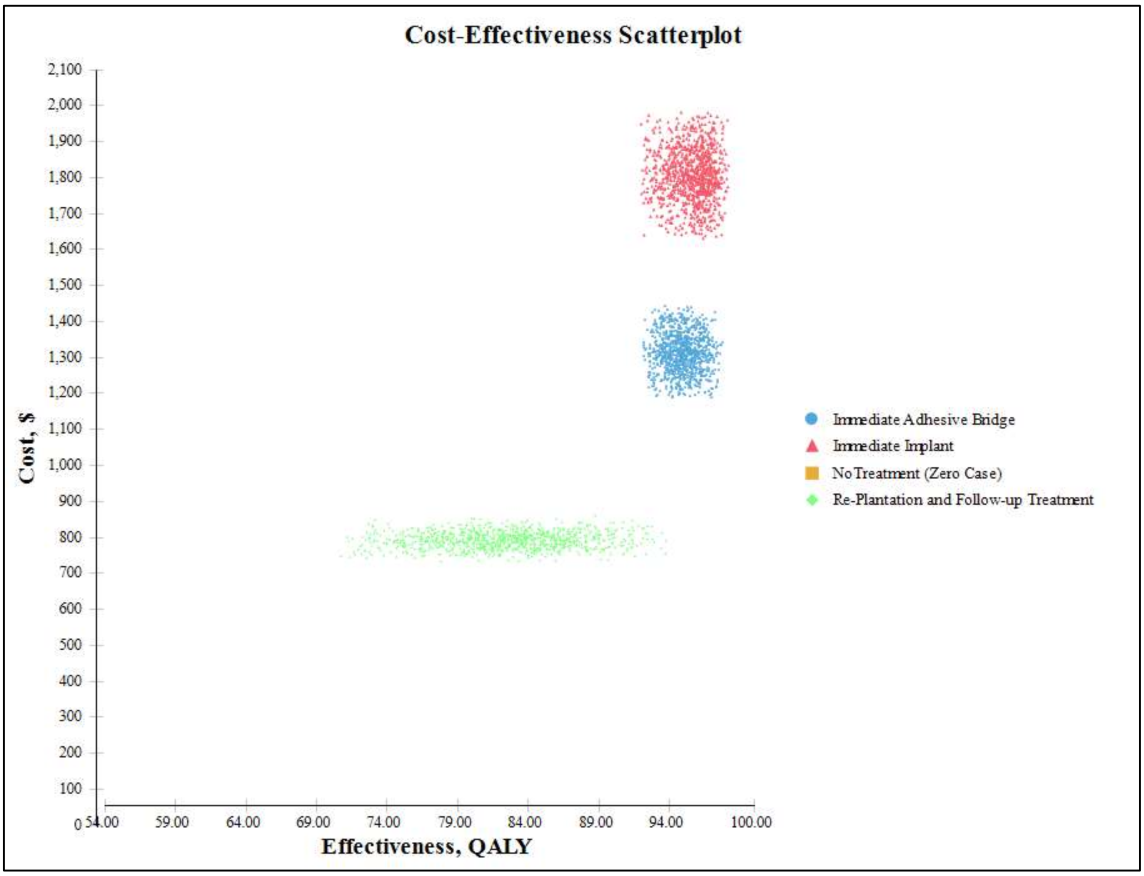


Figure 27: Monte Carlo Sampling of Variances for Avulsed Tooth Treatment Options (Effectiveness & Cost) 28: Monte Carlo Sampling of Variances for Avulsed Tooth Treatment Options (Effectiveness & Cost)

5.6.4 Overall Summary

In a 10-year model, a comparative analysis shows that cost effectiveness of re-plantation is positively correlated with less dry time of an avulsed tooth:

- **In a +60 min dry time scenario**, re-plantation is not cost-effective. Cost-effective treatment solutions are adhesive bridge and implant.
- **In a 20-60 min dry time scenario,** re-plantation just meets cost effectiveness and, due to variances, can be recommended to a risk-taking decision maker. However, further in-depth analysis is needed to make further recommendations. Adhesive bridge and implant are also cost-effective, but with higher ICERs.
- **In a 0-20min dry time scenario,** re-plantation is cost-effective. An in-depth analysis of the cost effectiveness plane and extended analysis of variances and Willingness to Pay was performed.

It was shown that cost effectiveness changes depending on the dry time of the avulsed tooth. In a 0-20 min dry time scenario, replantation should be preferred in the first place, with adhesive bridge and implant also being cost-effective. Under budgetary restrictions, a decision maker 1) willing to pay more than 880 EUR for the treatment of an avulsed tooth should decide for an implant, and one 2) not willing to pay more than 880 EUR for the treatment of an avulsed tooth should decide for an adhesive bridge.

5.7 Model Discussion

Based on the latest available clinical evidence and a cost model based GOZ, a cost-effectiveness analysis of avulsed tooth treatment alternatives was performed. Overall, the model in this chapter was established in order to determine whether a model can be based on and be derived from a clinical decision scenario in which only very limited clinical information is available. This was the case for the clinical situation for the treatment of an avulsed tooth. Furthermore, the approach aimed at discovering “how far” a model can be taken that is based on rather experimental clinical information in the first place. Ultimately, it was shown that even in cases of limited clinical information, data can be processed in such a way that plausible trends in cost effectiveness can be identified. This was done by performing a comparative cost effectiveness analysis.

However, there is the question of whether all factors required for a good cost effectiveness analysis were fulfilled (Tonmukayakul et al. 2015).

Factor 1 transparency of cost calculations: cost calculation was provided for in detail (see section 4.5).
Factor 2 cost discounting: 2% discounting was implemented into the model by using the discounting function in TreeAge Pro 2019.

Factor 3 quality of underlying clinical endpoints: Andreasen's underlying non-RCT on the clinical effectiveness of an avulsed tooth did not declare detailed information clinical endpoints. Neither were clinical endpoints of implant and adhesive bridge researched in detail. However, the purpose and nature of this model was to demonstrate how modeling can overcome limited clinical information, and therefore the limited information on clinical endpoints was accepted.

Furthermore, there might be certain limitations to this model that need to be discussed.

First, a limitation of CEA is that a model can only be as good as its underlying data. The analysis was based on Andreasens's non-RCT. However, as of today, and until further clinical studies are available, the data provided by Andreasen for avulsed tooth treatment is the best data available. Further clinical data with higher-quality evidence (e.g. meta-analysis) of clinical effectiveness could further improve the results of this study.

Second, due to limited clinical data, the model itself was kept simple. Due to a lack of survival curves in the underlying clinical data, no phasing of survival could be applied. The time horizon of the model was 10 years. In more sophisticated models, e.g. as in Chapter 3, time-dependent analyses could provide further insight into decision making. However, this was not possible in this case since long-term clinical data beyond 10 years was not available.

Third, it may be argued that clinical effectiveness for adhesive bridge (95%) might be overstated in Rammelsberg's study (Rammelsberg et al. 1993). However, it needs to be considered that the success rate of adhesive bridges in the study is based on the fulfillment of very specific design and treatment parameters for adhesive bridges. These are material selection (ceramics), preparation design (retentive preparation), and bonding requirement (roughening the tooth surface before adhesive bonding). An opposing argument can be made that many adhesive bridges fail in general practice due to non-fulfillment of these very specific design and treatment parameters. Since all these parameters can be implemented by a dentist in general practice, it can be inferred that reaching clinical success rates for adhesive bridges is feasible.

Fourth, it may be argued that an alternative to **comparative dry-time-dependent scenario analysis** could be **to integrate dry time as a variable into the model and analyze cost effectiveness depending on dry time under variance analysis.** However, this requires further research dealing with creating clinical effectiveness functions that merge three dry-time-dependent probability functions into one meta-effectiveness function in one model. If such a function was available, dry-time dependent analysis could be performed and a diagram could be drawn that depicts “likelihood of being cost effective” on the y-axis and “dry time” on the x-axis.

To conclude, even though the clinical data was very limited and the evidence level of available clinical effectiveness was low, modeling and comparative cost effectiveness analysis revealed a trend in cost effectiveness **(cost effectiveness is positively correlated to less dry time of an avulsed tooth)** that can still be used to support decision making in this highly competitive environment of avulsed tooth treatment. Until further research is available, and within the limitations of this model, the likelihood is high that in **a 0-20 min dry time scenario, re-plantation is a cost-effective treatment alternative**.

6 Concluding Part

6.1 Summary of Results

Within the possibilities and limitations of this dissertation in the field of dental health economics, the following three **research questions** were substantially explored:

1. Which of the currently available treatment options for **dentin hypersensitivity** is the most cost-effective? The hypothesis is that there might be treatment alternatives that are more cost-effective than the gold standard treatment (chemical occlusion).

2. There is evidence that **MTA** has a high clinical effectiveness when treating an **open pulp**. However, MTA is also more expensive than **CaOH** and treatment alternatives outside of pulp capping exist. The question then is which treatment option is cost-effective in the long run when cost and effectiveness of follow-up treatments are considered. The hypothesis is that application of transition state modeling enables long-term decision making.

3. Is **replantation** of an **avulsed tooth** a cost-effective treatment alternative in case of dental trauma? The hypothesis is that a robust model can be built upon limited clinical data available and that variance analysis can be applied for assessing the uncertainty of decision making.

The results of the models can be summed up as follows:

1. The Cost-effectiveness analysis compared **physical occlusion**, **chemical occlusion**, **nerve desensitization**, **laser** and **placebo** for the treatment of **dentin hypersensitivity**. **Physical occlusion** was considered **most cost-effective** with an **ICER** of **7.76 EUR for the reduction of 1.0 units on the SMD pain scale** (compared with placebo). Both, **chemical occlusion** and **nerve desensitization,** were **dominated**. The **ICER** of **laser** was considered cost-intensive with **6.4 EUR for the additional reduction of 0.1 units on the SMD pain scale** (compared with physical occlusion).

2. The Cost-effectiveness analysis showed that **MTA direct pulp capping** treatment has the **highest likelihood of being cost-effective** within the limitations of

the state transition model that was created to assess the long-term (48.55 years) effects of treatment alternatives **in an open pulp situation**. The **ICER** of **MTA** pulp capping was **403 EUR for 10.3 additional tooth life years** (compared with no treatment). Both alternatives, **CaOH direct pulp capping and Immediate RCT**, were **dominated**.

In situations, where **expected tooth life** is **less than 6 years** due to other reasons besides the open pulp, **CaOH direct pulp capping** should be **preferred**.

3. The Cost-effectiveness analysis showed that in an **avulsed tooth scenario re-plantation** has the **highest likelihood of being cost-effective when dry time of the avulsed tooth is limited to 0-20 minutes**. The **ICER** of re-plantation (compared with no treatment) was **792.60 EUR** for **8.3 additional tooth life years**. Both **alternatives**, **adhesive bridge** and **implant-supported crown**, were **not dominated**, but were more **cost-intensive**.

It was shown that **opportunities exist to increase and improve health outcomes from a micro-economics perspective by re-allocating resources and treatments towards the right treatment alternative in the field of pulpal disease management** (sections 3.7, 4.6, 5.8). This can result in making **better use of resources in the context of endodontic treatment decision scenarios**. Moreover, the **need for continuous research** into clinical effectiveness in endodontics was demonstrated (see section 3.13, 4.7, 5.7).

The results revealed that **EE techniques**, i.e. **CEA**, can be applied to **enable evidence-based decision making in the field of dental health economics** (section 5.1), thereby providing **unbiased and transparent information about the value for money in the field of endodontics**. **Moreover**, it was shown that **patient-centeredness** could be **implemented through decision analysis under a priori unknown budgetary constraints**. Therefore, the challenges that were formulated in the introduction of this dissertation could be substantially addressed.

The **technical limitations of the models** have been **discussed in the respective chapter** and can be found in sections 3.13, 4.7 and 5.9), but critical questioning of the overall impact of this dissertation will be addressed in the next section.

6.2 Discussion

The main chapters of this dissertation have answered the research question through technical modeling of clinical situations in endodontics, upon which conclusions were drawn. The question that remains is **what the implications of the results of this dissertation are for patients and dentists;** this will be discussed in section 6.2.3. Furthermore, there might be possible **limitations inherent to the CEA approach** itself, which will be discussed in section 6.2.2. Also, there might be several **limitations inherent to the methodical approach and modeling process** of this dissertation, which will start off the discussion.

6.2.1 Challenges within the CEA Modeling Processes

There were several **challenges** that came up during the process of applying CEA to the **three research questions of this dissertation**. The first challenge was to find appropriate clinical data for the effectiveness of the clinical situations derived from the research questions. Since the research questions covered multiple health states and treatments options, various sources of clinical data had to be accesses and evaluated. The next challenge was embedding these data sets into the modeling framework. It quickly became clear that three different research questions resulted in three heterogeneous data sets, and **each of the research questions therefore required its own distinct model**. While modeling was straightforward and standard for DHS treatment in chapter 2, the implementation of the long-term character in the open pulp in chapter 3 pushed the boundaries and a completely new model had to be implemented that included **transition probabilities** and **health state (Markov models)**. As for the re-plantation in chapter 4, evidence was so scarce that **comparative modeling** was introduced, i.e. the model was built and run three times for three different dry time scenarios with the endeavor to perform a model comparison and a trend analysis was finally possible.

Therefore, it can be stated that all data challenges could be overcome through **enhanced statistical models** and by **creating highly individualized distinct models for each research question** that allowed dealing with the research questions of this dissertation.

6.2.2 Limitations of CEA as a method in EE

Every methodology choice in health economics has its **pros and cons (Drummond et al. 1993)** and section 2.2 pointed out the reasons why CEA was chosen for this dissertation. However, there might have been limitations intrinsic to CEA, which will be critically reviewed at this point, i.e. there might be limitations due to the fact that CEA was the methodological choice for this dissertation:

- It can be argued that the **ranking of alternatives might have limitations in CEA**. Analyses might exist for which **dominance** may not be clear-cut and this might raise serious questions. In some cases, therapeutic options are ruled out due to being less effective and more expensive than a linear combination of two other therapeutic strategies, which is called **extended dominance** (Drummond 2001)**.** If applied to a population, this can result in a mixed strategy for a population, which **would leave part of a population** with an **inferior treatment choice** (Cantor 1994), and **ethical issues** might be raised when a mixed strategy is applied. Taking the ethical issues of CEA a step further, it has been argued that it might be inappropriate or **unethical to let cost influence clinical decision** making due to CEA (Loewy 1980). In contrast, the majority of researchers remain **neutral to the ethical discussion** due to the fact that in health economics, **cost should be rather seen as "opportunity cost"**, i.e. what resources need to be given up for an alternative treatment (Williams 1992), which is also the viewpoint of the author of this dissertation. However, it should be acknowledged that analyses might exist that require deeper investigation of the ethical issues.
- It can be argued that the introduction of **ICER analysis** into CEA – as also applied in this dissertation) **raises several questions** (Drummond 2001). ICER works in such a way that a choice is made when a threshold, i.e. hypothetical WTP, is lower than the ICER, which is the average cost per additional health outcome unit (see e.g. chapter 2 for DHS treatment). However, this implies the **assumption** of **perfect divisibility of resources within the models**. In real life however, resources or therapies are not perfectly divisible (e.g. if a root canal treatment costs 1000 EUR and lasts 20 years, the patient cannot choose to pay only 500 EUR and maintain his tooth for just 10 years – therapeutic choices are mainly all or nothing). This limitation may have a significant impact on analyses and the risk has to be properly assessed.

- It can be argued that CEA analysis can only **apply a one-dimensional primary endpoint** for **clinical effectiveness** (Hanusch 2011). This limitation of CEA was also experienced in the modeling process of this dissertation. When different sources of clinical data for the models were aggregated, it was required that all clinical endpoints be the same or at least comparable, which can sometimes be difficult due to the fact that some clinical data from different resources do not reveal full details on clinical endpoints. However, this aspect could be managed within the models of this dissertation (e.g. by using the meta-endpoint-scales). It needs to be admitted that there might be modeling situations where clinical endpoints cannot be harmonized and further clinical research is needed with comparable clinical endpoints.
- It can be argued that patients' preferences are only recognized by simulating budgets in this dissertation and in CEA. However, personal preferences might exist beyond budgetary constraints (e.g. the hypothetical fact that "*there might be patients who are indifferent to tooth loss and might assign zero value to an additional tooth life year*" may not be accounted for in CEA models). Therefore, the implementation of extended preferences into the models might have a significant impact on the results of this dissertation. This could be solved by e.g. the introduction of CBA or CUA. However, it needs to be noted that CEA was chosen due to the lack of evidence about patients' preferences in endodontics (see section 2.2). If this evidence was available, CBA and CUA could be introduced and economic evaluation could be improved. Further research is needed in this regard so that patients' preferences can be implemented into models on a higher level.
- It can be argued that there are certain **macroeconomic aspects** that CEA cannot take into account (Drummond 2001). **First**, CEA **cannot claim to take a sectoral view**, which means where all possible interventions are compared in order to decide on the right health care mix level. Therefore, CEA needs to be seen for what it was made for, namely to be used to compare several alternatives; it is used more for exploring decision making under budget restrictions. **Second**, CEA does not claim to deal with the whole wide range of decision making, taking all possible preventative, restorative, and prosthodontic possibilities into account that could benefit different groups of individuals differently. **Third**, CEA does not deal with finding the right health care mix on a very broad macro-economic level. However,

it can help to reveal that a current treatment is relatively cost-ineffective and identify some alternatives that are relatively cost-effective and that are not currently being fully utilized. But it can also be used as an **indicator** of **where to investigate into macro-economics and spark further research**. CEA should be seen as a first indicator of where potential for resource reallocation exists with the goal of improving the total health level (WHO 2003). **Fourth**, CEA cannot quantify the final outcome and the full impact of decision making on the total healthcare system. However, **the micro-economic results of this dissertation are a pivotal pre-requisite and the first step, i.e. a foundation for the macro-level assessments** as well as **extended health policy assessments** that take the "sectoral view". **Continuous research in public health on the macro-economic level of pulpal disease treatment can therefore significantly enhance the results of this dissertation**.

6.2.3 Limitations for Translation of Results into the Health Care System

The previous sections evaluated the impact that CEA can have on the micro-economic level and explained that the results of this dissertation can be a first indicator for macro-economic research. However, the question of what impact the results of this dissertation can have on the clinical decision maker level, i.e. the dentist, and what possible limitations exist for implementing the results into everyday clinical practice, remains. Therefore, I would like to direct the reader's attention towards the debate around reasons or explication that hypothetically exist that could prevent clinical decision makers from implementing results into day-to-day practice.

6.2.3.1 Factors Impeding Translation of Knowledge into Clinical Practice from a Social Sciences Perspective (Behavioral View)

The **translation of research results** beyond academia into everyday clinical practice **is slow**. Evidence exists that it takes about ***17 years*** on average to implement the clinical results of an RCT into everyday clinical practice (IOM 2001). As long as new **knowledge** (e.g. as provided by the three models of this dissertation) **is not translated into everyday clinical practice (micro-economic perspective),** there will be **no impact** on the overall **health** output of a healthcare system **(macro-economic perspective)**.

From a social sciences perspective (behavioral psychology), there are several reasons why the implementation of new knowledge into everyday **clinical practice is slow**. The **social sciences**, and in particular psychology, provide **different theories** that help **explain** the **delay** in translating knowledge into practice. Changing human behavior is not always easy**. Habits** are an essential part of human behavior and are defined as "behaviors that are performed automatically in a certain situation because they have been performed in the past" (Wood and Runger 2016). Individuals **stick to habits** because they know that at the end of a habit cycle there will be a certain **reward**. Therefore, it is very difficult for an individual to change habits since in many situations it is not clear what the reward will be for performing an alternative behavior (Verplanken 2018).

One can apply habitual theory to clinical decision making in dentistry: **dental treatments** performed by a dental health decision maker can be **compared to a habit**. As an example, a dentist experiences the situation "open pulp" (certain situation) and automatically performs the treatment "pulp capping with CaOH" as a habitual response to the situation. It is **difficult** for a dentist to **break away from the habit cycle** and instead treat an open pulp with MTA. Changing to MTA treatment involves a **risk**, and the **reward is unclear**, e.g., there is a risk that it will be more difficult and time-consuming to apply MTA compared with CaOH. **Another reason** why decision makers stick to a treatment even though they "**know**" better is because evidence shows that an increase of information/knowledge does not necessarily change behavior, even when newly adopted intentions are strong (Walker et al. 2014).

It can therefore be derived that the **likelihood is high that dental health decision makers will stick to habitual treatment options, despite the evidence and knowledge about better treatment alternatives**. The translation of knowledge into action can be hampered by the psychological factors just discussed.

However, **habit changes can be triggered by additional incentives**, e.g. through "rewards". From an economics perspective, the "reward" must be higher than the "cost" of changing the habit. Therefore, it becomes clear that providing information is necessary, but not necessarily sufficient to change habits within the dental health environment. The means through which healthcare systems can spark change at the micro-economic level are dealt with in the discipline of **Public Health Economics**. **Further research on incentive systems in dental care is needed**.

6.2.3.2 Evaluation of the Impact of this Dissertation on Ideal Health Output and Peak Performance of Health Systems

The question of measuring the impact of the results of this dissertation on increasing the total dental health output still remains. A way of analyzing this would be to see what the characteristics of high performing health care systems are and whether the results of this dissertation can contribute to such characteristics.

The **Institute of Medicine (IOM)** is a public US organization that is devoted to providing inputs on how to close the gap between the current and ideal state of a healthcare system. In 2009, the IOM published *Crossing the Quality Chasm*, a publication dealing with the question "**How can a health care system better deal with translating knowledge into clinical practice**" (Appendix 7.7). A comprehensive strategy is presented on how to re-invent and improve the quality of care – with the ultimate goals of re-designing the whole healthcare system towards delivering **high-quality care** to patients and towards **improving the overall health output of the healthcare system** (IOM 2001).

The starting points for re-designing the healthcare system are, first, creating supportive payment and regulatory environments, and second, facilitating patient-centered organizations in healthcare. The focus is then placed on re-designing the whole healthcare system and processes (e.g. re-engineering of care processes, increased use of IT in healthcare, coordination of processes and services, etc.). The IOM strategy defined **six** pivotal **factors aimed** at the improvement of healthcare systems: delivery of **safe, effective, efficient, personalized, timely and equitable health services to patients.** It is argued that when major improvements are gained in all these factors, quality of care will appreciate, and the overall health output of the healthcare system will increase.

Applying these factors and the IOM approach for knowledge translation into clinical practice to the results of this dissertation, the following IOM pivotal aims can be supported by the results of this dissertation. **First**, the results of this dissertation can contribute to the aim of delivering **effective and efficient** health services to patients in the field of pulpal disease treatment, as was explored in the CEAs in Chapters 3-5. Basically, CEA provides formal decision support in decision making situations, when a decision needs to be made between two or more alternatives. **Second**, the results of this dissertation can contribute to reaching the aim of delivering **personalized** health services to patients by creating evidence for decision making of a priori unknown budgetary restraints.

Therefore, the results of this dissertation can certainly contribute to the improvement of crucial **two out of six IOM factors** within the field of endodontics towards creating a **high-performing health care system for pulpal disease management**.

6.3 Conclusion and Outlook

Coming now to a final conclusion, several recommendations can be made based on the results and critical review of this dissertation. Continuous **clinical research** is needed in the area of **pulpal disease treatment**. The models presented in this dissertation can benefit from advanced systematic reviews/meta-analyses in the area of pulpal disease treatment. Once this data is available, models can be adjusted and advanced. It was also shown in this dissertation that creating economic evaluation models in dental health economics is only a **prerequisite for improving total health care systems and macroeconomic research is needed**. The translation of knowledge of the results of cost effectiveness analyses in the area of pulpal disease into implementation in everyday clinical practice and the re-design of a healthcare system towards patient-centered care is another challenging research area in **public health** that needs to be established for endodontics, i.e. pulpal disease treatment. As of today, cost effectiveness analysis will continue to be a very relevant tool for advancing the concept of patient-centered healthcare in the future, until more advanced evaluation prerequisites, e.g. monetary values for the benefits of endodontic treatments, become available for economic evaluation in dental healthcare.

To provide an **outlook**, a tentative roadmap for continuous research and progression of results towards translating dental health economic research into practice can be depicted as follows:

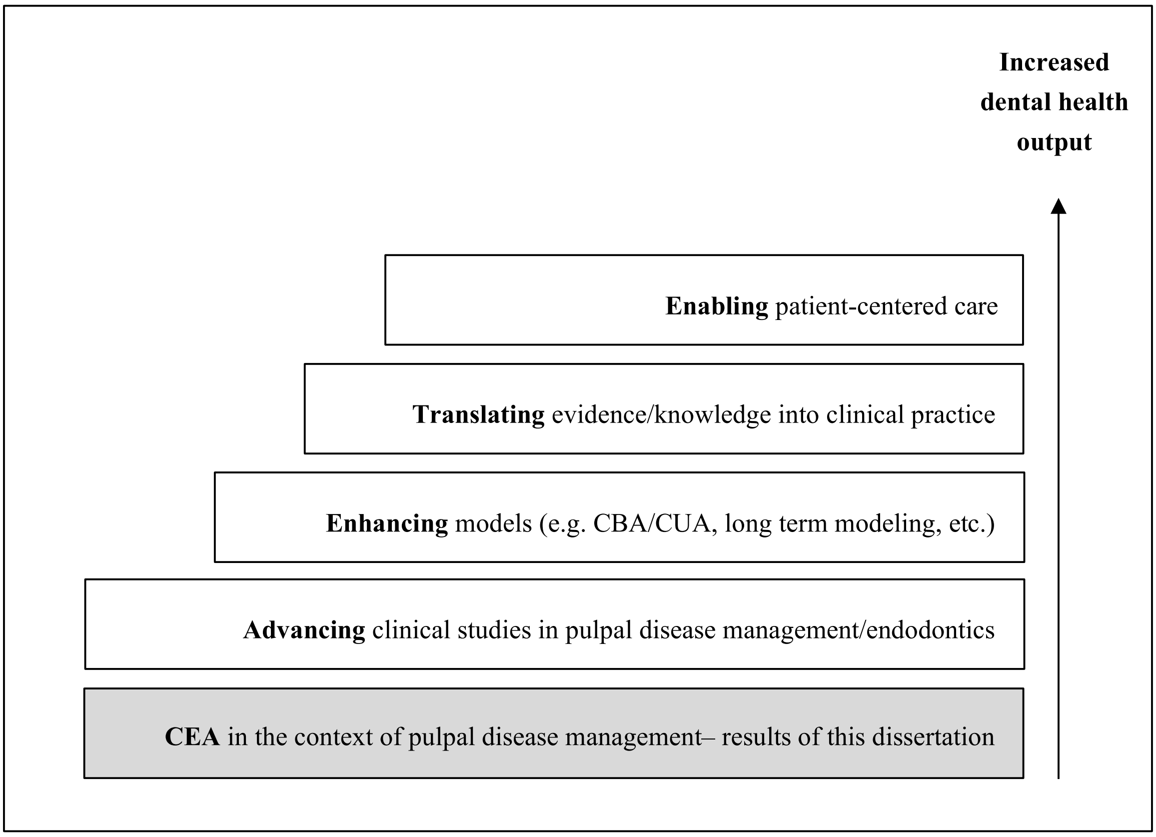


Figure 29: Roadmap for Continuous Health Economics Research in the Context of Pulpal Disease Treatment (own)

The roadmap shows that CEA in endodontics is the very basic micro-economic foundation that can ultimately lead towards improving quality of care and increasing the overall dental health output. It may be noted that even though the results of this dissertation might start out small, all things have to start somewhere.

“Knowing is not enough; we must apply. Willing is not enough; we must do”

Johan Wolfgang von Goethe (1749-1832)

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8 Appendix

8.1 Cost & Effectiveness Variance Analysis for MTA vs. CaOH Treatment Options in an Open Pulp Scenario

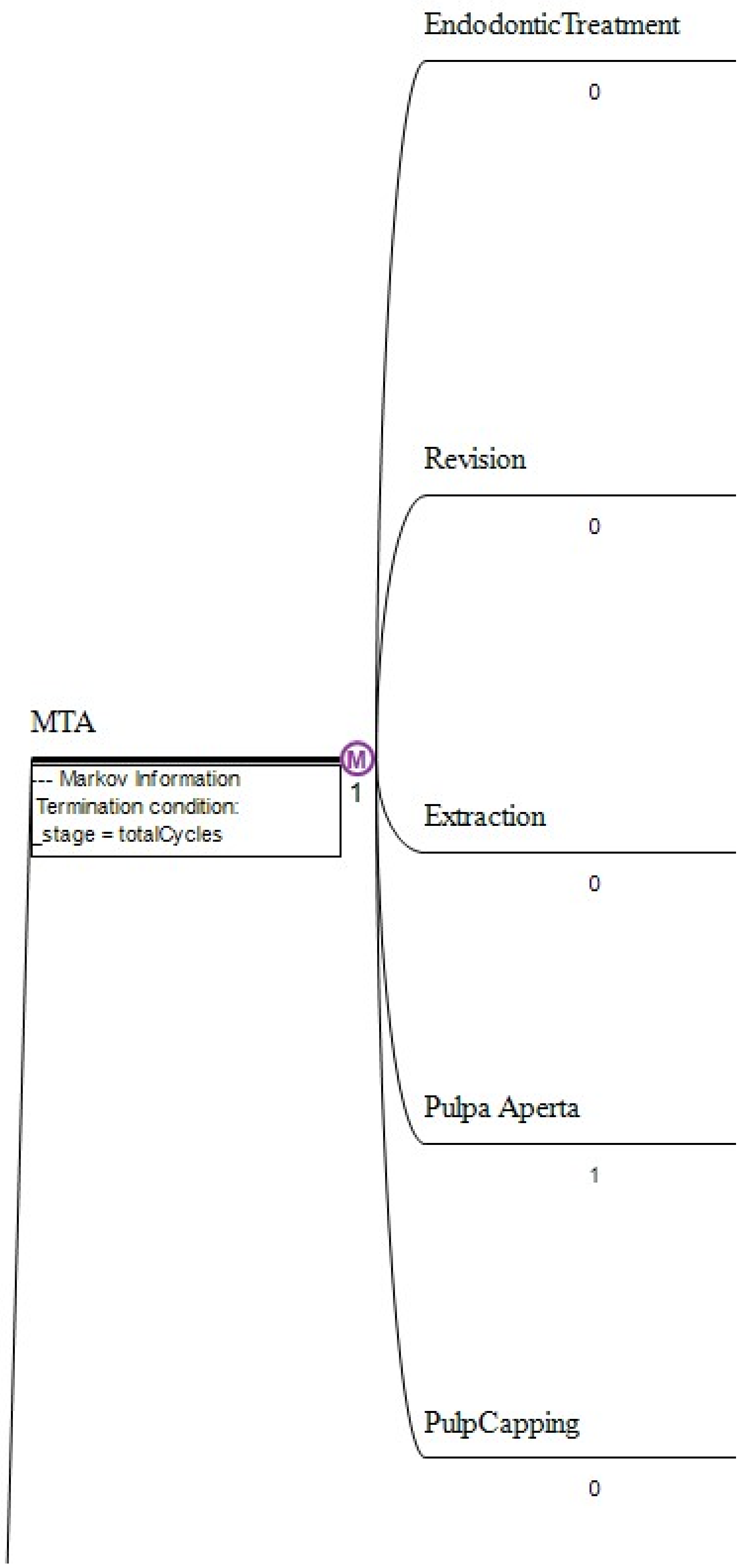
Attribute	Statistic	MTA	Immediate RCT	CaOH
Cost				
	Mean	404.72	742.11	514.16
	Std Deviation	9.61	18.62	10.66
	Minimum	375.82	696.34	482.00
	2.5%	386.13	711.01	493.64
	10%	392.05	719.17	500.39
	Median	404.77	740.28	514.02
	90%	417.27	768.46	528.15
	97.5%	423.25	780.87	535.23
	Maximum	438.63	801.25	549.88
	Sum	4,047,184.84	7,421,121.45	5,141,583.61
	Size (n)	10,000.00	10,000.00	10,000.00
	Variance	92.29	346.76	113.66
	Variance/Size	0.01	0.03	0.01
	SQRT[Variance/Size]	0.10	0.19	0.11
Eff				
	Mean	10.43	9.68	10.25
	Std Deviation	0.25	0.18	0.52
	Minimum	9.72	9.13	8.80
	2.5%	9.94	9.33	9.22
	10%	10.09	9.44	9.55
	Median	10.43	9.68	10.26
	90%	10.76	9.93	10.95
	97.5%	10.90	10.03	11.24
	Maximum	11.14	10.21	11.64
	Sum	104,280.53	96,838.30	102,522.11
	Size (n)	10,000.00	10,000.00	10,000.00
	Variance	0.06	0.03	0.27
	Variance/Size	0.00	0.00	0.00
	SQRT[Variance/Size]	0.00	0.00	0.01

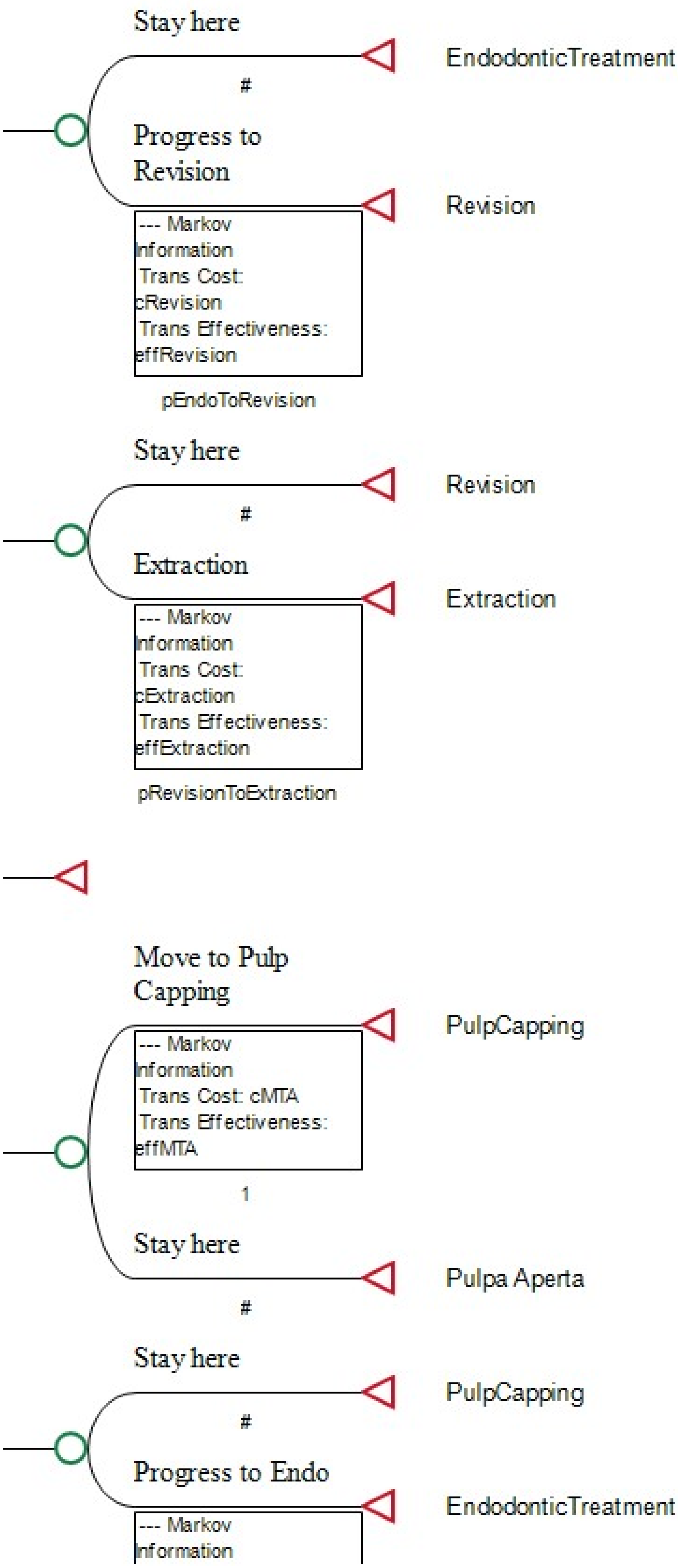
8.2 Cost & Effectiveness Variance Analysis for Avulsed Tooth Treatment Options (0-20 min dry time)

Monte Carlo Simulation C-E Statistics

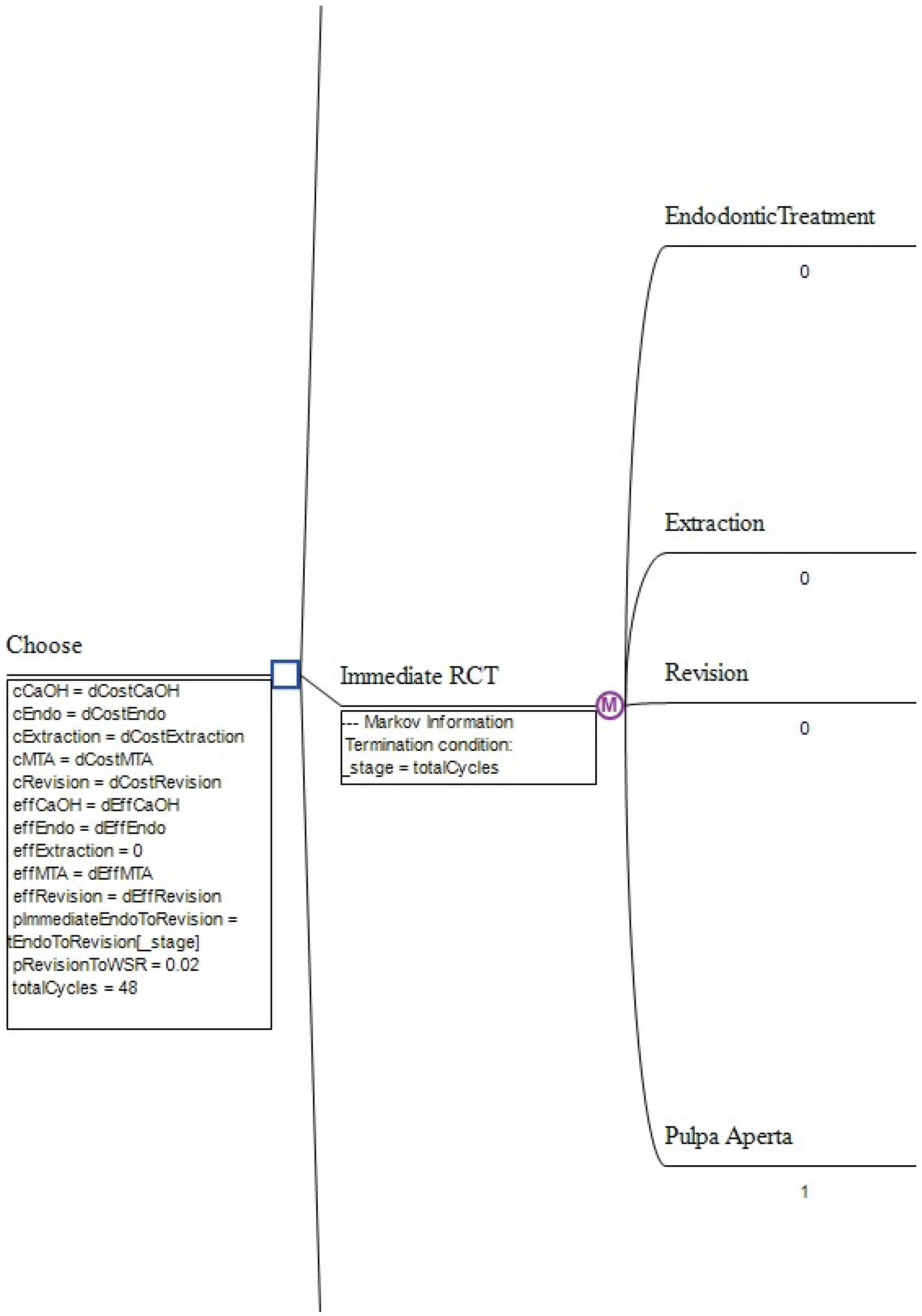
Attribute	Statistic	Re-Plantation and Follow-up Treatment	NoTreatment (Zero Case)	Immediate Implant	Immediate Adhesive Bridge
Cost					
	Mean	792.49	0.00	1,807.21	1,311.18
	Std Deviation	23.78	0.00	73.50	54.19
	Minimum	720.86	0.00	1,628.01	1,180.88
	2.5%	746.59	0.00	1,666.08	1,208.29
	10%	761.60	0.00	1,707.53	1,238.17
	Median	792.64	0.00	1,807.71	1,310.98
	90%	823.47	0.00	1,905.93	1,385.16
	97.5%	838.35	0.00	1,947.19	1,413.10
	Maximum	860.81	0.00	1,986.45	1,440.51
	Sum	7,924,901.84	0.00	18,072,120.75	13,111,849.55
	Size (n)	10,000.00	10,000.00	10,000.00	10,000.00
	Variance	565.48	0.00	5,402.48	2,936.56
	Variance/Size	0.06	0.00	0.54	0.29
	SQRT[Variance/Size]	0.24	0.00	0.74	0.54
Eff					
	Mean	82.27	0.00	95.53	94.99
	Std Deviation	4.76	0.00	1.37	1.17
	Minimum	70.32	0.00	91.83	92.19
	2.5%	73.19	0.00	92.65	92.76
	10%	75.81	0.00	93.53	93.40
	Median	82.28	0.00	95.72	94.99
	90%	88.73	0.00	97.20	96.58
	97.5%	91.28	0.00	97.75	97.20
	Maximum	94.12	0.00	98.26	97.84
	Sum	822,700.61	0.00	955,321.19	949,893.32
	Size (n)	10,000.00	10,000.00	10,000.00	10,000.00
	Variance	22.66	0.00	1.88	1.37
	Variance/Size	0.00	0.00	0.00	0.00
	SQRT[Variance/Size]	0.05	0.00	0.01	0.01

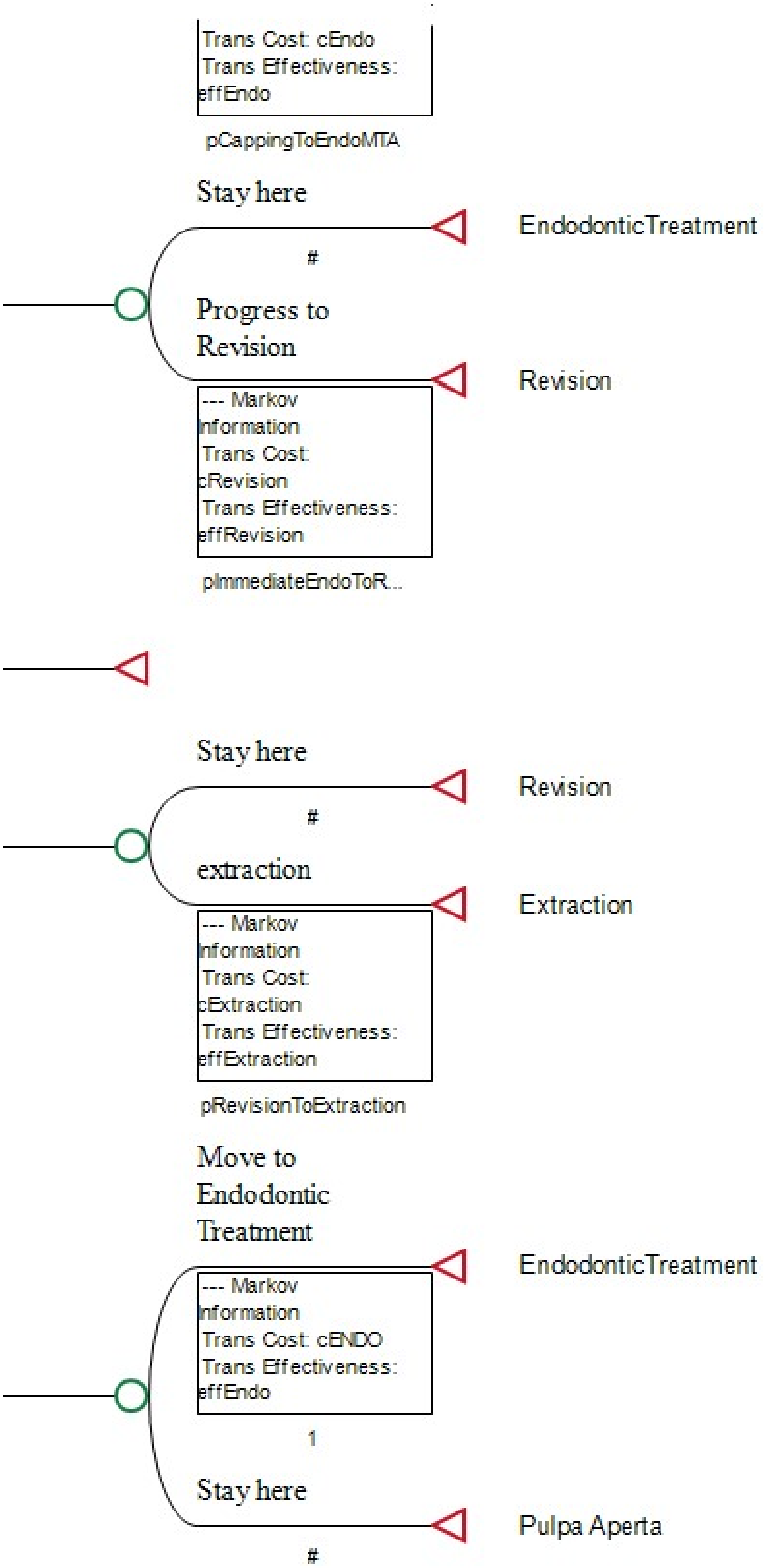
8.3 Detailed Markov Transition State Model – MTA vs. CaOH

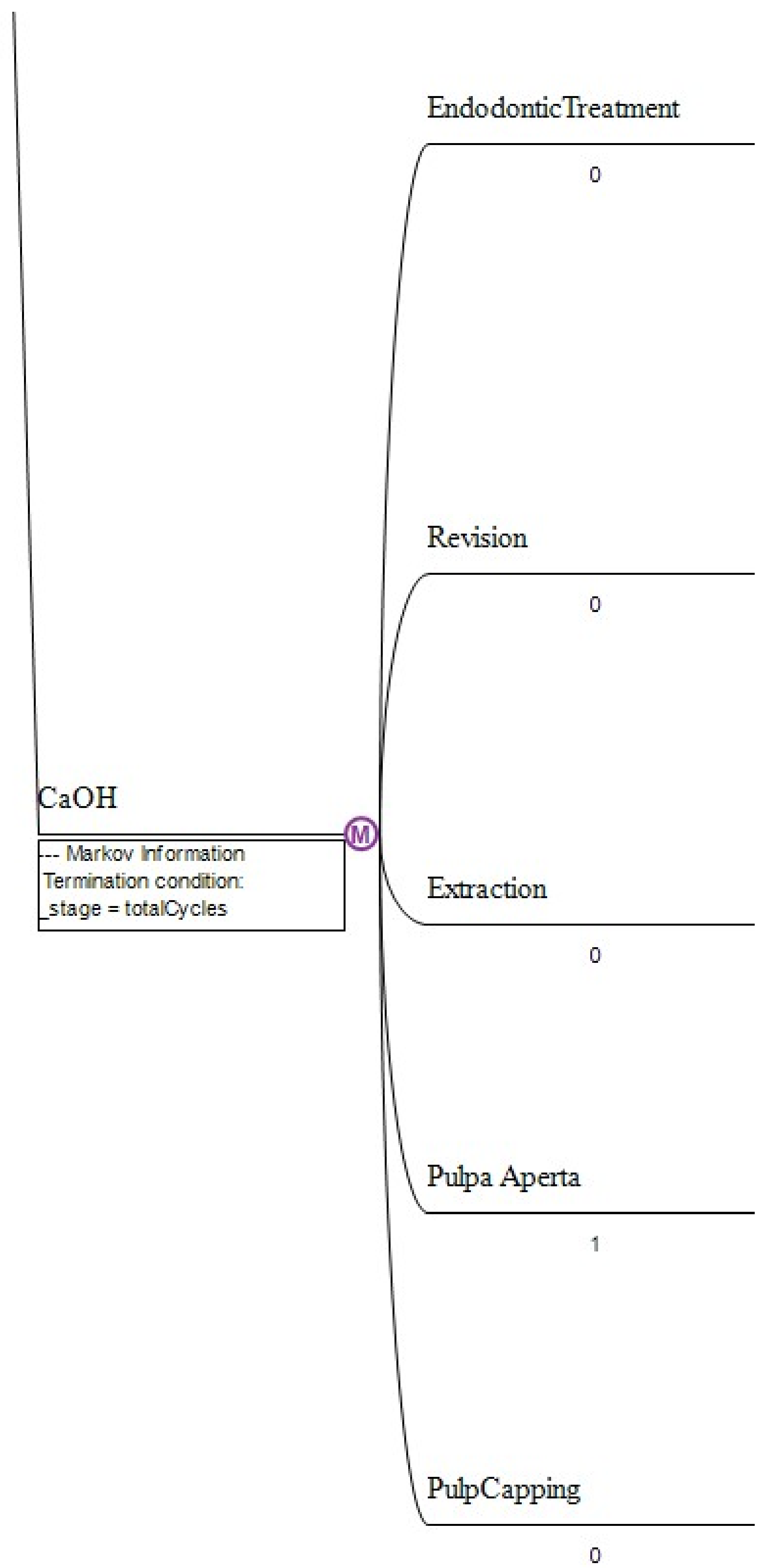


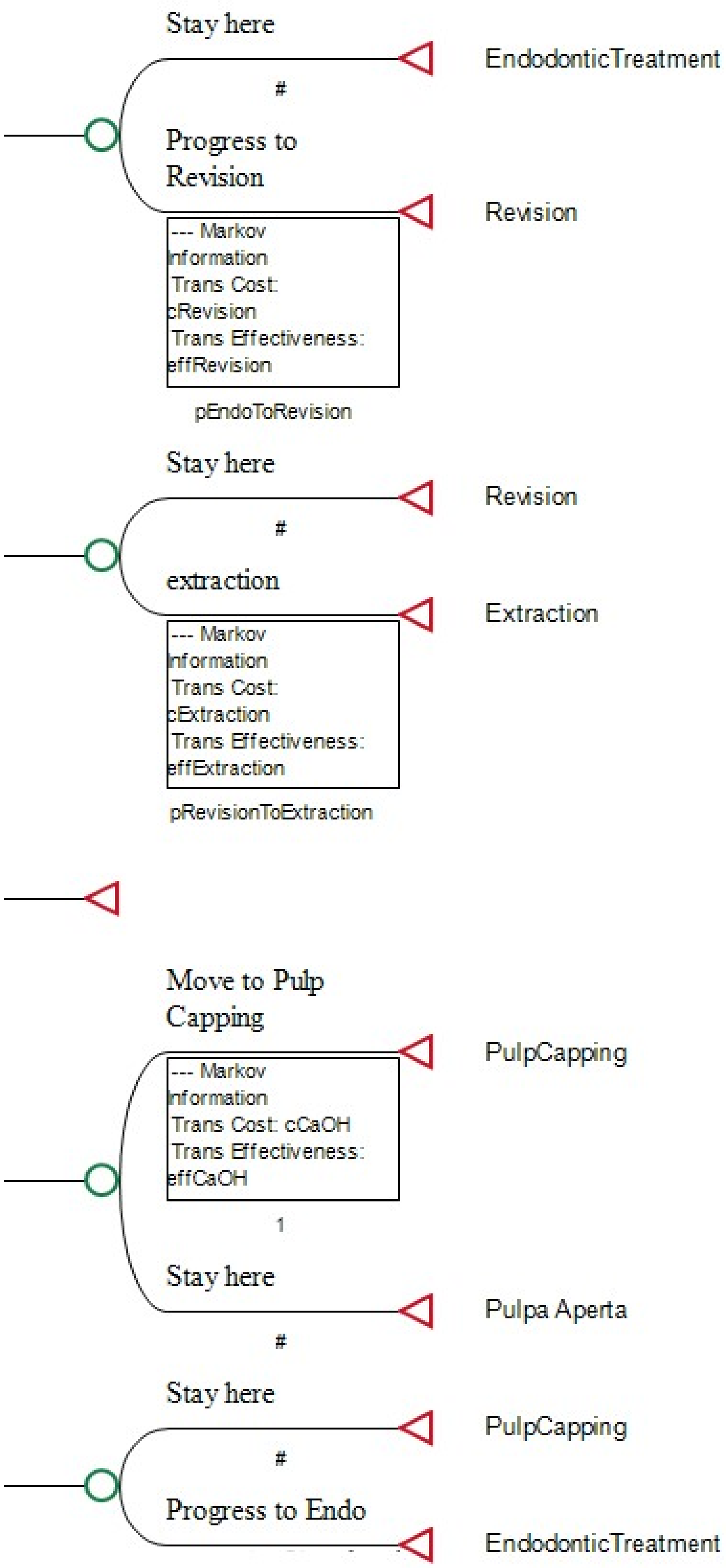


Stay here
EndodonticTreatment
#
Progress to Revision
Revision
--- Markov information
Trans Cost: cRevision
Trans Effectiveness: effRevision
pEndoToRevision
Stay here
Revision
#
Extraction
Extraction
--- Markov information
Trans Cost: cExtraction
Trans Effectiveness: effExtraction
pRevisionToExtraction
Move to Pulp Capping
PulpCapping
--- Markov information
Trans Cost: cMTA
Trans Effectiveness: effMTA
1
Stay here
Pulpa Aperta
#
Stay here
PulpCapping
#
Progress to Endo
EndodonticTreatment
--- Markov information

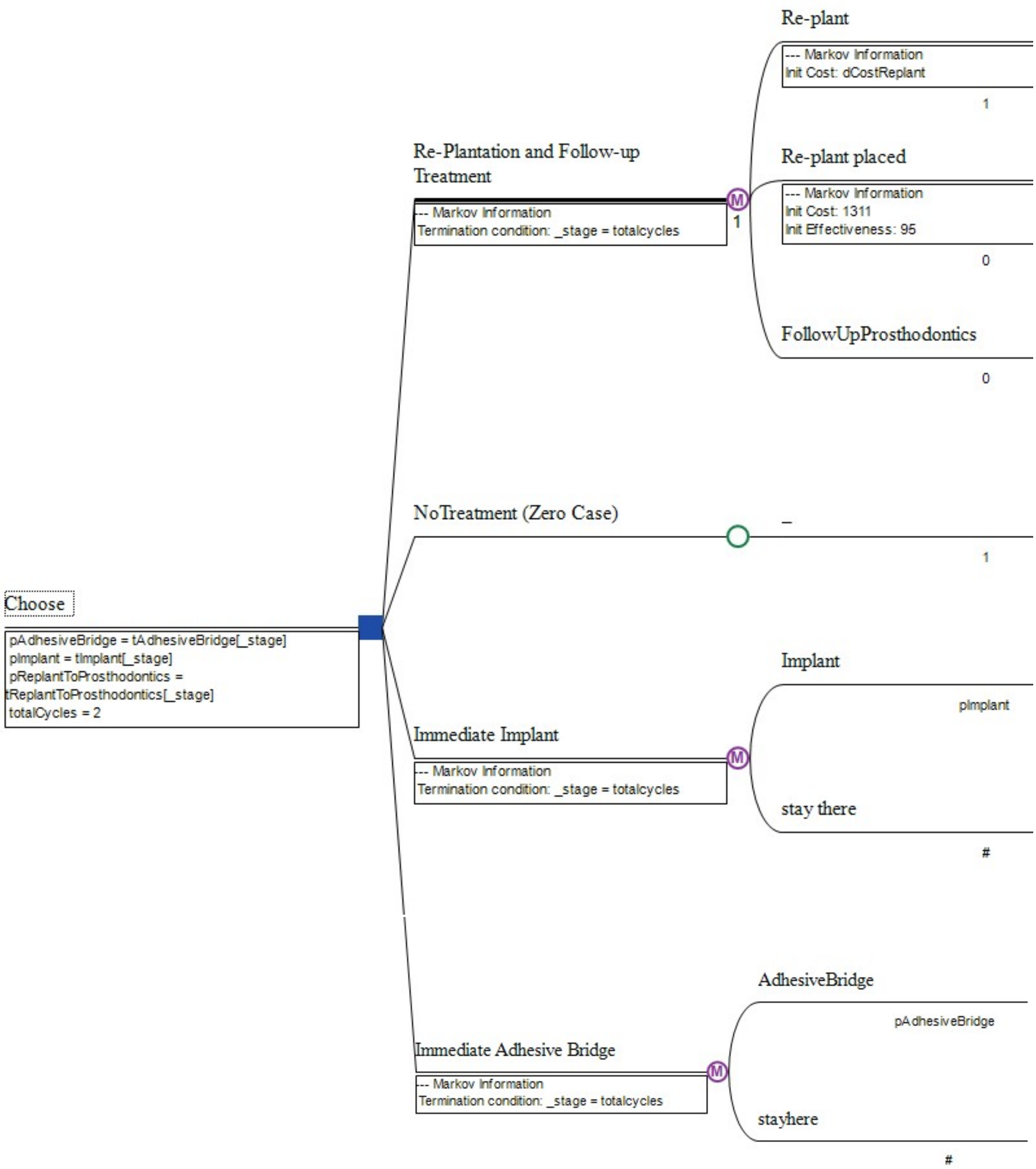

EndodonticTreatment
0
Extraction
0
Choose
cCaOH = dCostCaOH
cEndo = dCostEndo
cExtraction = dCostExtraction
cMTA = dCostMTA
cRevision = dCostRevision
effCaOH = dEffCaOH
effEndo = dEffEndo
effExtraction = 0
effMTA = dEffMTA
effRevision = dEffRevision
pImmediateEndoToRevision =
tEndoToRevision[_stage]
pRevisionToWSR = 0.02
totalCycles = 48
Immediate RCT
--- Markov Information
Termination condition:
_stage = totalCycles
Revision
0
Pulpa Aperta
1

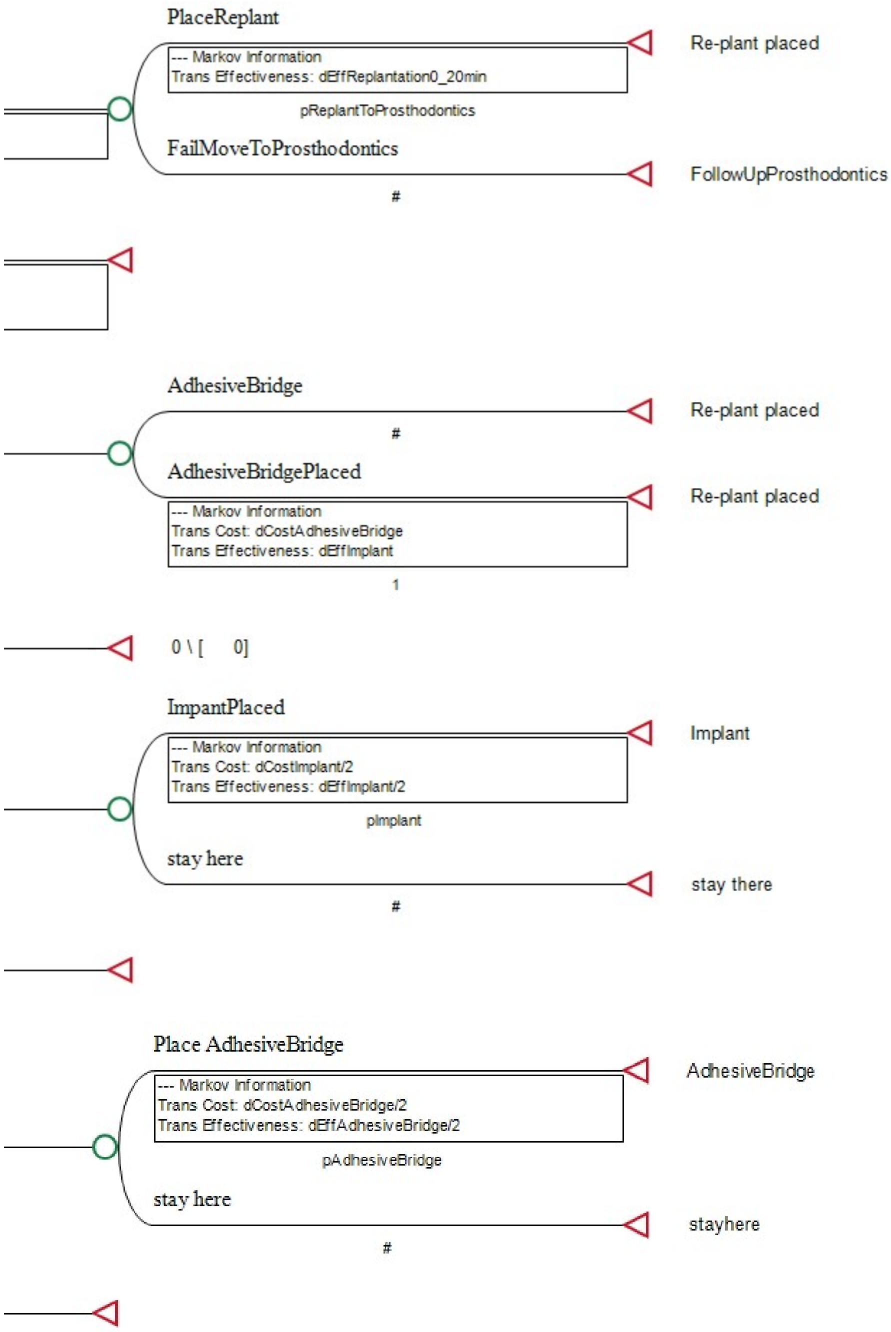

Trans Cost: cEndo
Trans Effectiveness: effEndo
pCappingToEndoMTA
Stay here
EndodonticTreatment
#
Progress to Revision
Revision
--- Markov Information
Trans Cost: cRevision
Trans Effectiveness: effRevision
pImmediateEndoToR...
Stay here
Revision
#
extraction
Extraction
--- Markov Information
Trans Cost: cExtraction
Trans Effectiveness: effExtraction
pRevisionToExtraction
Move to Endodontic Treatment
EndodonticTreatment
--- Markov Information
Trans Cost: cENDO
Trans Effectiveness: effEndo
1
Stay here
Pulpa Aperta
#


EndodonticTreatment
0
Revision
0
CaOH
--- Markov Information
Termination condition:
_stage = totalCycles
Extraction
0
Pulpa Aperta
1
PulpCapping
0


Stay here
EndodonticTreatment
#
Progress to Revision
Revision
--- Markov information
Trans Cost: cRevision
Trans Effectiveness: effRevision
pEndoToRevision
Stay here
Revision
#
extraction
Extraction
--- Markov information
Trans Cost: cExtraction
Trans Effectiveness: effExtraction
pRevisionToExtraction
Move to Pulp Capping
PulpCapping
--- Markov information
Trans Cost: cCaOH
Trans Effectiveness: effCaOH
1
Stay here
Pulpa Aperta
#
Stay here
PulpCapping
#
Progress to Endo
EndodonticTreatment

8.4 Detailed Markov Transition State Model – Avulsed Tooth





PlaceReplant
--- Markov Information
Trans Effectiveness: dEffReplantation0_20min
pReplantToProsthodontics
FailMoveToProsthodontics
#
Re-plant placed
FollowUpProsthodontics
AdhesiveBridge
#
AdhesiveBridgePlaced
--- Markov Information
Trans Cost: dCostAdhesiveBridge
Trans Effectiveness: dEffImplant
1
Re-plant placed
Re-plant placed
0 \ [0]
ImpantPlaced
--- Markov Information
Trans Cost: dCostImplant/2
Trans Effectiveness: dEffImplant/2
pImplant
stay here
#
Implant
stay there
Place AdhesiveBridge
--- Markov Information
Trans Cost: dCostAdhesiveBridge/2
Trans Effectiveness: dEffAdhesiveBridge/2
pAdhesiveBridge
stay here
#
AdhesiveBridge
stayhere

8.5 Cost & Effectiveness Variance Analysis for Avulsed Tooth Treatment Options

Attribute	Statistic	Re-Plantation and Follow-up Treatment	NoTreatment (Zero Case)	Immediate Implant	Immediate Adhesive Bridge
Cost					
	Mean	792.49	0.00	1,807.21	1,311.18
	Std Deviation	23.78	0.00	73.50	54.19
	Minimum	720.86	0.00	1,628.01	1,180.88
	2.5%	746.59	0.00	1,666.08	1,208.29
	10%	761.60	0.00	1,707.53	1,238.17
	Median	792.64	0.00	1,807.71	1,310.98
	90%	823.47	0.00	1,905.93	1,385.16
	97.5%	838.35	0.00	1,947.19	1,413.10
	Maximum	860.81	0.00	1,986.45	1,440.51
	Sum	7,924,901.84	0.00	18,072,120.75	13,111,849.55
	Size (n)	10,000.00	10,000.00	10,000.00	10,000.00
	Variance	565.48	0.00	5,402.48	2,936.56
	Variance/Size	0.06	0.00	0.54	0.29
	SQRT[Variance/Size]	0.24	0.00	0.74	0.54
Eff					
	Mean	82.27	0.00	95.53	94.99
	Std Deviation	4.76	0.00	1.37	1.17
	Minimum	70.32	0.00	91.83	92.19
	2.5%	73.19	0.00	92.65	92.76
	10%	75.81	0.00	93.53	93.40
	Median	82.28	0.00	95.72	94.99
	90%	88.73	0.00	97.20	96.58
	97.5%	91.28	0.00	97.75	97.20
	Maximum	94.12	0.00	98.26	97.84
	Sum	822,700.61	0.00	955,321.19	949,893.32
	Size (n)	10,000.00	10,000.00	10,000.00	10,000.00
	Variance	22.66	0.00	1.88	1.37
	Variance/Size	0.00	0.00	0.00	0.00
	SQRT[Variance/Size]	0.05	0.00	0.01	0.01

9 Summary (German)

Heutzutage stehen bei der Entscheidungsfindung bezüglich **Therapien** bei **Erkrankungen der Zähne** und des **Zahnhalteapparats** eine **Vielzahl** von **Behandlungs-Alternativen** zur Verfügung. Zumeist unterscheiden sich diese nicht nur in der **klinischen Wirksamkeit,** sondern auch hinsichtlich der **Kosten**. Im deutschen Gesundheitssystem sind viele zahnärztliche Leistungen **mit Zusatzkosten für die Patienten verbunden** - insbesondere im Fachbereich der **Endodontie**. Hieraus resultiert die Anforderung, dass im **klinischen Alltag** der **Mehrwert der angebotenen Leistungen durch den Zahnarzt transparent kommuniziert wird**. Ebenso gewinnen **personalisierte Mundgesundheits-Strategien** an Bedeutung, weshalb die Entscheidungsfindung zunehmend **unter Berücksichtigung der individuellen Budget-Restriktionen der Patienten** stattfindet. Diesen Anforderungen gerecht zu werden stellt bei der **aktuellen Evidenz-Situation** eine **Herausforderung** im **klinischen Alltag** dar.

Ziel dieser Arbeit war es, gesundheitsökonomische **Entscheidungs-Modelle** herzuleiten, um die **kosten-wirksamsten Therapie-Alternativen** in verschiedenen **klinisch relevanten Entscheidungsszenarien** in der **Endodontie zu identifizieren.** Die Szenarien waren:

1. Analyse von Therapie-Alternativen bei schmerzempfindlicher **Reizung der Pulpa** (**Dentin-Überempfindlichkeit**)
2. Analyse von Therapie-Alternativen bei direkter **Pulpa-Überkappung** mit MTA vs. Calcium-Hydroxid bei **Pulpa Aperta**
3. **Zeit-Szenario-Analyse** von Therapiealternativen im Falle eines **avulsierten Zahnes** (**Pulpales Trauma**)

Einen geeigneten **methodischen Untersuchungsrahmen** stellte die **gesundheitsökonomische Evaluation** (**Kosten-Wirksamkeit-Analysen**) ausgehend von **Entscheidungsbaumanalysen** und **in Verbindung mit Markov-Chain-Monte-Carlo-Simulationen** dar. Die **Identifikation der kosten-wirksamsten Alternativen** erfolgte durch Modellierung der klinischen Entscheidungssituation auf Basis von 1) der aktuell verfügbaren **Evidenz von klinischer Wirksamkeit** und 2) der aktuell verfügbaren **Kosten** innerhalb des **Kontexts des deutschen Gesundheitssystems**.

Unter Berücksichtigung der Grenzen der Entscheidungsmodelle **konnten folgende Ergebnisse erzielt** werden:

1. Der Vergleich der Kosten-Wirksamkeit von Physische Okklusion, Chemische Okklusion, Nerv-Desensibilisierung, Laser und Placebo zeigte, dass die **Physische Okklusion** die kosten-wirksamste Alternative bei der Behandlung der **Dentin-Hypersensibilität** ist. Der **ICER** von **Physische Okklusion** stellte sich (gegenüber Placebo) mit **7,76 EUR** für die Reduktion von **1,0 Einheiten auf der SMD Schmerz-Skala** dar. Sowohl Chemische Okklusion als auch Nerv-Desensibilisierung wurden **dominiert**. Der **ICER** von **Laser** stellte sich (gegenüber physischer Okklusion) mit **6,4 EUR** für die Reduktion von **0,1 Einheiten auf der SMD Schmerz-Skala** als kostenintensive Alternative dar.
2. Der Vergleich der Kosten-Wirksamkeit zeigte, dass die **direkte Überkappung mit MTA** bei **Pulpa Aperta** die kosten-wirksamste Behandlungsalternative in einem langfristigen Transition-State Modell ist. Die Alternativen **Überkappung mit CaOH** sowie **Wurzelkanalbehandlung** wurden **dominiert**. Der **ICER** von **MTA** stellte sich (gegenüber No-Treatment) mit Durchschnitts-Kosten von **403 EUR für 10,3 Jahre Zahn-Überleben** dar. Bei einem zu erwartenden Zahn-Überleben von **unter 6 Jahren** sollte aus gesundheitsökonomischer Sicht die Behandlung mit **CaOH** bevorzugt werden.
3. Der Vergleich der Kosten-Wirksamkeit zeigte, dass die **Re-plantation** eines Zahnes die Kosten-wirksamste Behandlungsalternative darstellt, wenn der avulsierte Zahn einer extraoralen **Trockenzeit von 0-20 Minuten** ausgesetzt wurde. Der **ICER** von **Re-plantation** stellte sich (gegenüber No-Treatment) mit Durchschnitts-Kosten von **792,60 EUR** für **8,3 Jahre Zahn-Überleben** dar. Die **Adhäsiv-Brücke** und **Implantat-getragene Krone** wurden **nicht dominiert**, stellten aber **kostenintensivere Alternativen** dar.

Es wurde somit aufgezeigt, dass auf der Basis der aktuell verfügbaren Kosteninformation und klinischen Evidenz **robuste Modelle zur Entscheidungsfindung** im **Fachbereich Endodontie** der Zahnheilkunde erstellt werden konnten. Inwieweit die Ergebnisse dazu geeignet sind, eine **Implementierung in den klinischen Behandlungsalltag zu ermöglichen, ist weiterhin zu klären**. Hierzu werden zusätzliche Evidenz aus makro-ökonomischen Modellen und Public Health Studien sowie weitere klinische Studien für die Endodontologie benötigt.

10 Summary (English)

When decisions are made for the treatment of **dental diseases**, different **treatment options** are available, which in most cases do not only **differ** in regard to **clinical effectiveness**, but also in regard to **cost**. Within the **context of the German health care system**, many treatment options require **co-pay from patients** – especially in the field of **endodontics**. Therefore, **benefits of recommended treatments** need to be **transparently communicated** by dentists to patients in **everyday clinical practice**. Furthermore, **personalized oral health care strategies** significantly gain importance, for which highly **individual budget restrictions** of patients need to be **taken into account when treatment decisions are made**. **Meeting these requirements** is **challenging** for clinical decisions makers with currently only **limited evidence available**.

Goal of the dissertation was to develop different **health economics decisions models** for the identification of **most cost-effective therapeutic alternatives** for relevant and clinically meaningful scenarios in **endodontics**, which were:

1. Analysis of therapeutic alternatives for the treatment of **painful irritation of the pulp** (**dentin hypersensitivity**)
2. Analysis of therapeutic alternatives for the treatment of an **open pulp** (MTA vs. CaOH - **direct pulp capping**)
3. Time-Scenario-Analysis of therapeutic alternatives for the treatment of an **avulsed tooth** (**pulpal trauma**)

A methodical framework that was used for conducting economic evaluations of the given scenarios was **Cost-Effectiveness-Analysis**. Scenarios were embedded through **decision tree analyses** in combination with **Markov Models** and **Monte-Carlo Simulations**. Models were detailed with 1) currently available **clinical evidence** for the **effectiveness** of treatments of teeth and the periodontal system in case of pulpal disease treatment, and 2) available **cost** information within the context of the public and private **German health care system.**

Within the given limitations of this dissertation, the results can be summed up as follows:

1. The Cost-effectiveness analysis compared **physical occlusion**, **chemical occlusion**, **nerve desensitization**, **laser** and **placebo** for the treatment of **dentin**

hypersensitivity. **Physical occlusion** was considered **most cost-effective** with an **ICER** of **7.76 EUR for the reduction of 1.0 units on the SMD pain scale** (compared with placebo). Both, **chemical occlusion** and **nerve desensitization,** were **dominated**. The **ICER** of **laser** was considered cost-intensive with **6.4 EUR for the additional reduction of 0.1 units on the SMD pain scale** (compared with physical occlusion).

2. The Cost-effectiveness analysis showed that **MTA direct pulp capping** treatment has the **highest likelihood of being cost-effective** within the limitations of the state transition model that was created to assess the long-term (48.55 years) effects of treatment alternatives **in an open pulp situation**. The **ICER** of **MTA** pulp capping was **403 EUR for 10.3 additional tooth life years** (compared with no treatment). Both alternatives, **CaOH direct pulp capping and Immediate RCT**, were **dominated**. In situations, where **expected tooth life** is **less than 6 years** due to other reasons besides the open pulp, **CaOH direct pulp capping** should be **preferred**.

3. The Cost-effectiveness analysis showed that in an **avulsed tooth scenario replantation** has the **highest likelihood of being cost-effective when dry time of the avulsed tooth is limited to 0-20 minutes**. The **ICER** of re-plantation (compared with no treatment) was **792.60 EUR** for **8.3 additional tooth life years**. Both **alternatives**, **adhesive bridge** and **implant-supported crown**, were **not dominated**, but were more **cost-intensive**.

It was shown that **robust economic models could be built based on currently available clinical evidence** and **cost information** in the field of **pulpal disease management**. However, the **results** of this dissertation **might be limited**. **Further research is needed** for the assessment to which extent the results of this dissertation can be translated into everyday clinical practice. Therefore, **additional evidence from macro-economic health models, public health studies and additional endodontic clinical evidence is required** for further assessment of the models.

11 Curriculum Vitae

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PERSONAL INFORMATION

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1999 — 2000 Community Service Pestalozzischule für geistig behinderte Kinder

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12 Eidesstattliche Versicherung

Bei der eingereichten Dissertation zu dem Thema

Economic Decision Modeling in Dental Care: Towards Making Better Use of Resources in the Context of Pulpal Disease Management

handelt es sich um meine eigenständig erbrachte Leistung.

2. Ich habe nur die angegebenen Quellen und Hilfsmittel benutzt und mich keiner unzulässigen Hilfe Dritter bedient. Insbesondere habe ich wörtlich oder sinngemäß aus anderen Werken übernommene Inhalte als solche kenntlich gemacht.

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Ort und Datum Unterschrift

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