Innovating pharmaceutical business models with value-based healthcare

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Master thesis

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Innovation management

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Preface

This has been a challenging undertaking. I would like to sincerely thank my academic supervisors, my family, friends and everyone at Sanofi for their continuous dedication, efforts and patience.

Management summary

In this thesis, it has been studied how the concept of value-based healthcare can be used to innovate the business models of pharmaceutical companies. In modern countries like the Netherlands, where high quality healthcare is considered a given, steadily increasing costs are threatening the sustainability of the healthcare system. In a reaction, a movement known as value-based healthcare (Porter & Teisberg, 2006) is rapidly being adopted by healthcare providers and payers in the Netherlands (Economist Intelligence Unit, 2016). The overarching goal of value-based healthcare is to maximize the health outcomes achieved per monetary unit spent on healthcare. Only those care providers, medical technology suppliers and pharmaceutical companies that excel in creating and delivering patient value will prosper in a new, value-based healthcare landscape (Porter & Teisberg, 2006).

While healthcare costs are rising, suppliers of pharmaceutical products are experiencing the expiration of their current business models. The dominant pharmaceutical business model, known as the block-buster model, is slowly but steadily losing its profitability due to changes in the market and pressures from the external environment (Ding et al., 2013; Capo et al., 2014). Pharmaceutical companies are realizing that their business models might not be effectively creating, delivering and capturing value for all relevant stakeholders in the healthcare system. These business models must be innovated for the company to reman successful (Kaitin & DiMasi; 2011).

Companies can innovate their business models by seizing new opportunities in their environment (Amit & Zott, 2012; Christensen et al., 2016). Value-based healthcare might provide a solid opportunity for pharmaceutical companies to innovate their business models with. However, innovating the business model with value-based healthcare is difficult, especially for suppliers. The topic is still much debated and predominantly explored from the perspective of direct care providers. There is little guidance for pharmaceutical suppliers that wish to engage in value-based healthcare. To address this gap, this thesis aims to answer the following central research question:

"How can value-based healthcare be used to innovate pharmaceutical business models?"

The question is addressed with a case study on Sanofi's Lemtrada® product, an innovative pharmaceutical treatment for relapsing-remitting multiple sclerosis. It is suspected that Sanofi does not have an effective business model to capture value from innovative pharmaceutical products like Lemtrada®. The objective is to develop a decision-support approach for effective pharmaceutical business model innovation based on value-based healthcare. This approach is made of two separate, but complementary, components. The first component is a framework of analysis that integrates value-based healthcare in business model theory. The second component is a tool that suggest business model innovations that are rooted in value-based healthcare, based on that analysis.

First, literature reviews were performed on the topics of business models, business model innovation and value-based healthcare. Theory by Osterwalder (2004, 2010), Porter & Teisberg (2006) and Yang et al. (2017) were combined into in new framework for value-based business model innovation. This framework can be used to analyze current business models and for the development of business model innovations rooted in value-based healthcare. To apply this framework, two separate inputs are required: issues in the current BM of Lemtrada® and the value of Lemtrada®.

To obtain the first input, interviews were held with Sanofi employees that perform commercial functions for the multiple sclerosis franchise. Results were analyzed and condensed in order to draw conclusions on the interview data and to provide the first input for the framework. To obtain the second output, outcome data and cost estimates from a large-scale clinical study on Lemtrada® were analyzed. It was concluded that value cannot directly be extracted from such data but must first be operationalized.

To facilitate operationalization of value and provide business model innovations suggestions for decision-support, the second component of the approach was developed. The design specifications and application of a morphology matrix led to the development of the 'Sanofi Digital VBHC Tool'. With this tool, the clinical trial data could be reassessed to provide the second input for the framework. The framework could then be applied to the Lemtrada case®.

With the framework, six problematic areas were identified in Lemtrada's® BM that inhibit value capture. The Sanofi Digital VBHC Tool was consulted to provide suggestions for value-based business model innovations to combat these problem areas. Six business model innovations rooted in value-based healthcare were selected, one to combat each problem identified in the framework.

While the suggested business model innovations have not yet been implemented in practice, this research demonstrates that the newly developed approach for pharmaceutical business model innovation based on value-based healthcare can successfully be applied to a research case. Once companies have obtained insight in their product's BM and patient value, they can start searching the BM for wasted value capture and the tool to obtain a proposed set of business model innovations.

A new approach has been developed that consists of a value-based framework of analysis for pharmaceutical BMs and a tool that can operationalize patient value and suggest business model innovations. With this approach, pharmaceutical companies can use the concept of value-based healthcare to drive business model innovation that leads to more effective value creation, delivery and capture for all stakeholders involved in the healthcare system.

Contents

1. Introduction

1.1 A changing healthcare system

A steady flow of discoveries and innovations ever expands the landscape of options and potential solutions for combatting health predicaments. At the same time, these developments of the last decades made the public healthcare system increasingly complex, fragmented and too expensive. Developed OECD countries, with the Netherlands being no exception, are being put under severe pressure by these developments (Parkinson et al., 2015). Serious change is essential to the sustainability of modern healthcare systems.

This reforming change is most often envisioned in the form of value-based health care (VBHC), a movement ignited by business academics Michael Porter and Elizabeth Teisberg (2006). Even though interpretations and implementations differ amongst scholars and practitioners, the main premise is simple: high value for patients must become the overarching goal of health care delivery, with value defined as the health outcomes achieved per dollar spent (Porter, 2010). Or, more directly put, patient-relevant medical outcomes divided by cost (Value-Based Health Care Centre, n.d.).

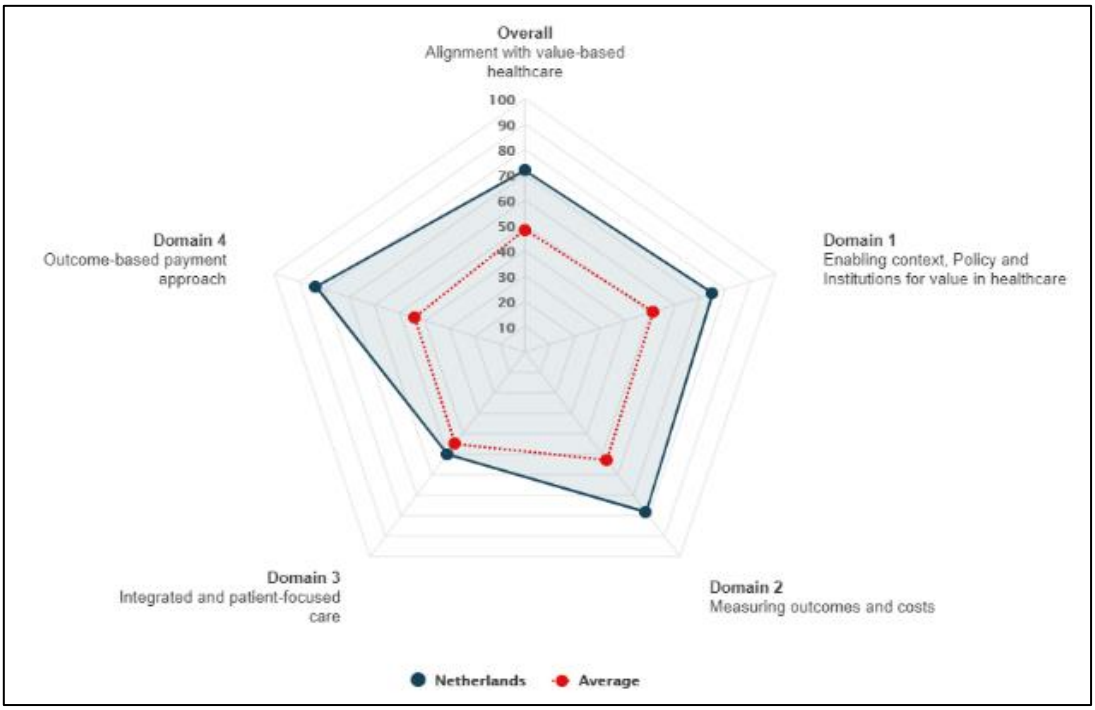

Figure 1. VBHC alignment evaluation results summarized in a radar graph (EIU, 2016).

In the Netherlands, VBHC is on its way to becoming an integrated part of healthcare. According to Porter himself, the Netherlands is a true frontrunner in VBHC implementation (VBHC Prize, 2015). The Ministry of Health, Welfare and Sport is already running tests and trials surrounding VBHC (Schippers & Van Rijn, 2017). The same holds for hospitals and medical technology suppliers. (VIG, n.d.). The Santeon hospital group, a true pioneer in VBHC, has already reported on its first successful implementations (Boston Consulting Group, 2018). A large-scale research initiative by the Economist Intelligence Unit (2016) measured and compared the alignment of VBHC components in 25 countries. The overview in figure 1 shows that the Netherlands (blue line) is positioned well above average (red line). There is an unambiguous commitment to progress value-based healthcare in the Dutch healthcare system. For pharmaceutical companies in the Netherlands, this can either be considered as a threat or an opportunity.

1.2 Value: the common denominator

A successful shift towards VBHC requires the involvement of all primary elements of the healthcare system, including suppliers (Porter & Teisberg, 2006). Policy makers, healthcare providers and health insurance companies in the Netherlands have already set the pace for the shift towards VBHC. These moving trends are real and material, and the pharmaceutical industry will have to keep up (Larsson et al., 2012).

Engaging in VBHC, however, is challenging for suppliers in healthcare, as it could destabilize prevailing business models (Tessadro, 2019). A business model (BM) describes the rationale of how an organization creates, delivers, and captures value (Osterwalder & Pigneur, 2010). The past fifty years, the prolific BM in the pharmaceutical industry was built upon the discovery of drugs that are likely to reach global sales of more than $1 billion (Ding, Eliashberg & Stremersch, 2013). This model is known as the 'blockbuster model'. Today, the blockbuster model that guaranteed high profitability for many years is under threat (Ding et al., 2013; Capo et al., 2014; Dierks et al., 2016). The R&D engine that has powered earlier success is showing signs of fatigue: costs are skyrocketing, breakthrough innovation is ebbing, competition is intense, and sales growth is flattening (Munos, 2010; Dierks et al., 2016).

With lesser technologies reaching the market, the legitimate concern arises that the total revenues earned are no longer adequate to sustain the industry's ability to innovate in this time of rising costs in R&D. Yet instead of blaming lower R&D productivity, one can conclude that the problem rather lies with an extant business model that is not well calibrated to today's market (Kaitin & DiMasi, 2011).

In response to these detrimental developments, pharmaceutical companies are innovating their BMs. Business model innovation (BMI) in the pharmaceutical industry currently occurs in the form of network strategies, large-scale mergers and acquisitions, outsourcing of production and R&D, and last but not least, more patient-centric strategies for therapy launch and therapy promotion (Ding et al., 2013). An industry that has always been focused on products, must now become patient-focused.

VBHC could function as the leading foundation for value-driven and patient-oriented BMI. Especially in the Netherlands, where VBHC is quickly developing into an integral part of the healthcare system. This requires pharmaceutical companies to shift their focus from research and development towards market access and commercialization (Figure 2).

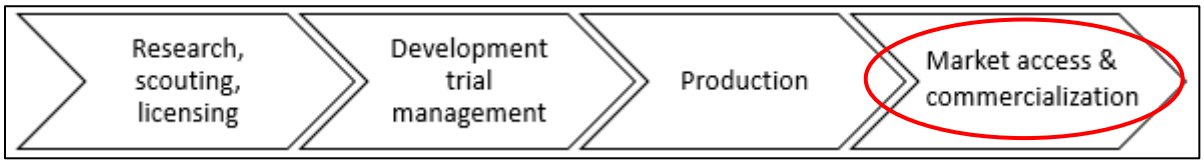

Figure 2: The renewed pharmaceutical value chain (Capot et al., 2014).

The future of brand drugs depends on the capability of the pharmaceutical industry to go 'beyond the pill' and facing the new value-driven landscape by adopting tailor-made disease management solutions (Dierks et al., 2016). Pharmaceutical companies that wish to remain successful must focus on demonstrating the value of the newly developed product to healthcare payers and providers (EIU, 2012; Stegemann et al., 2014).

2. Problem statement and research questions

In order to properly grasp the intricacies of the research case and the relevance of VBHC, a case description is presented in appendix A.

2.1 Problem statement

Sanofi Genzyme's relapsing-remitting multiple sclerosis (RRMS) treatment Lemtrada® presents high efficacy, quality of life and for some patients even improvement in functionality (please refer to appendix A). Its non-chronic treatment structure means that significant cost savings can be achieved. It is a remarkable technology due to its ability to grant a patient a life free of both active RRMS and treatment. The prescription count of Lemtrada®, however, is below the expectations of Sanofi.

How can the uptake and revenues of a pharmaceutical innovation with high efficacy and cost-saving potential like Lemtrada® be below expectations? It is not likely that it is provoked by irrationally high expectations on Sanofi's side. Zorginstituut Nederland (2019) has stated that the prescription count of Lemtrada® is below their own estimations as well. A possible explanation might be the premise that technological innovation has no objective value in and of itself. It requires commercialization via a BM (Chesbrough, 2010).

BM theory argues that BM is the link between a technology and firm performance. This link moderated by the environment (Zott & Amit, 2007). And unless a suitable and effective BM can be found, technologies will yield less value to the firm than they otherwise might have (Chesbrough, 2010). An ineffective BM could thus be the problem. During the orientation phase of the research, multiple sources were consulted to identify potential causes for BM ineffectiveness. The sources, key findings and a general grouping they can be fitted in is presented below (Table 1).

Source	Key finding	Category
MS franchise management	Care providers tend to overestimate treatment risks, complexity, costs and underestimate the benefits.	D
Sales manager	Hospitals are only interested in low costs in the short term.	A
Sales manager	Sanofi is not allowed to deliver marketing information or study outcomes directly to the patients.	B
Market access team	Lemtrada® can bring big cost savings, but only after two years of higher costs. It is hard to explain and sell that proposition.	A,
Market access team	The active compound of Lemtrada® was first used to treat a form of cancer. It was sold at a lower price but had a different effect and administration routine.	A, D
Lemtrada product manager	Care providers are anxious to use Lemtrada®. They often think it is too risky and don't offer it to patients.	B, E
Lemtrada product manager	A lot of care providers only decide to decide for Lemtrada® treatment when nothing else has worked.	E
MS franchise management	Even though it is considered to be specialty care, there are over 5 competing treatments with different offerings for RRMS.	C, E
2019 Brand plan	Patient awareness and engagement is low.	B
Market intelligence reports	Care providers think that Lemtrada® is the most effective but also the riskiest treatment.	E
Market intelligence reports	Care providers think that Lemtrada® scores low on safety data, monitoring convenience and adverse event manageability.	D

Table 1: Preliminary cause of the problem.

The findings from the orientation phase in table 1 have been used to construct a preliminary overview of causes thought to be related to the BM of Lemtrada® not being effective. The causes on the left side of figure 3 are linked to the letters from table 1. Subsequently, the recognized detrimental effects of the ineffective BM were formulated and added to the right side of figure 3.

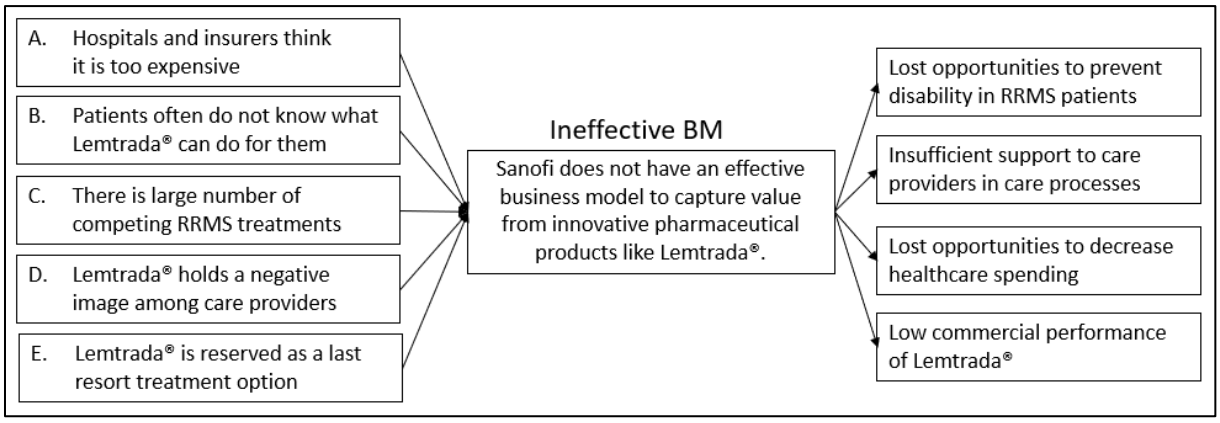

Figure 3: Preliminary cause and effect diagram of the identified problem.

The diverse negative effects caused by the problem illustrate that having an effective BM involves more than making a profit. There is a broader meaning that incorporates multiple stakeholders, since the ineffective BM not only negatively affects Sanofi's bottom line. An example of another detrimental effect is the lost opportunity to prevent irreversible disability in RRMS patients with timely adequate treatment. Having an effective BM means being able to create, deliver and capture value for all stakeholders. In the case of Lemtrada, these stakeholders are patients, care providers, Dutch citizens and Sanofi as a company. They all have their own role in the healthcare system and hold their own perception of value in relation to an effective BM, as shown in figure 4.

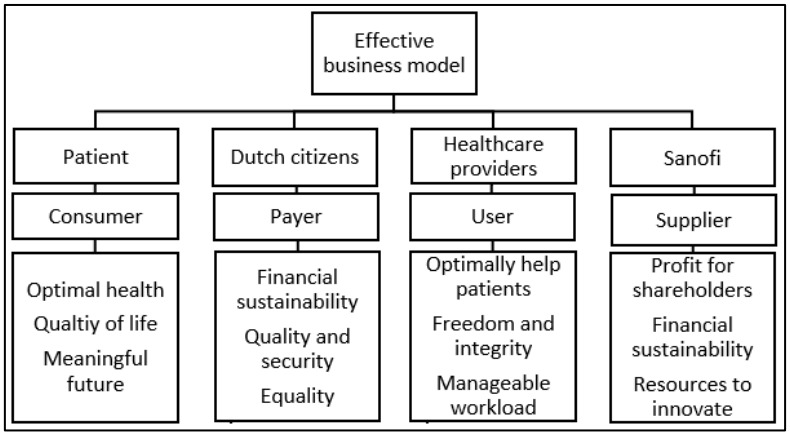

Figure 4: Stakeholders, roles and perceptions of value.

With the understanding that an effective business model incorporates value for all stakeholders also comes the realization that the BM view, with its focus on value for supplier and the direct customer, is too narrow for this problem. Value to other stakeholders like patients and the people responsible for financing the healthcare system is not included. Fortunately, VBHC can be used to broaden the perspective because it focuses on patients and financial sustainability while still acknowledging the need for medical professionalism and business incentives for innovation. It is therefore crucial that the principles and practices of VBHC are incorporated in pharmaceutical BMs, as the two of them combined can offer a perspective in which value to all relevant stakeholders is represented.

The identified detrimental effects in figure 3 indicate that the current BM for Lemtrada® is not capable of realizing the different forms of value for all different stakeholders, indicating that the current BM is ineffective. Even though multiple stakeholders are affected by this ineffective BM, the cause and the research initiative lie with Sanofi. The definition of the problem should therefore adopt Sanofi's point-of-view. Consequently, the following problem statement was formulated:

"Sanofi does not have an effective business model to capture value from innovative pharmaceutical products like Lemtrada®."

2.2 Research objective

By now, Lemtrada® has already been developed and approved. This means that the technology and the product itself cannot be altered. Moreover, it means that a large amount of costs has been incurred that cannot simply be written off. It is important that the effectiveness of Lemtrada's® BM is enhanced to compensate for the costs that have been incurred in research, development and approval. If not, the sustainability of Sanofi and its ability to develop biotechnological innovations are no longer safeguarded. In situations like these, the BM must be innovated to enhance its ability to effectively capture the value created by a certain technology (Teece, 2010; Massa et al., 2017).

A company can do so by exploiting new opportunities in the market (Amit & Zott, 2012; Christensen et al., 2016). VBHC provides such a new opportunity. Lemtrada's® notable health outcomes and limited long-term burden on the national healthcare budget in combination with the prevalence of VBHC in the Dutch healthcare landscape have motivated Sanofi to consider VBHC as an opportunity for BMI that can help increase the effectiveness of the current BM. Unfortunately, there are two barriers that make innovating a pharmaceutical BM with VBHC challenging.

First, VBHC is seldomly approached from a BM angle. Most VBHC publications and efforts are focused on lowering overall costs from a care provider perspective, which can be explained by the fact that it is the central topic in the influential early VBHC publications (Porter & Teisberg, 2006; 2007; Porter, 2010). The supplier perspective, to which BM theory is related, is often left out of the picture.

The second barrier is the fact that the concept of value in VBHC is still abstract and debated. Porter (2010) himself acknowledges that value is a complex concept that involves various interdependent factors and indicators. Even though an increasing number of healthcare professionals and organizations have begun using value-based approaches, definitional issues, measurements, and the relationship between cost and outcomes have yet to be understood by all stakeholders (Mkanta et al., 2016; Lingsma, Roozenbeek & Hazelzet, 2018).

As of now, little guidance exists on how pharmaceutical companies can innovate their BMs with VBHC and which BMIs are suitable for what product. A new approach is needed that adopts the viewpoint of the supplier while maintaining a broad and inclusive definition of value and BM effectiveness. A method is needed that explores what value-based BMI opportunities are available to pharmaceutical companies and that offers guidance on which of those BMIs are most likely to lead to increased BM effectiveness. This thesis aims to realize this through the following research objective:

"To create a decision-support approach for effective pharmaceutical business model innovation based on value-based healthcare".

Because pharmaceutical BMI with VBHC is faced with two distinct barriers mentioned on the previous page, it requires two separate components to address them: a framework of analysis that integrates VBHC in BM theory and a tool that can suggest BMIs based on that analysis. The framework can be used to identify value capture problems in the current BM. Correspondingly, the tool can help address these problems by providing suggestions for value-based BMIs that can be implemented to increase BM effectiveness (Figure 5).

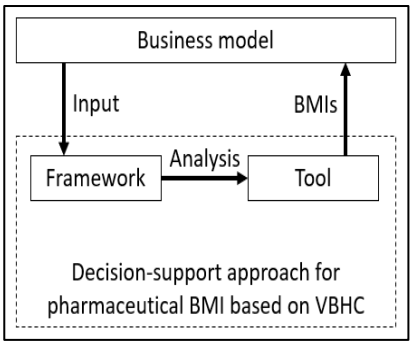

Figure 5. Diagram of the approach.

2.3 Research questions

In order to achieve this objective, it must be studied how BM theory can incorporate VBHC and how VBHC can guide effective BMI. Accordingly, the following research question is proposed:

"How can value-based healthcare be used to innovate pharmaceutical business models?"

In order to answer this question, the following supporting questions need to be answered:

Theoretical questions	**Empirical questions**
Q1. How can BMs of pharmaceutical companies be defined and conceptualized?	**Q4.** What is Lemtrada's® current BM and where do problems occur?
Q2. What is value according to value-based healthcare? **Q2a.** What are patient relevant outcomes and how can they be measured and quantified in VBHC? **Q2b.** How must costs be measured and allocated in the Dutch healthcare system?	**Q5.** What is Lemtrada's® value according to value-based healthcare? **Q5a.** What are patient relevant outcomes for RRMS patients and how does Lemtrada® perform? **Q5b.** What costs are incurred by Lemtrada treatment in the Dutch healthcare system?
Q3. How do BMI and patient value in value-based healthcare interact with each other?	**Q6.** Which innovations should be implemented in Lemtrada's® BM to increase BM effectiveness?

Table 2. Supporting research questions.

2.4 Thesis structure

The remainder of this thesis is structured in the following way. The next chapter is dedicated to the research methodology. After that, the theoretical framework will be addressed. Chapter 4 will provide a theoretical overview on BMs and BMI and an answer to the first sub-question. Once BMs have been addressed, chapter 5 outlines the theoretical foundations of VBHC together with an answer to Q2. The theoretical framework is concluded in chapter 6 by merging the two theoretical concepts into a single framework and formulating an answer to Q3. With an established theoretical framework for analysis, the results of the interviews are presented and analyzed in chapter 7, together with answer Q4. Chapter 8 describe the analysis of the CARE-MS II and the issues that ensued. This is followed up by chapter 9, which describes the development process of the tool that addresses these issues. Chapter 10 describes the application of the developed approach to the Lemtrada® case and provides the answers to Q5 and Q6. Finally, chapter 11 will address the central research question as well as the research's limitations, theoretical and practical implications and future research suggestions.

3. Method

As mentioned previously, this chapter encompasses the methodological aspects of this research. First, an overview of the general research design is provided. After that, the steps and decisions that were taken to answer each of the different sub-questions are described in further detail. These descriptions are then complimented by an overview of how the sub-question and research methods are interrelated. The reflection process is addressed last.

3.1 The reflective cycle

The practical problem combined with the lack of substantial direction for BMI with VBHC in this context make design research well-suited for this particular situation. The reflective cycle of Van Aken (1994) is appropriate in these situations where both a practical solution as well as further theoretical developments are desired. The reflective cycle is a research approach in which problem cases are solved with Van Strien's (1997) regulative cycle (number 3 in figure 6). The process is then reflected on in order to draw conclusions about general theory (Kerssens- van Drongelen, 2001). Due to time and resource constraints, the implementation and evaluation steps of Van Stien's regulative cycle are only performed to a limited extent. The research implications of this decision are considered in the discussion chapter.

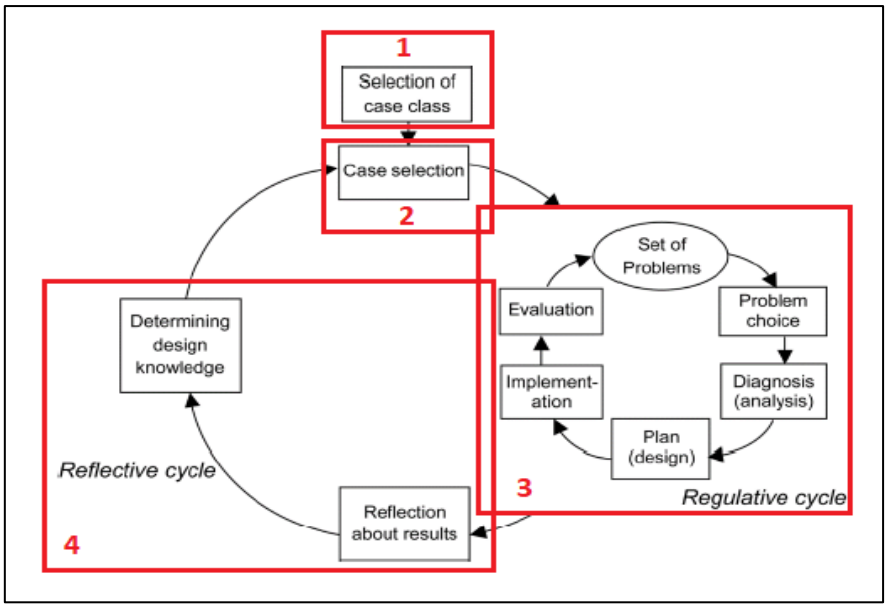

Figure 6. The reflective cycle (Van Aken, 1994).

3.2 Theory elaborating case research

Lemtrada's® ineffective BM was addressed with BMIs rooted in VBHC. Such BMIs, and guidance on their implementation, are not readily available for companies in the pharmaceutical industry and therefore had to be designed to the specific context. A case study that focuses on the contextualized logic of general theory can be described as theory elaborating case research. In theory elaborating research a general theoretical logic is applied, but instead of testing the general theory, theory-elaborating case research aims to elaborate that theory through a process of adaptation. Theory elaboration can take place by introducing new concepts to the general theory and shaping them by empirical analysis from the specific context (Ketokivi & Choi, 2017). In this particular research case, the new concept of VBHC was introduced to the general theory of BMs. The pharmaceutical company setting comprised the context.

3.3 Research design and research strategy

On the right, the conceptual research design for Lemtrada's® business problem is presented (Figure 7). VBHC was introduced to the established field of BMs and the sub-stream of BMIs. The three represent the main theoretical fields that were consulted to address the existing business problem. They were used to describe the as-is situation, analyze problems and issues, design the solution and to provide the needed BMI suggestions.

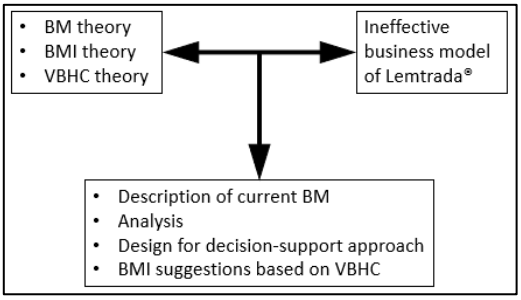

Figure 7. Conceptual research design.

In order to implement the research design, multiple methods and sub-questions were employed. The actions that were carried out to answer each research question are individually addressed below.

3.3.1 Strategy for Q1

In order to find a means to conceptualize and describe pharmaceutical BMs, a review was performed of BM and BMI literature. Because of the extensive body of available literature, a journal list was used to filter out the most significant publications. The journal list of this literature review consisted of management, strategy and entrepreneurship journals that are considered 'the absolute top' by the Erasmus Research Institute of Management (ERIM). The list included both academic research journals and general management journals. The list is provided in table 3.

1.	Journal of Business Venturing	8.	The Academy of Management Review
2.	Journal of International Business Studies	9.	Administrative Science Quarterly
3.	Journal of Management Studies	10.	Journal of Management
4.	Organization Science	11.	Management Science
5.	Organization Studies	12.	California Management Review
6.	Strategic Management Journal	13.	Harvard Business Review
7.	The Academy of Management Journal	14.	MIT Sloan Management Review

Table 3. Included journals from the ERIM journal list.

The following search query was used in the ERIM database:

TITLE: ('Business' AND 'model') AND LANGUAGE: (English) AND DOCUMENT TYPES: (Article)

Articles had to be published between 1995 and 2019, as suggested by Massa et al. (2017). The query resulted in 83 articles on BMs and BMI. The abstracts of articles with an average yearly citation rate higher than 5 were reviewed. This citation cut-off was not used for articles published in 2018 or later.

3.3.2 Strategy for Q2

To understand and operationalize the three central VBHC concepts of value, outcomes and costs, a second literature review was performed on VBHC. Due to the novelty of the field, academic publications on value-based healthcare are limited and published in a wide variety of management, public policy and healthcare journals. A different approach was therefore used for the literature on VBHC compared to the one on BM(I)s. First, all publications on the topic of VBHC by the concept initiators Michael Porter and Elizabeth Teisberg were assessed. This was done to acquire a proper understanding of VBHC in its elementary form and the original ideas and arguments that underlie it.

Subsequently, additional literature on the topic of VBHC was obtained by inserting the following search query into the Web of Science, Abi/Inform and Jstor databases:

TITLE: ((‘Value-based’ OR ‘value based’) AND (‘healthcare’ OR ‘health care’))

To be included, search results had to be published after publication date of the initial VBHC publication by Porter & Teisberg in 2006. 102 articles were initially identified. No journal list or citation count was used to filter the results, for reasons mentioned earlier. Instead, articles were hand-picked based on the relevance of the title and abstract.

3.3.3 Strategy for Q3

Once a theoretical understanding of the two fields was established, the new concept of VBHC was introduced to the more established field of BM(I) as a means of theory elaboration. The definitions and frameworks that were used to answer sub-questions Q1 and Q2 were assessed on overlaps and differences. Common themes were further explored and connected. Gaps between the two were closed by the introduction of a third concept. The three theoretical concepts were then consolidated into a new framework for BM analysis and value-based BMI exploration. The exact processes that underlie this consolidation are described in further detail in chapter 6. The resulting framework would require two inputs: one based on the BM (Q4) and one based on value (Q5).

3.3.4 Strategy for Q4

The original BM conceptualization was functioned as the basis for the framework in Q3 was first used to make an initial assessment of the current BM. This was done in two subsequent sessions with the MS franchise head and MS therapeutic area manager. The assessment approach was taken from the authors of the original BM conceptualization (Osterwalder & Pigneur, 2010). After each session, the omitted findings were verified and completed with short interviews and internal documents.

Once a general description of the current BM was developed, the first input for the framework of analysis was gathered. Diagnosis interviews were held with members working for the MS franchise to find the causes of the BM’s ineffectiveness, which provide the first input for the framework. Functions can be split up into two broad groups: commercial and support. Support functions are by no means related to capturing value. Providing medical information is an example of such a support function. That is why only the eight organization members performing commercially-oriented functions for the MS franchise were included in semi-structured interviews that ranged from 45 to 100 minutes.

Formal team	Function title	Number of respondents
MS franchise	Hospital account manager	3
	Sales manager	1
	Lemtrada® key account manager	1
	Lemtrada® product manager	1
	MS franchise head Benelux	1
Market access	Market access and launch manager MS	1

Table 4. Interview participants, their functions and the focus of the interview.

Problem causes derived from the interviews and their frequency were then listed and structured. To determine interrelationships and find root causes, a current reality tree was constructed. To establish a focus on the most pressing issues, a selection process based on relevance was performed. A root cause had to be recognized by at least 4 interview respondents to be included in the final analysis.

3.3.5 Strategy for Q5

The actions performed for Q4 provided the BM input for the framework. The consecutive step was to provide the second input for the framework, which is based on value. High-quality data, from carefully managed clinical trials for example, are required to assess value (O'mahony et al., 2018).

The outcome data for this case came from the so-called CARE-MS II clinical trial study. The study was designed, conducted, recorded, and reported in accordance with the principles of Good Clinical Practice as stated in the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use and any applicable national or international laws. The data can therefore be regarded as valid and reliable. More information on the CARE-MS II is publicly available via www.clinicaltrials.gov. Data on the total costs of an average Lemtrada® treatment in the Netherlands were obtained from the 2018 Dutch Lemtrada® cost-minimization analysis that was published in the Journal of Medical Economics (Piena et al., 2018). The consumption estimates for this research were also derived from the CARE-MS II.

Initial analysis of the CARE-MS II revealed that descriptive clinical study data is an unsuitable indicator of value, that cannot directly be used as the second input for the framework developed in Q3. Chapter 8 will discuss this matter in more detail.

3.3.6 Strategy for Q6

In order to deal with the problem incurred in Q5, the second component of the approach was developed: the tool. The development process is described in chapter 9. The tool was applied and validated by re-assessing the CARE-MS II data, which provided workable value measures the second time. With both inputs for the framework obtained, the newly developed approach was applied to the research case. Uncaptured value was identified, and value-based BMIs that were most suitable to Lemtrada's® value were obtained. The resulting BMI suggestions are further discussed in chapter 10.

3.3.7 Methods overview

Figure 8 provides a schematic overview of the underlying structure of methods and sub-questions.

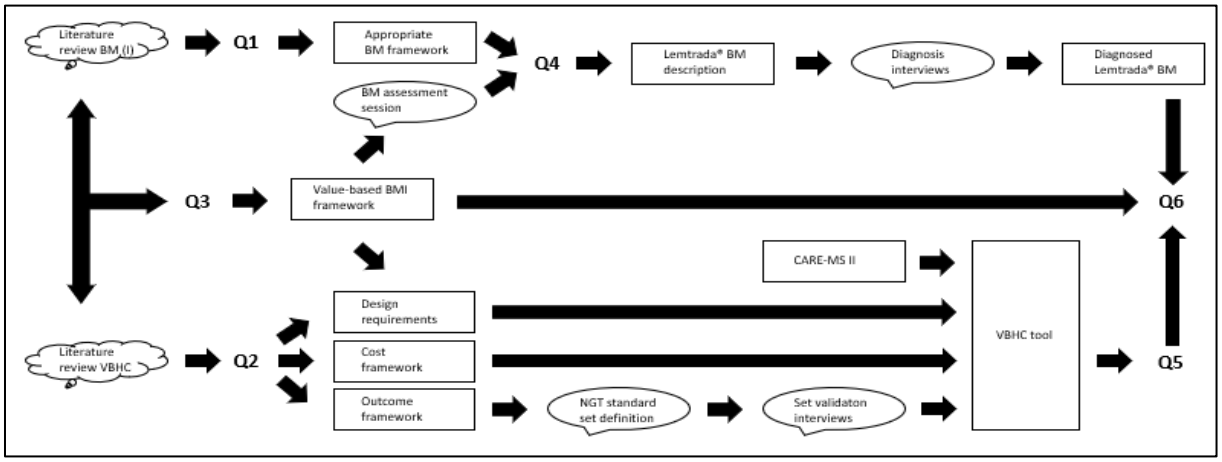

Figure 8. Structure of research methods and sub-questions.

3.4 Reflection

The reflective cycle was concluded by reflecting on the case research process and the generated results, which is described in chapter 9. This final chapter will describe the research's limitations, the theoretical and practical implications. It will also provide the newly generated design knowledge for future designs as well as some directions for future research. This marks the end of the methodological chapter. The theoretical framework will be addressed next.

4. Theory on business models

A solution to Sanofi Genzyme's problem might be to exploit the new VBHC opportunity by innovating Lemtrada's® BM with VBHC elements to enhance its effectiveness and ability to capture value. In order to do so, a relevant and substantiated theoretical framework is required. This chapter will first discuss the general concept of the BM, its function in management research and the sub-stream of BMI. The remainder of the chapter is dedicated to finding a BM framework that can be used to describe pharmaceutical business models in order to provide an answer to Q1.

4.1 The business model concept

While BMs themselves have existed for ages, the concept of BMs as an object of study emerged only in the mid-nineties (Zott et al., 2011). Since then, a steady flow of publications emerged that has not yet slowed down (Massa et al., 2017). The quantity and diversity of publications, however, has led to disagreement on what a BM exactly is and what its purpose is in management science (Zott et al., 2011; George & Bock, 2011; Foss & Saebi, 2017). As a result, some management scholars question the integrity and value of BMs as an independent field of research. Among the critics is Porter, who once stated that the definition of a BM is "murky at best" (2001, p. 73). This is a view that is shared by more management scholars (Massa et al., 2017).

An extensive review of BM research by Zott et al., (2011) notes that throughout the years, BMs have been referred to as a statement, a description, a representation, an architecture, a conceptual model, a structural template, a framework and a set. Fortunately, there are overlapping elements. Foss and Saebi (2017) found that in the influential BM literature reviews, specifically Zott et al., (2011), George & Bock (2011) and Wirtz, Pistoia, Ullrich, & Gottel (2016), the definition of a BM seems to have converged to the definition as stipulated by David J. Teece. Teece provides the following basic definition of a BM: "*a BM describes the design or architecture of the value creation, delivery, and capture mechanisms employed by a firm*" (Teece, 2010, p. 191).

4.2 Function of a business model

There exists a close interrelationship between the concepts of BMs and strategies, but they are not the same construct (Wirtz et al., 2016, Foss & Saebi, 2017). BMs should be perceived as extensions of business strategies in analyzing performance and characterization (Zott et al., 2011). BMs provide a more generic overview, whereas strategy development is a more detailed and interactive concept (Teece, 2010; George & Bock, 2011). At the same time, BM literature relaxes most of the hard theoretical assumptions that are inherent to the strategic literature field in order to be closer to reality and take the focus off of competition (Massa et al., 2017). The broader scope of BMs can be used to tackle certain issues that were largely ignored before. Value capture in innovative markets is one of those issues (Massa et al., 2017).

From a VBHC perspective, this complementary view seems promising. The VBHC movement was ignited by a book by two strategy authors that was titled 'Redefining healthcare: creating value-based competition on results' (Porter & Teisberg, 2006). Critics, however, pointed out that while competition in current healthcare systems might be broken, reshaping competition is unlikely to be the ultimate solution to the critical situation in healthcare (Gray, 2006; Miller, 2006; Verdier, 2006). By now, the primary focus of VBHC has shifted away from competition. Thereby allowing room for the BM perspective to come in and play a complementary role, as it aims to provide answers to the questions 'who is your customer', 'what does he or she value' and 'how do you deliver value at an appropriate cost' (Casadesus-Masanell & Ricart, 2011).

4.3 Business model innovation

The first chapter of this thesis mentioned the dissolution of the dominant business model in the pharmaceutical sector. The profitability and sustainability of searching for blockbuster drugs is slowly but steadily crumbling under heavier regulations, increasing development costs, decentralization, counterfeiting, new needs from emerging markets, aging populations, technological developments that increase competition and environmental pressure (Dierks et al., 2016). For pharmaceutical firms to survive, their BMs must be re-calibrated to their new environments (Kaitin & DiMasi; 2011).

The re-calibration of BMs is referred to as BMI. BMI, simply defined as "designing a new, or modifying the firm's extant activity system" (Amit & Zott, 2010, p. 2), has matured into a separate sub-stream in contemporary BM research. In this sub-stream, BMs are considered both an enabler of innovation as well as a subject of innovation on their own (Teece, 2010; Zott et al., 2011).

BMI as a separate subject of innovation is a powerful concept that can complement the traditional subjects of process, product, and organizational innovation (Massa et al., 2017). Product and process innovations are often expensive and time-consuming, as Lemtrada® perfectly illustrates. The development and approval of the technology has taken years and has cost hundreds of millions. The inherent outcome uncertainty turns these product and process innovations into high-stake 'bets' (Amit & Zott, 2012). This 'all-or-nothing' blockbuster model is the exact thing that the pharmaceutical sector needs to move away from. Organizational innovation, on the other hand, might help increase the effectivity or efficiency of certain activities within the organization, but has an internal focus that comprises little interaction with the organization's environment.

BMI is quicker and more flexible than product or process innovation, thereby allowing to react more swiftly to market demands. Companies have come to view the ability to innovate with BMs as equally if not more important (Economist Intelligence Unit, 2005). Once a certain technology has been created, BMI presents opportunities for new future revenues and competitive advantages as the focus shifts to delivering better products that can be sold for higher prices to the existing market (Amit & Zott, 2012; Christensen et al., 2016).

The pharmaceutical industry is a popular subject in the field of BMI due to the demise of the blockbuster model and distressing developments in its direct environment (Chesbrough, 2010; George & Bock, 2011; Ding et al., 2013). These changes have distinctly revealed the limitations of the traditional types of innovation and have fueled the need for new revenues and competitive leverage; two potential merits that BMI holds. In order to reap the potential benefits of BMI, firms must consider environmental uncertainty as a potential source of opportunities (Christensen et al., 2016). Literature supports the idea that in a highly knowledge-intensive environment, such as biopharmaceutics, a strong orientation towards innovation from the environment of the firm is critical for business success (Downs et al., 2019). This requires high sensitivity to external opportunities and the ability to exploit them. VBHC represents such a new market opportunity that can lead to new revenues and a competitive advantage. The question, however, is how exactly the BM must be innovated to exploit the opportunity.

4.4 Selecting a business model framework

This thesis aims to provide Sanofi with a set of value-based BMIs that can be implemented to exploit the VBHC opportunity and enhance the effectiveness the BM and its ability to capture value from the Lemtrada® technology. But before any innovations can be recommended for existing BM, it must first be described and evaluated. A coherent theoretical framework is required to assess the as-is state.

4.4.1 Formal conceptualizations

When the aim of a study is to provide detailed descriptions on certain aspects of an organization's activities, it can be classified as a formal conceptual representation (Massa et al., 2017). These conceptualizations can be especially useful for trying to make sense of the complexity that is inherent to BMs, since the BM is regarded as the blueprint of how a company does business (Osterwalder et al., 2005). Such a blueprint or architecture allows for systematic and holistic BM analysis (Teece, 2010; Foss & Saebi, 2017). The formal conceptualization approach is well-suited for this research, as it provides an immediate answer to the first sub-question and it can be applied to a single case.

4.4.2 Potential frameworks

The next step is to find out what formal conceptualization is best suited for this context. This is a particularly difficult task. For instance, the paper of Massa et al. (2017) alone identified 17 exemplar formal conceptual representations that were published within the period between 2004 and 2016. Moreover, each of these conceptualizations has its own definitions, elements, interrelationships and functions. It would be possible for academics to devote entire papers to the comparison of these frameworks. That is why they have.

4.4.3 Multi criteria analysis

To find the most appropriate framework for this research, the comparison of business modeling methods by Alberts (2011) has been selected. Alberts' publication was chosen as it includes all frameworks that were published in the top 25 MIS journals in the 15 years prior to the research and because it specifically focuses on formal conceptual representations. An elementary multi criteria analysis is used to identify the conceptualization that is most suited to this particular research.

Even though Alberts compares the conceptualizations on eleven criteria, not all criteria are applicable or relevant to the case research. An example of such a criterion is the academic background of the authors of a conceptualization. Five criteria from the paper where chosen to determine the suitability of a framework. Each criterion is briefly described, together with a relative weight. Since there are five criteria, the initial weight of each criterion was 20%. The description of each criterion also provides a short argumentation on added or retracted relative weight.

Formality: the purpose of Q1 is to find a way to describe BM. It is thus important that the BM can be expressed in natural language, a formal modeling language or as computable software. In order to compare the conceptualizations, Alberts provided each framework with a formality score. Due to the link with Q1, this criterium is considered fairly important, and is therefore assigned a weight of 25%.

Core similarity: in the scattered field of BM, attention must be given to the conceptual validity of a framework. In this case, validity is assessed by the degree to which the core elements of a conceptualization show connotational overlap with core elements of other BM frameworks. Because similarity to similar frameworks alone cannot fully comprehend validity, it has only been assigned a weight of 15%.

Functional applicability: BM frameworks are created for varying purposes. This research objective demands a framework that can be used to describe a BM and to develop a decision-support approach. The score on this criterium is based the overlap between Alberts's description of the framework's function and the research objective. The link with the research objective leads to a weight of 25%.

Situational applicability: since the thesis is conducted in a pharmaceutical context, it is crucial that the selected framework can be applied to pharmaceutical companies. The score on this criterium is based on the overlap between Alberts's description of the framework's area of application and the pharmaceutical research context. If a framework cannot be applied to the case, there is no point to it. This criterium is therefore regarded equally important as formality and functional applicability.

Maturity: a more evolved and established BM framework would be preferred over a newer and less adopted framework, as they are likely to be more robust and have more literature on them. The verdict of whether a framework can be considered mature is provided by Alberts. Maturity, however, is more of a preference rather than a hard requirement. It therefore holds a 10% weight.

4.4.4 Selecting the most suitable framework

Table 5 provides an overview of the multi criteria analysis of the different frameworks. The ten frameworks are on the vertical axis. The horizontal axis describes the criteria, their relative weight and the scale that was used to score each framework on the different criteria.

	Criterium:	Formality	Core similarity	Functional applicability	Situational applicability	Maturity	
	Rating:	0: Minimum 10: Maximum	0: Minimum 10: Maximum	2: undefined 4: classification 6: description 8: visualization 10: tool creation	2: very low 4: low 6: medium 8: high 10: very high	5: not mature 10: mature	
	Weight:	25%	15%	25%	25%	10%	
Activity System		4	6	4	8	10	5,9
e3-value		9	9	10	6	10	8,6
RCOV		6	8	8	6	10	7,2
BM Concept		7	8	8	6	5	6,95
BM Ontology		8	8	10	8	10	8,7
Entrepreneur"s BM		5	9	6	6	5	6,1
Social BM		4	5	10	8	5	6,75
BM Guide		1	1	6	4	5	3,4
4C Internet Typology		2	4	4	2	10	3,6
Internet BM		3	4	6	2	5	3,85

Table 5. Multi criteria analysis of potential BM conceptualizations.

As the table above shows, the BM Ontology by Osterwalder (2004, 2005, 2010) emanates as the most suitable framework. The difference in total score with the e3-value framework by Gordijn (2004), however, is absolutely minimal. To make sure that the right decision is made, a paper published by the two respective authors comparing the two frameworks was consulted.

While the two frameworks play the same ontological role, yet there are different focal points strengths to both (Gordijn, Osterwalder & Pigneur, 2005). The comparison of the two frameworks asserted the decision for Osterwalder's BM Ontology. First of all because Osterwalder defines and centers the BM around a specific firm, whereas Gordijn considers the BM as a network of enterprises and customers. Second, because the BM ontology is applicable to a wider range of business settings, while the e3-value model was specifically developed for e-business models. The BM Ontology is thus preferred.

4.5 Osterwalder's business model ontology

The 9-element conceptualization by Osterwalder was first proposed in a doctoral thesis in 2004 and has its fundament in information systems engineering and management. Driven by a lack of clear and applicable conceptualizations in combination with the rise of IT and the internet, the central research goal was to provide an explicit conceptualization of a generic BM, although the term 'ontology' is preferred by Osterwalder (2004). The framework consists of nine elements or 'blocks', which in turn are placed within four pillars (Table 6).

Pillar	BM element	Description
Product	**Value proposition**	A value proposition is an overall view of a company's bundle of products and services that are of value to the customer.
Customer interface	**Customer segment**	A segment of customers a company wants to offer value to.
	Distribution channel	A distribution channel is a means of getting in touch with the customer.
	Relationship	The relationship describes the kind of link a company establishes between itself and the customer.
Infrastructure Management	**Value configuration**	The value configuration describes the arrangement of activities and resources that are necessary to create value for the customer.
	Capability	A capability is the ability to execute a repeatable pattern of actions that is necessary in order to create value for the customer.
	Partnership	A partnership is a voluntarily initiated cooperative agreement between two or more companies in order to create value for the customer.
Financial aspects	**Cost structure**	The cost structure is the representation in money of all the means employed in the business model.
	Revenue model	The revenue model describes the way a company makes money through a variety of revenue flows.

Table 6: The 9 BM elements (Osterwalder, 2004).

While the four pillars function as a theoretic categorization, the nine elements are the core of the ontology (Osterwalder, 2004). Each element is composed of a set of sub-element indicators. These indicators allow for a more detailed assessment of a given BM. The value proposition, for example, is divided into a set of elementary 'offerings'. An offering, on its turn, is an individual product, service or feature inherent to that value proposition. A more basic and practice-oriented model was later published in the form of the 'Business Model Canvas' (Osterwalder & Pigneur, 2010).

4.6 An answer to Q1

After assessing the general research field, it is concluded that pharmaceutical business models can be defined and conceptualized through Osterwalder's business model ontology (2004) and the scaled-down business model canvas (2010). Osterwalder's formal conceptualization of the BM is arguably the most comprehensive BM template (Ovans, 2015), and it serves as a promising approach for BMI research (Chesbrough, 2010; Schaltegger, 2012). It was developed with the specific objective to create a fundament that can be used for tool development, scenario analysis and simulation (Osterwalder, 2004). This perfectly aligns with the research objective of designing a decision-support tool. The fact that the pharmaceutical sector is prominently featured in two business cases described in Osterwalder & Pigneur's 2010 publication illustrates that the framework can successfully be applied to pharmaceutical companies. With the establishment of a suitable framework, the theoretical chapter on BMs is concluded.

5. Theory on value-based healthcare

Value-based healthcare is a relatively new concept in healthcare and policy that has taken modern nations like the Netherlands by storm. While it is popular, its true implications are often poorly understood (Fredriksson et al., 2015). The aim of this chapter is to provide a comprehensible overview of what VBHC exactly is and how it should take form in a practical design setting. The topics that will be discussed are the definition of the core concepts value, outcomes and costs. In that specific order.

5.1 Defining value

Regardless of the popularity and adoption in practice, there is still debate on what exactly constitutes as VBHC and what does not (Mkanta, 2016). What most parties at this point have agreed on is that VBHC is centered around increasing patient value, with value defined by the equation in which health outcomes achieved are the numerator, and costs per patient in delivering those outcomes are the denominator (Porter & Teisberg, 2006, 2010, 2013; Raspe, 2016; Mkanta, 2016; Ministerie van Volksgezondheid, Welzijn en Sport, 2017; Federatie Medisch Specialsiten 2018).

The fundamental message that value in healthcare should be defined as health outcomes achieved per monetary unit spent, and centered around the patient rather than the provider, accounts for much of the rise in popularity and experimentation of VBHC. Even though the initial publication is not convincing on all fronts. “There is room for disagreement about how best to measure and structure care in the system, but it is hard to argue that what we have now cannot be improved” (Verdier, 2006, p. 971). The looming threat of a struggling health system and the promise of better outcomes at lower cost have captivated physicians, policymakers, healthcare managers and payers and permitted the ‘outcomes divided by costs’ philosophy to become a topic of mass interest.

5.1.1 An answer to Q2

To the initial sub-question; ‘what is value according to value-based healthcare?’, a decisive answer can be provided. Value is defined by the equation in which health outcomes relevant to patients achieved are the numerator, and costs per patient in delivering those outcomes are the denominator. This answer, of course, immediately triggers two follow-up questions. Namely ‘what outcomes?’ and ‘what costs?”. Both questions will be separately addressed in the next sections.

5.2 Defining outcomes

In a reaction to the sudden interest in VBHC and the amount of questions about its practical implementation, the article ‘What is value in healthcare?’ (Porter, 2010) was published. The article is, at this point in time, the most cited VBHC publication. It aims to provide insight on what outcomes need to be measured to implement VBHC and improve patient relevant health outcomes. The primary insight comes in the form of the ‘outcomes hierarchy’ (Porter, 2010). Figure 9 depicts the outcomes hierarchy together with an application example for breast cancer care.

The hierarchy is an abstract representation of relevant patient outcomes. Its purpose is not to dictate exact outcome measures but rather to force care providers and policy makers to adopt a broad and long-term perspective when it comes to assessing the quality of care. Porter (2010) envisions each medical condition to have its own unique set of outcome measures, and therefore its own custom outcome hierarchy. The question, then, is what outcomes must be included for a specific condition and who decides on these outcomes.

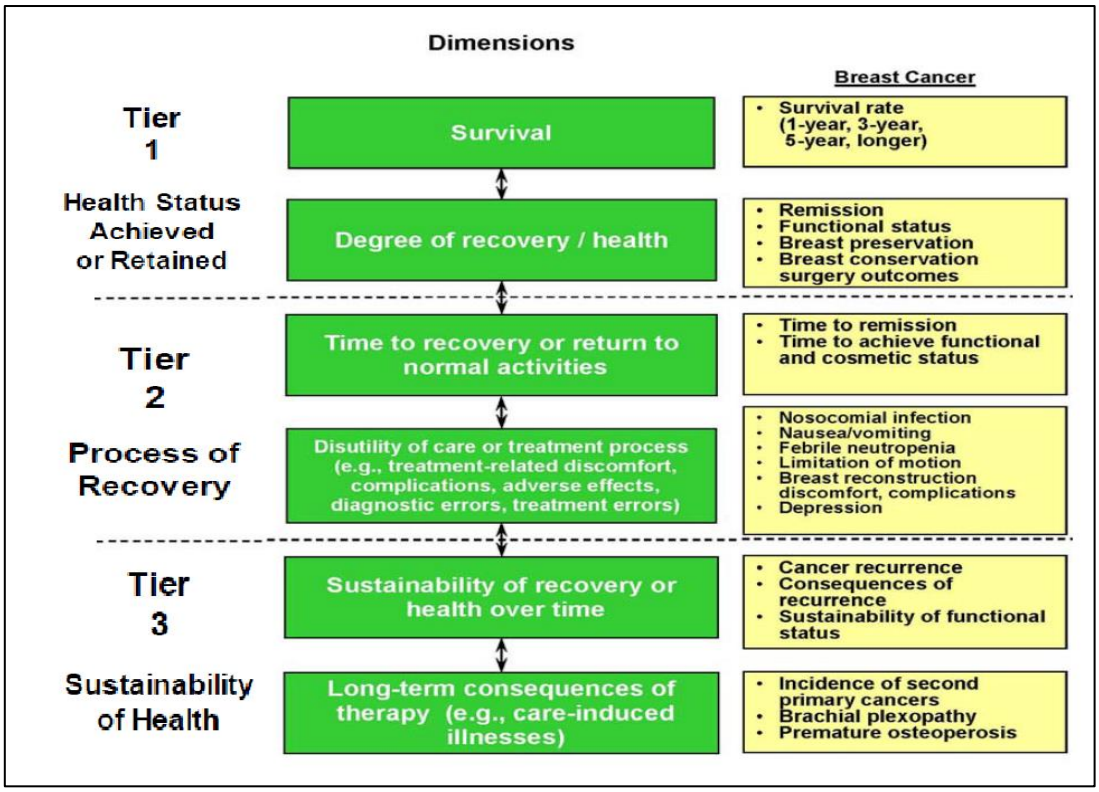

Figure 9. Outcomes hierarchy. (Porter, 2010).

5.2.1 Applying the outcomes hierarchy: ICHOM

The outcome specification question led to a more practical step towards implementation of the VBHC concept: the founding of the International Consortium for Health Outcomes Measurement (ICHOM). ICHOM was founded in 2012 by Michael Porter, Martin Ingvar and the Boston Consulting Group. ICHOM's mission is to "unlock the potential of value-based health care by defining global standard sets of outcome measures that really matter to patients for the most relevant medical conditions and by driving adoption and reporting of these measures worldwide" (www.ichom.org, n.d.).

Unfortunately, no standard set has been developed or announced for MS. However, fourteen articles on the development of ICHOM standard sets have been published in academic journals. The systematic analysis of published ICHOM articles has resulted in a structured description of process steps and selection criteria, as well as an outcome measures framework. By combining the two, new outcome sets can be developed. The above-mentioned results from the ICHOM literature review can be found in appendix B.

5.2.2 An answer to Q2.a

Precise instructions on outcome measurement and quantification are not directly available. However, a systematic review of development papers by the global institute dedicated to the acceleration of VBHC combined with general VBHC principles can lead to a practicable answer. Patient relevant outcomes are healthcare outcomes that patients experience in their daily life. These outcomes are determined by each individual patient in accordance with the patient's individual situation and the moment in time. Such outcomes can be structured and measured using Porter's outcomes hierarchy. Relevant outcome domains can be identified by applying ICHOM's standardized process for outcome set development and can be visualized and combined through normalized radar charts. A conclusive framework and protocol for standard set development is included in appendix B.

5.3 Defining costs

The value fraction poses that value improves if outcomes improve at equal or lower cost, or if outcomes are stable at meaningfully lower cost (Porter, 2010). This does not sound complicated. The concept of costs in healthcare, however, is not as straightforward as it might seem.

5.3.1 Cost measurement in value-based healthcare

Currently, there is only a poor understanding of how much treating a patient actually costs (Kaplan et al., 2014; Hamid et al., 2014). This is alarming, as accurately allocating costs is important for two reasons. First, it enables decision makers to accurately detect drivers of costs. Thereby highlighting the areas in which the biggest improvements could be made. Second, it reduces the possibilities for cost-shifting amongst parties in the healthcare landscape. A new method has been suggested for cost calculation and allocation in VBHC, known as time-driven activity-based costing (Kaplan & Porter, 2011). Unfortunately, this approach is complex and limited to interventional care in a hospital setting.

While that may be the case, cost calculation for pharmaceutical treatments is not a novelty in itself. In the next section, an overview of cost measurement and cost allocation of pharmaceuticals in the Netherlands will be examined.

5.3.2 General cost measurement in pharmaceuticals

The evaluation of costs incurred by the payer is a common practice in the realm of pharmaceuticals. The last two decades, it has become more common to also develop thorough assessments of what can be regarded as sufficiently effective and which pharmaceutical treatments should be reimbursed (Zorginstituut Nederland, 2016).

Without reimbursement from the basic insurance package, a treatment will in most cases rarely be prescribed in the Netherlands because the hospital or patient are unlikely to contribute themselves. It is therefore critical to the pharmaceutical supplier that the product is included in the basic health insurance. The Minister of Health, Welfare and Sport is responsible for this decision, which stands on a formal recommendation by Zorginstituut Nederland (ZiN). The 'guideline for economic evaluations in healthcare' has been developed with the aim to facilitate suppliers, researchers and policymakers in performing and assessing cost-analyses in economic evaluations of healthcare interventions (ZiN, 2016, p. 3). Since VBHC literature offers no guidance for pharmaceutical cost calculation and allocation, this guideline will be used instead to calculate the costs incurred with pharmaceutical treatment. As proof of the validity of this substitute, a side-to-side comparison of the general costing principles from VBHC and ZiN can be found in appendix C.

5.3.3 An answer to Q2.b

Costs make up the second half of the value equation and are often regarded as the more enticing element of the two. Rising healthcare costs were the primary driver behind the whole idea of VBHC after all. It is therefore remarkable that so little attention has been paid to cost measurement and allocation in VBHC publications. As mentioned before, the solutions currently offered are limited to hospital and clinic settings. What is more, is that these solutions are so complex and overly reliant on IT that most care providing institutes are unable to implement them at this point in time. In order to fill the gap, this research turns to the official guideline published by ZiN. The guideline represents the golden standard for measuring and analyzing the economic impact of pharmaceutical products in the Netherlands. It is the definitive reference guide for economic decision-making used by all major healthcare authorities. The considerable overlap with the general costing principles of VBHC make it the best substitute for clear-cut VBHC costing protocols for pharmaceuticals at this moment.

6. Theory elaboration: BMI with VBHC

Now the individual fields of BMs and VBHC have been discussed, the question that remains is how the two can be combined. Since BMs are considered both an enabler as well as the subject of innovation and VBHC is still developing, there is little reason to assume that one dictates the other. That is why this chapter aims to elaborate BMI theory by exploring the relationship between BMI and VBHC. First, similarities and conflicts between the two theories are examined in chapter 6.1. Conflicting interests of the two concepts are resolved through the formulation of two basic rules for value-based pharmaceutical BMs. Chapter 6.2 initiates the development for a framework that integrates VBHC in BM theory. Theoretical concepts that create a link between the two are gradually introduced in chapter 6.3 through 6.5. Chapter 6.3 introduces the notion of value uncaptured, which functions as the first segment of the framework. In chapter 6.4, BM elements on the value-side of Osterwalder's framework are linked to VBHC implications by Porter & Teisberg to provide the second segment. The last segment is described in chapter 6.5. In chapter 6.6, the three segments and the two rules formulated in 6.1 are combined into a single framework for value-based BMI.

6.1 Examining the shared concept of 'value'

So far, the term 'value' has persistently been used throughout this thesis. It is a fundamental concept in BM and VBHC literature and is pivotal in the theoretical definition of both. But is 'value' as understood in the BM literature the same as 'value' in VBHC? While the term value holds a similar meaning in both, it is perceived from two different perspectives.

6.1.1 Overlap in interpretation

A crucial similarity is that both fields acknowledge that value is not a single inherent figure, but rather defined by the context. "Importantly, different prospective customers may desire different latent attributes of the technology. Thus, there is no single inherent value for the technology" (Chesbrough & Rosenbloom, 2002, p. 8). "Outcomes, the numerator of the value equation, are inherently condition-specific and multidimensional" (Porter, 2010, p. 2477). Both fields acknowledge that the inherent value is determined by a certain situation-dependent need. Be that as it may, when the value cannot be established beforehand, what should be paid? This question reveals the main difficulty in uniting these two fields, because the BM and VBHC adopt opposing views in the same argument.

6.1.2 Difference in interpretation

BM theory adopts the perspective of the business; an entity prompted to sell something. Here, value is an economic concept. It is not primarily measured in physical performance attributes, but rather what a buyer is willing to pay for a product or service (Chesbrough & Rosenbloom, 2002). This makes sense, since the business does not use the products or services itself. The value to the buyer, therefore is not the primary concern. The primary aspiration of the seller is to capture as much value as possible for a created value, with a minimum that must be captured for the business to remain sustainable. Aside from that, all additional captured value is surplus.

VBHC on the other hand, takes the perspective of the collective bodies that consume and pay for healthcare; the buyer's perspective. Here, value is functional. It is determined by the value delivered to patients that use the products and services (Porter, 2010). Whether or not that value is captured by the selling party is not the primary concern to this buying side. The primary aspiration of the buyer is to have as much value created to them as possible. Again, there is a minimum value that must be created for the system to remain sustainable. But other than that, all additional value created and delivered by the seller to the user is surplus.

6.1.3 Resolving the issue

The interests of pharmaceutical BMs and VBHC might seem incompatible at first glance, as the two are in a constant struggle for surplus and sustainability. Both sellers and buyers, however, are benefited by a transaction. Suppliers that don't sell their technology cannot prosper. The same holds for those who do not buy necessary health solutions. The only reconciling solution, then, is to make sure that the value created for the user roughly equals the value captured by the supplier.

This requires suppliers to adopt the VBHC view that value not only encompasses standard efficacy numbers and revenues but also a patient's personal well-being, future health and societal costs. To the buyers this means that they must accept that additional value does not necessarily have to be free. Following the reasoning of Porter's definition of value, costs can go up if outcomes increase with an equal or larger amount. This realization leads to two major insights, which will be referred to as rules for the remainder of this thesis. The two rules for value-based pharmaceutical BMs are:

Rule 1. To capture more value, more value must be created. Only create value that can be captured.
Rule 2. Serious effort must be put into the processes through which created value is captured.

6.2 An approach for value-based BMI

While the two formulated rules provide some initial insight on how the fields of BMs and VBHC can be integrated to complement each other, they do not provide guidance on which value-based BMIs are available to pharmaceutical companies. Let alone, how they can increase the effectiveness of the BM and solve the business problem. In order to do that, a new approach for effective pharmaceutical BMI based on VBHC is needed. The approach should have a dual focus: value-based BM analysis and value-based BM innovation. Its two components must fit that focus. The first component is a framework that can be used to analyze the BM for areas of ineffectiveness that inhibit value capture and for the identification of value-based BMI opportunities for pharmaceutical companies. Chapter 6.3 through 6.5 describe the development of this framework.

6.3. Value uncaptured

To align the interests of BMs and VBHC, the concept of 'value uncaptured' is adopted into the context. It is a theoretical concept by Yang et al. (2017) that underlies their new framework for BMI (Figure 10). Value uncaptured describes the potential value that could be captured but has not been captured.

The definition of value, here, is broader than just monetary value. The framework was specifically designed to incorporate all stakeholders in the value system (Yang et al., 2017). While the concept was originally created from a sustainable BMI perspective, the idea behind value uncaptured and certain aspects of the corresponding framework can be applied the healthcare system as well.

Figure 10. Five steps for using value uncaptured for sustainable for BMI (Adapted from Yang et al., 2017).

The framework by Yang et al., which makes up the upper half of figure 11, is well-suited to the two purposes of the approach. The original framework includes four forms of value uncaptured. The sustainable manufacturing origin of value uncaptured and associated framework for BMI do limit their use in other fields, however. As a result, only two of the initial four forms of value absence can be incorporated into value-based BMI for pharmaceutical companies

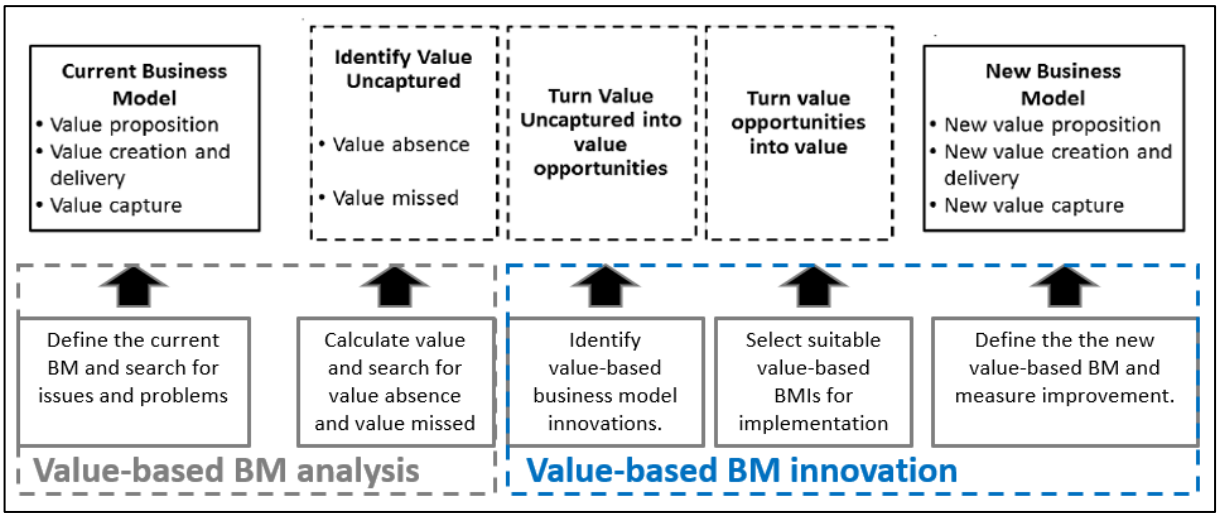

Figure 11. Using Yang et al.'s (2017) for value-based BM innovation in the pharmaceutical context.

6.3.1 Value absence

The first is value absence, "which can be regarded as needs that could have been met but have not yet been met" (Yang et al., 2017, p. 1797). Value absence is caused by a lack of efforts or resources. In this thesis specifically, it is conceptualized as unrealized value potential that can be materialized by making changes to the BM without drastically altering the technology itself. It consists of value-creating improvements that could be made but have not yet been mad. In order to eliminate value absence in a pharmaceutical BM, additional value must be created. This means that the first rule for for value-based pharmaceutical BMs must be adhered.

6.3.2 Value missed

The second form of value uncaptured adopted in this framework is value missed, which is "value that exists and is required, but not exploited" (Yang et al., 2017, p. 1797). Examples of value missed are underutilization and inefficient use of resources. In this context, value missed is value that is created by the current technology and BM but not captured. This value should nevertheless be captured by the supplier by applying the second rule.

In line with the research objective and the adopted framework, the two forms of value uncaptured and the two rules serve two distinctive but complementary purposes: value-based BM analysis and value-based BM innovation (Figure 12).

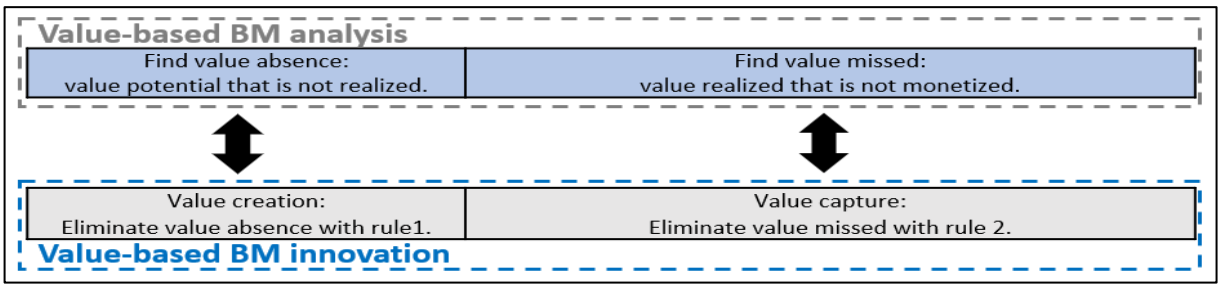

Figure 12. The link between the formulated rules and the two forms of value uncaptured.

6.4 Linking BM theory to VBHC theory

The previous section lied the theoretical foundation of the value-based BMI approach. The link between value uncaptured and the defined rules showcased conceptually overlapping areas between BMs and VBHC, but not a basis that is concrete enough for analysis or innovation. To provide such a basis, this section will explore uniting elements between the theoretical frameworks that emerged from sub-questions Q1 and Q2.

6.4.1 Implications of VBHC for BM elements

The role of suppliers in VBHC is considered indispensable (Porter & Teisberg, 2006), yet barely discussed. In academic literature, the topic is yet to be taken up. Some current knowledge can be found in the grey literature. However, the BM implications of VBHC discussed in these articles are often educated guesses, since no results have been observed yet. How suppliers can benefit from VBHC is even more seldomly addressed. This leaves suppliers with little incentive to actively contribute to the shift towards VBHC. The only direction for suppliers is offered in the original VBHC book (2006), where the authors describe six explicit implications of VBHC for suppliers in healthcare systems. These six implications and practical steps to their implementation are listed in box 1.

1. Compete on delivering unique value over the full cycle of care.
    - Base strategies on unique value for patients.
    - Focus on cycles of care rather than narrow product use.
    - Sell not just products, but provider and patient support.
2. Demonstrate value based on careful study of long-term results and costs.
    - Use evidence of long-term clinical outcomes and costs to demonstrate value compared to alternative therapies.
    - Conduct new types of long-term comparative studies in collaboration with providers and patients.
3. Ensure that products are used by the right patients.
    - Increase the success rate instead of maximizing usage.
    - Target marketing and sales to minimize unnecessary or ineffective therapies.
4. Ensure that products are embedded in the right care delivery processes.
    - Help providers to utilize products better and minimize errors.
5. Build marketing campaigns based on value, information and customer support.
    - Concentrate marketing efforts on value, not volume and discounts.
6. Offer support services that add value rather than reinforce cost shifting.
    - Support provider efforts to improve results and halt old-style cost shifting.

Box 1. VBHC implications for suppliers (Porter & Teisberg, 2006).

The first of the six implications is rather broad. It spans the most pages in the book and shows considerable overlap with some of the other implications. The remaining five implications, however, seem to concern topics similar to the five BM elements that reside on the right side of Osterwalder's framework. The right side of the framework is also known as 'the value-side' of the framework and consists of the delivery channels, customer segments, value proposition, revenue model and customer relationships (Osterwalder & Pigneur, 2010). As one might have suspected, the value-side of the BM is where the supplier implications of VBHC and the supplier's BM elements overlap. Each of the latter five VBHC supplier implication listed in box 1 provides some basic guidance on how a firm must design a certain BM element on the value-side in a way that is in line with the principles of VBHC.

Figure 13 shows how the five value-oriented BM elements of Osterwalder's framework (upper side) can be linked to the supplier implications of VBHC formulated by Porter & Teisberg (lower side).

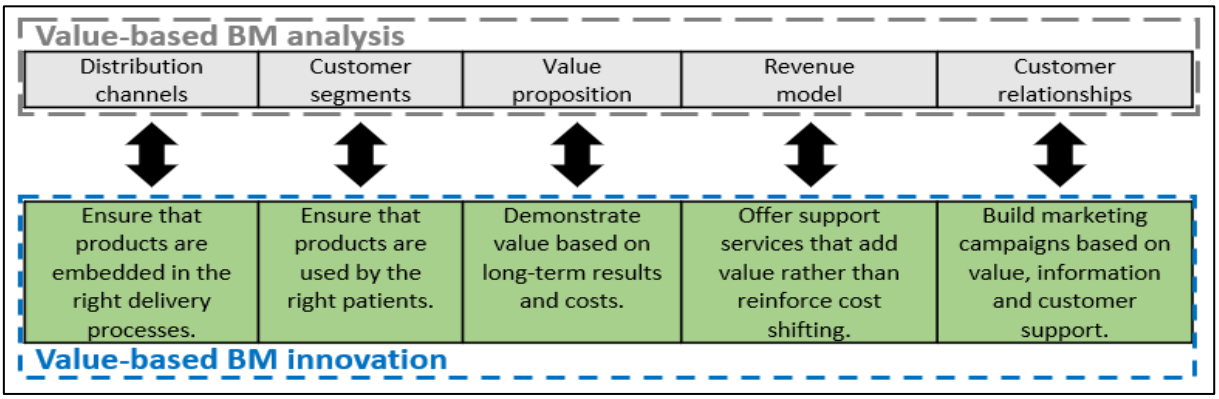

Figure 13. The link between the five value-oriented BM elements and the supplier implications of VBHC.

6.5 Applying the shared concept of value

The supplier implications for VBHC provide some basic insight on innovating BM elements that reside on the value-oriented side of Osterwalder's framework with VBHC elements. A final issue to resolve in order to establish a new approach for effective pharmaceutical BMI based on VBHC is deciding what kind of BMIs are likely to increase the BM's effectiveness and ability to capture value. In chapter 6.3.1, it was established that the only way to reconcile the interests of both fields would mean to balance value created and value captured. The shared concept of value should thus be the key driver of decisions on pharmaceutical BM innovations based on VBHC. Q2 revealed that value can be defined as outcomes divided by costs. Outcomes, in turn, can be sub-divided into three tiers (Porter, 2010). The result is shown in figure 14.

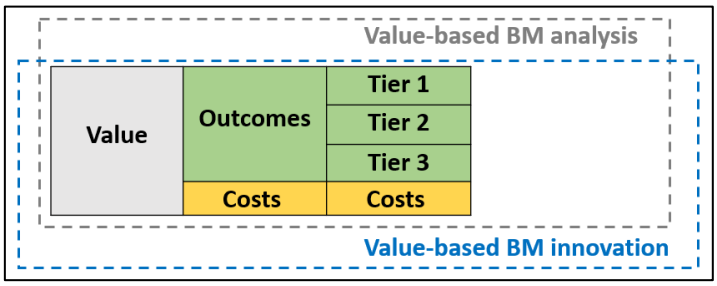

Figure 14. Value as defined by Porter (2010).

6.6 An answer to Q3

In order to provide an answer to the question 'how do BMI and patient value in value-based healthcare interact with each other?', this chapter introduced the concept of VBHC to the established general theory on BMs and BMI. The common theme of value was examined on overlaps and differences. The dual purpose of the approach for effective pharmaceutical BMI based on VBHC was reiterated and the two theoretical frameworks that emerged from Q1 and Q2 were linked to each other and to the research objective through with the concept of value uncaptured and the accompanying framework for BMI. The result is the first component of the approach: a framework that can be used to analyze the BM for areas of ineffectiveness that inhibit value capture and for the identification of value-based BMI opportunities. This framework is presented on the next page.

By combining the previously discussed concepts of value absence and value missed with the two formulated rules, the five BM elements on the value-side of Osterwalder's framework, their matching supplier implications and the VBHC definition of value, a new framework for value-based BMI is created (Figure 15). Elements originating from BM theory are in grey, while the elements that stem from VBHC are in green (except for costs, which is orange). The elements that originate from value uncaptured are in blue.

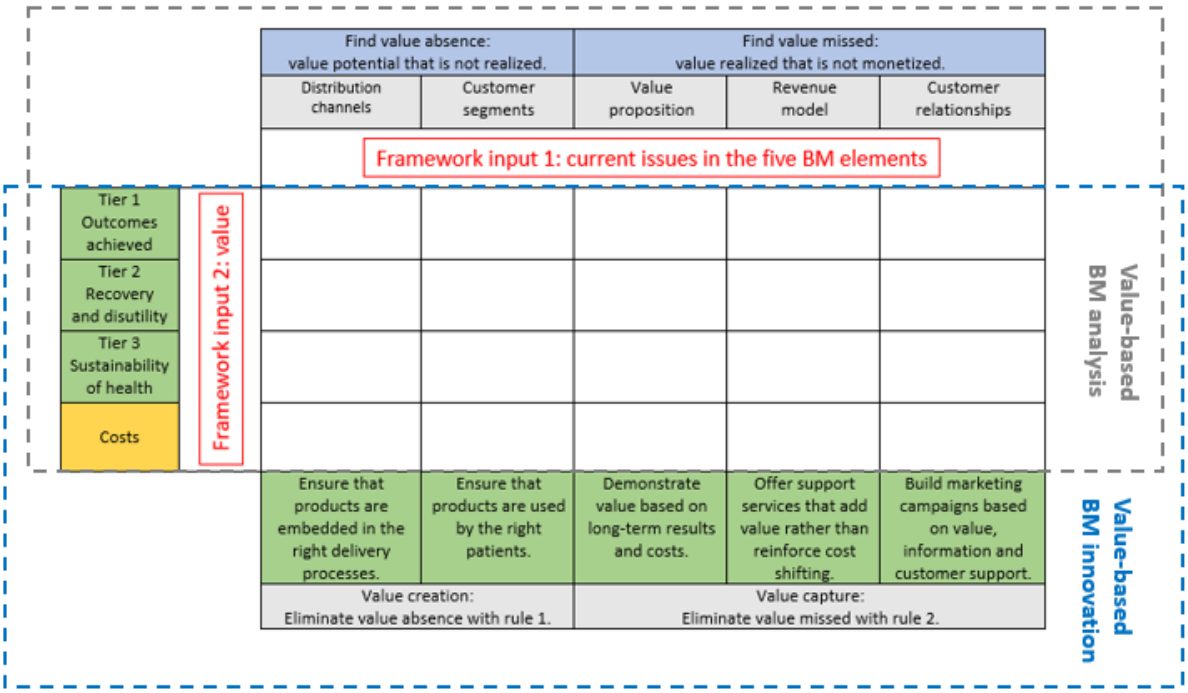

Figure 15. A framework for value-based BMI.

This dual purpose is maintained in the resulting framework. The upper side is intended for BM analysis, while the lower half can be used to develop innovations for the BM based on VBHC. To apply the framework proposed framework in a research setting, the basic steps of the value uncaptured framework that were outlined in Figure 11 can be followed.

6.6.1 Framework for analysis

For value-based BM analysis, the framework requires two distinct inputs. The first is a set of current BM issues acknowledged for a product that occur in the five value-oriented BM elements that make up the upper horizontal axis of the framework. The second input is that product's value as defined by the four outcome tiers on the vertical axis. Cross-referencing the two axes can reveal sources of value uncaptured in the BM. Cross referencing low value on a tier with problems in the creation-focused distribution channels or customer segments signals value absence. A high value on a tier combined with problems in the capture focused value proposition, revenue model or customer relationships indicates value missed.

6.6.2 Framework for Innovation

The next step is to develop a set of value-based BMIs that can tackle the two forms of value uncaptured. The lower horizontal axis of the framework provides direction for the development of such BMIs. The value assessment of the product on the vertical axis can then be used to determine which BMIs best fit with the product's value and are thus more likely to lead to a more effective BM.

7. Interview results and analysis

Now that the theoretical fundament for the research has been discussed and a framework for analysis has been established, the results of the empirical research can be addressed to generate the necessary framework inputs. This chapter begins with a description of the current BM and the general value capture problem. After that, a detailed list of problems and issues in the value-oriented BM elements are presented and analyzed to answer Q4 and provide the first input for the framework.

7.1 Description of Lemtrada's business model

As suspected, Lemtrada's® BM can competently be described using the formal conceptualization by Osterwalder (2004) and Osterwalder & Pigneur (2010). Based on the initial BM assessment sessions, both a high-level and a detailed overview of the current as-is state of the BM have been created. After the interviews, newly acquired insights led to some modifications and expansions of the BM descriptions. For practical reasons, these have been excluded from the main text. The business model canvas and ontology for Lemtrada's® entire current BM are presented in appendix D and appendix E, respectively.

7.2 Validating the value capture focus

After a basic descriptive image of the BM for Lemtrada® was developed, interviews with members of the MS franchise were held. These interviews led to several valuable findings. First of all, the interviews reinforced the notion that the problems with the current BM can best be addressed with a focus on value capture.

The erroneous assumption that when an impressive technology is created vale will automatically be captured was also held by the MS franchise during the preparations of Lemtrada's® launch in 2014. The market access manager who was part of Lemtrada's® launch summarized it in the following way:

> "Most Sanofi Genzyme therapies are such unique products, you don't need to put in a lot of effort with regard to awareness. These are therapies that the patient will request themselves. With Lemtrada®, I think, we had the same idea: 'this is such a fantastic substance, it will sell itself. People will be standing in line to get it'. And I think, being Genzyme, that we overestimated that".

The other argument reinforcing the value capture focus was that the value creation process, the development and approval of Lemtrada® treatment, has already been concluded in the past. Tenacious legal and financial barriers make it impossible to alter the technology. The MS franchise head for the Benelux aptly summarizes the situation:

> "Do we have an attractive product? Yes and no. […] But we simply can't adjust it. We are inflexible in that sense. Lemtrada has one single method of disease suppression: resetting the immune system. It simply is… this one product."

Lemtrada® might be inalterable due to legal and financial barriers, its BM certainly is not. The rise of VBHC in the Netherlands brings new opportunities for the BM that can be exploited to increase its effectiveness and ability to capture value from innovative pharmaceutical products like Lemtrada®. Before a solution can be designed and implemented for the problem, however, a deeper understanding of the problems and issues of the current BM must be developed.

7.3 Interview data

The framework presented in chapter 6.5 served as the principal foundation for the structure of the interviews. The direct results of the interviews are presented in table 7. The horizontal axis of table 7 contains the interview participants. The vertical axis lists all issues related to the five value-oriented BM elements that were distilled from the interviews. The issues are categorized using the five value-oriented BM elements of the framework. A checked box in the white grid between the axis indicates that the respondent in that column has acknowledged the BM issue in that specific row. The column on the far right indicates how many respondents have acknowledged a certain issue. An unchecked box does not necessarily mean that the respondent denies or disagrees with an issue, but rather that he or she did not explicitly acknowledge that issue during the interviews. Several boxes in the column that belongs to the market access manager are marked 'not applicable' (n.a.). This indicates that this person was not interviewed on these parts of the BM due to the nature of his function.

Respondents									
Franchise head									
Market access manager									
Lemtrada® product manager									
Lemtrada® key account manager									
Sales manager									
Hospital accountmanager 1									
Hospital accountmanager 2									
Hospital accountmanager 3									
Issues per BM element	HAM	HAM	HAM	SM	KAM	PM	MA	FH	
Value proposition									
1. Monitoring and administration is perceived as a burden by care providers.	✓	✓	✓	✓	✓	✓	✓	✓	8
2. Lemtrada® is perceived as a high-risk treatment by care providers.	✓	✓		✓	✓	✓		✓	6
3. Cost savings not of interest to decision-making care providers.		✓	✓	✓	✓	✓	✓		6
4. Value to the patient does not directly translate to value to the care provider.	✓	✓		✓	✓			✓	5
5. Perceived 'initial hurdle' to introduce Lemtrada® as a treatment option.	✓	✓	✓	✓			✓		5
6. The patient's interest not always the care provider's top concern.	✓	✓				✓		✓	4
7. Limited grasp of care providers on effects of treatment on the patient's life.				✓	✓	✓		✓	4
8. Lemtrada® treatment sometimes considered too risky by patients.		✓		✓		✓			3
9. Long-term value of Lemtrada® mismatches with short-term view of patients.		✓		✓		✓			3
10. Non-chronic structure not perceived as a benefit by all care providers.					✓	✓	✓		3
11. Current inability to customize/individualize the value proposition.		✓		✓				✓	3
12. Lemtrada's® inability to demonstrate 'what is in it for the doctor'.				✓				✓	2
13. Patient thinks Lemtrada treatment involves too much inconvenience.		✓							1

Table 7. Problems and issues with Lemtrada's® BM.

Customer segments									
14. Patient's voice and influence in decision-making process is limited.	✓		✓	✓	✓		n.a.	✓	5
15. Not all hospitals have the expertise or experience required for Lemtrada®.		✓	✓	✓	✓		n.a.	✓	5
16. Decision-making randomness within and between hospitals.	✓	✓		✓	✓	✓	n.a.		5
17. Large portion of (past) patients that receive Lemtrada as 'last resort'.		✓		✓	✓	✓	n.a.		4
18. No segmentation on adoption among care providers.					✓	✓	n.a.	✓	3
19. Emotional decision-making by care providers.	✓	✓					n.a.	✓	3
Distribution channels									
20. Value proposition to patients is distorted by care providers.	✓	✓	✓	✓	✓	✓	n.a.	✓	7
21. Patient is often not fully informed about disease and treatment options.	✓		✓		✓		n.a.	✓	4
22. Lemtrada® is not offered as a treatment option to patients.		✓		✓	✓		n.a.	✓	4
23. Uncontrollable indirect (online) channels distribute invalid information.	✓	✓		✓	✓		n.a.		4
24. Limited number of care providers that are 'Lemtrada® ambassadors'.					✓	✓	n.a.		2
Customer relationships									
25. No patient input.			✓	✓	✓		n.a.	✓	4
26. Little to no accurate feedback on Lemtrada's performance in patients.	✓			✓	✓		n.a.	✓	4
27. Little to no feedback on patient's treatment experience.	✓			✓			n.a.		2
28. Poor understanding of who the patient is.						✓	n.a.	✓	2
Revenue model									
30. High initial investment does not stroke with annual reimbursement.		✓		✓			✓	✓	4
31. Payers hold short-term financial view.	✓	✓		✓	✓				4
32. Issues regarding Lemtrada® reimbursement.		✓		✓		✓			3
33. Care providers not accustomed to non-chronic MS treatment.					✓		✓		2
34. Reimbursement requires additional efforts to be made by the hospital.						✓	✓		2

Table 7. Problems and issues with Lemtrada's® BM (continued).

The table presented above consists of all issues that were recognized by the respondents during the interviews. The aim of the next section of this chapter is to analyse and condense the results listed in table 7, in order to maintain a more focused research scope. First, a current reality tree is constructed from table 7 to determine which issues are root causes and which causes are intermediate causes or causes that are not deemed relevant. After that, the data is condensed by making a selection of the most relevant issues. In order to be considered relevant, the number of interview candidates that acknowledge the issue must meet a threshold of four. These key issues are described in further detail with supporting quotes by the interview respondents. Six conclusions are then drawn based on the analysis of the BM. The process is concluded with an answer to Q4.

7.4 Analysis of interview data

To understand the interrelation of the issues and problems that were identified in the interviews, and to find root causes to problem, a current reality tree (CRT) was constructed. A CRT is a form of cause-effect diagram that can be used to provide a basis for understanding complex systems and issues (Mabin, 1999). A CRT represents the most probable chain of causes and effects, given the situation and the answer of the interview candidates. Its primary function is to show the structure of the problem (Figure 16). A larger version of the CRT can be found in appendix F. The starting point of tree consists of the undesirable effects defined in chapter 2.1. The CRT did not reveal one single vital root cause to the problem. However, a CRT can help achieve other objectives as well (Mabin, 1999).

First of all, a CRT helps differentiate intermediate causes from root causes. Since only root causes can be directly addressed, the intermediate cause have been marked **grey** in figure 16 and table 7.

A CRT also helps identify causes that lie beyond the span of control. These are also ruled out, as these causes cannot be addressed by the company. They are marked **red** in figure 16 and table 7.

Finally, a CRT focusses on the current situation. Issues that are no longer deemed to be relevant were thus dismissed as it is undesirable to develop solutions for problems in the past. An example of such an issue is the fact that many hospitals were not able to resolve the reimbursement of Lemtrada® in the initial period after its launch. This posed a very serious problem back then but has been resolved by now. These are marked **orange** in figure 16 and table 7.

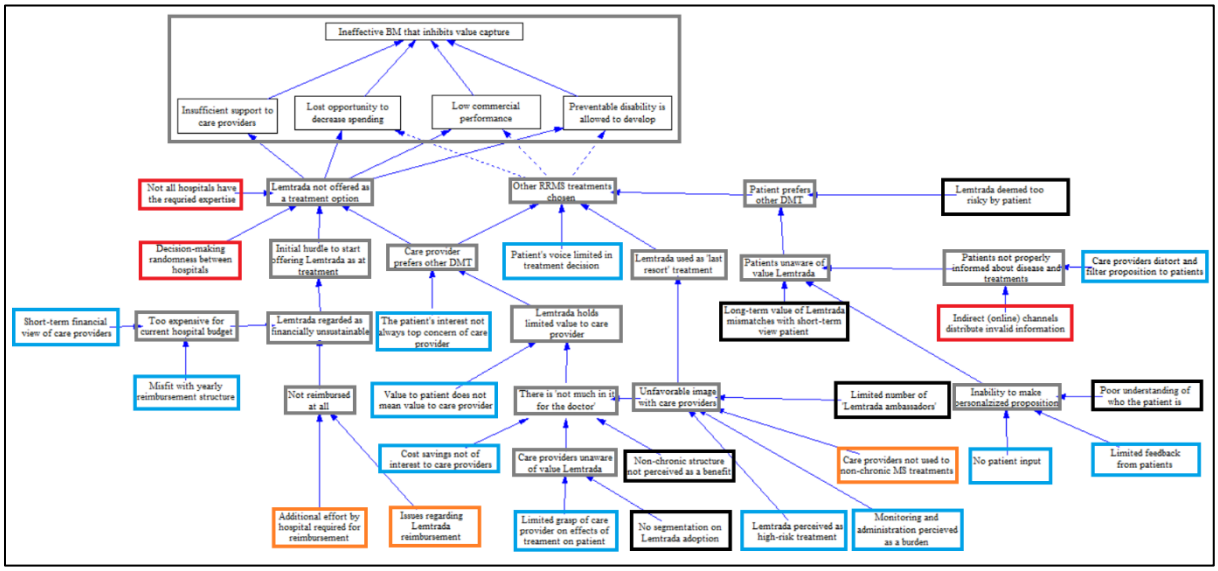

Figure 16. Current reality tree.

While the CRT did help define root causes, more focus is required. For deeper analysis core problems must be isolated. Only the issues that were deemed to be most relevant were condensed from the set. In order to meet the relevance criterium, an issue had to be recognized by at least half (4) of the interview respondents. These key root causes have been marked **blue** in table 7 and figure 16. The key issues are described in more detail in 7.4.1 to 7.4.5. The conclusions of the analysis forms the first input for the framework.

7.4.1 Value proposition

Lemtrada's® value proposition is the primary problematic BM element. The difficulty lies in the fact that patients are the primary beneficiary of Lemtrada® treatment, but that care providers primarily make the treatment decision. For them, Lemtrada® is less appealing (Table 7, issue 4). "The doctor decides in the end. Always. Patients are considered, but the treating physician has the responsibility, and makes the final decision. Which means that when the physician does not agree or does not see a beneficial benefit-risk ratio, he does not offer it as a treatment option to the patient. And we see that in most hospitals in The Netherland, Lemtrada is not actively offered as an option" (FH).

The most important reason is the additional monitoring (Table 7, issue 1). "Monitoring is a substantial toll on the time of nurses and the physicians. On top of that, there is the big significance of monitoring combined with the fact that they cannot guarantee that they won't overlook some patients or adverse events. … In quite some hospitals they still work with paper folders in which this monitoring process is documented and checked by hand. Or no system at all" (PM). The second-most important downside is related to the risk of adverse events, especially those that result in new autoimmune disorders (Table 7, issue 2). "The largest group is thyroid disorders, something neurologists know little to nothing about. When it is diagnosed, they must refer their patient to an internist, which means they must hand over their patient to someone else. On top of that, there is this feeling of guilt or remorse" (KAM). One would expect that a care provider only has the interest of the patient in mind when making a decision, but that is often not the reality (Table 7, issue 6). "There are some considerable risks. And I think that that is the main challenge for the MS franchise. … Physicians say: 'in that case I will choose a lower efficacy, because it saves a lot of squabble'" (SM). Especially the additional effort and time related to Lemtrada® seems bothersome (Table 7, issue 1). HAM (J): "I asked professor [neurologist] 'what makes it that you are not willing to start with Lemtrada?'. And he says he just thinks that it is a hassle" (HAM).

Even when care providers set aside their own interests and solely focus on the interest of the patient, they do not always understand what a treatment like Lemtrada® can mean for a patient outside of basic clinical measures (Table 7, issue 7). "Very often, the translation to what this can mean to the life of the patient is not clear" (KAM). Because these professionals only have a limited amount of time they can spend on each patient, the benefits of Lemtrada® on quality of life, career or family can go unnoticed. Aside from the benefits that go unnoticed, there are benefits that do not seem of value to care providers. The potential cost savings (Table 7, issue 3) are a strong example: "physicians are barely concerned with the cost effectiveness of the treatments they prescribe. They often don't know what is what and how it works. And like I said before, they often do not have a clue of what the substance costs" (SM). Based on the analysis of the highly relevant issues relating to the value proposition element, the following two conclusions can be drawn.

Lemtrada® has two different propositions for two different stakeholders: patients and care providers. The value and benefits of Lemtrada® are primarily experienced by patients. For care providers, Lemtrada® brings additional inconvenience compared to other treatments. These inconveniences can lead to improved patient outcomes and cost benefits. These benefits, however, are not perceived as value by the care providers that are dealing with the drawbacks of Lemtrada®.
C1. Value delivered by Lemtrada® to patient and society are not perceived as value by care providers.
Because the care providers are responsible for the patient and do not fully understand or appreciate the additional benefits that Lemtrada® can bring, they are also less motivated to take the perceived additional risk in order to secure those benefits.
C2. Lemtrada's® risk-benefit ratio for care providers is not convincing.

7.4.2 Customer segments

Since care providers do not fully understand the impact that Lemtrada® can have on a patient's daily life (Table 7, issue 7), but do carry responsibility for the patient, they adopt a different attitude towards risk than their patients. "It is the chance at a life free of MS and a higher quality of life. And a chance at adverse events, but patients are generally willing to accept those risks, as the gains are proportionate as well" (FH). In many cases, the care provider is not willing to take those risks. "But the patient says: 'This is my life right now. This is what I want with my life, what product is most suitable?' And what we hear back is that patients are willing to take far more risks than their treating physicians are" (PM). Unfortunately, the value of Lemtrada® must be proven to both the patient and the care provider. This proves difficult, since the proposition is more attractive to patients than to physicians. Since the latter has the most power in the treatment decision, Lemtrada® is often not the first choice, or not even offered at all (Table 7, issue 14). "What you see is that the physician, in reality, has already decided for the patient" (HAM). By combining these insights with the realization that the value proposition towards care providers is not particularly alluring, a third conclusion can be formulated.

Lemtrada® must demonstrate value to two customers: the patient and the care provider. As established before, Lemtrada® mainly delivers benefits to the patient while the responsible care providers mainly experience inconveniences that are not rewarded in their point of view. The latter has the most power in the final decision, creating a disadvantage for Lemtrada®.
C3. Value of Lemtrada® primarily created and delivered to patient rather than care provider, but care provider is the key decider.

7.4.3 Distribution channels

Strict regulation withholds pharmaceutical companies from directly approaching potential Lemtrada® patients. As a result, Sanofi can only reach potential patients via indirect channels. A structural disadvantage of these channels is that Sanofi has limited control over them, or in some case no control at all. This is a severe problem that manifests itself in different ways. Sanofi's information and messaging is distorted or filtered by these indirect channels, with an incomplete or inaccurate message to the patient as a result (Table 7, issue 20). "The physician will provide a number of options to the patient, who will then further discuss it with the nurse. And the first thing you notice is that they both have weighed in their own perspective, it never is objective. … Incomplete information as well" (KAM). In other instances, Lemtrada® is not even picked up by the indirect channels and never reaches the patient. "More often than not we see that the physician is anxious for Lemtrada and does not offer it to the patient" (SM). When the care provider holds a negative image of a treatment, this negative image is likely to be transferred to the patient. "It is the communication with the physician that provides a patient with the confidence to choose a treatment. … And with so much noise and personal opinions on these channels, little remains from the original message" (PM). It can be stated that Lemtrada® does not have any direct channels towards patients. The indirect channels do not seem to function in Lemtrada's® interest, but are outside of Sanofi's direct control, leading to conclusion four.

Another disadvantage of Lemtrada's® BM is that the care providers, to whom Lemtrada's® value proposition is not appealing, are the main distribution channel of information and recommendations towards patients.
C4. Value primarily created and delivered to patients, but care providers are the primary distribution channel of value proposition.

7.4.4 Customer relationships

The same legal barriers prohibit Sanofi from actively engaging patients that are receiving the treatment. This makes it difficult to showcase the positive Lemtrada® patients and cases. "On all of the 300-and-something patients that have been given Lemtrada up to this moment, we have little to no picture" (SM). It also limits the ability to acquire feedback from patients (Table 7, issue 26). On rare occasions, special events are organized to acquire additional insights, but the options are extremely limited. "Those interactions are transactional, one-time only and there is no feedback involved whatsoever. Besides, they are anonymous. How can one maintain a relationship with a patient that is anonymous?" (FH).

Because care providers have limited time and Sanofi is restricted by protection laws, patients turn to the internet. While the internet has a huge offer of diverse content, reports are quite often subjective or outright false. With no means to interact with those patients, such information cannot be clarified or validated. This also means that the Lemtrada® team is unable to make improvements based on patient feedback (Table 7, issue 25). "Some patients are negatively influencing other patients online, with their n=1 story. But there is nothing you can do. You can't react to them" (HAM). The lack of relationships with Lemtrada® patients restricts the MS franchise in gathering feedback, actively supporting patients and using real-world examples as arguments. This leads to conclusion five.

One might expect Lemtrada's® efficacy and quality of life benefits can easily be leveraged in Lemtrada's® advantage. However, the lack of customer relationships with current or past Lemtrada® patients restricts Sanofi's ability to gather feedback, integrate patient input and use real-world examples as arguments or evidence.
C5. Lemtrada® is a complex but potent treatment, yet little is known about who receives the treatment.

7.4.5 Revenue model

Finally, there is the unusual structure of revenue model. Lemtrada's® administration structure and non-chronic character are unconventional in MS care. The two-course, or sometimes three-course, treatment that requires addition investment in the first year that will create perpetual saving after only three years. Hospitals, however, perceive this as a problem rather than a selling point. It starts with the fact that Lemtrada® is more expensive than competing treatments (Table 7, issue 31). "We heard that a lot, about the costs that the hospital had to incur in the first year. 'It is a lot of money for one patient' is what many said to us" (MA).

To make matters worse, reimbursement works with annual budgets. Because pharmaceutical treatment ideally stops after two years, reimbursement for medication will also stop. This means that hospitals are disadvantaged by the initial high price, but unable to enjoy the benefits from the cost savings that start after the second year (Table 7, issue 30). "They receive budgets for the coming year. Every year, these budgets are renegotiated. So the system kind of works against Lemtrada. Because when you only look at the first year it is relatively expensive" (SM). The short-term view of the insurance companies is automatically taken over by the hospitals that depend on the yearly reimbursements. A six conclusion can be drawn based on the current BM's revenue model.

Lemtrada® treatment stops after two or three years. During these years the acquisition costs are higher, but they significantly decrease once treatment stops. The short-term view of payers and yearly reimbursement structure nullify the cost benefits, making Lemtrada® seem rather expensive.
C6. Lemtrada® leads to cost savings on long term, but payers utilize a short-term perspective.

7.5 An answer to Q4

Multiple empirical sessions were held in order to provide an answer to the question 'what is Lemtrada's® current BM and where do problems occur?' and to provide the first input for the framework developed in Q3. Lemtrada's® current BM was defined using the conceptualization by Osterwalder (2004) and the method by Osterwalder and Pigneur (2010). The BM Ontology and BM Canvas for Lemtrada can be found in appendix D and E, respectively.

The interviews with Sanofi employees on the five value-oriented BM elements of the framework revealed a large and diverse set of problems. A CRT was developed to structure the issues and to establish root causes. While the CRT did help structure the problem and causes, it did not provide the focus required by the framework. This was done by condensing the core issues from the set. These are issues which were explicitly acknowledged by at least 4 participants during the interviews. The core issues were described in further detail, and six conclusions were drawn from them (Table 8).

BM element	Root cause and relevance			Conclusion
Value proposition	7. Limited grasp of care providers on effects of treatment on the patient's life.	4		**C1.** Value delivered by Lemtrada® to patient and society are not perceived as value by care providers.
	3. Cost savings not of interest to decision-making care providers.	4		
	2. Lemtrada® is perceived as high-risk treatment by care providers.	6		**C2.** Lemtrada's risk-benefit ratio for care providers is not convincing.
	1. Monitoring and administration is perceived as a burden by care providers.	8		**C3.** Value of Lemtrada® primarily created and delivered to patient rather than care provider, but care provider is the key decider.
	4. Value to the patient does not directly translate to value to the care provider.	5		
	6. The patient's interest not always the care provider's top concern.	4		
Customer segments	14. Patient's voice and influence in decision-making process is limited.	5		
Distribution channels	20. Value proposition to patients is distorted by care providers.	7		**C4.** Value primarily created and delivered to patients, but care providers are the primary distribution channel of value proposition.
Customer relationships	25. Little to no accurate patient feedback.	4		**C5.** Lemtrada® is a complex but potent treatment, yet little is known about who receives the treatment.
	26. No patient input.	4		
Revenue streams	31. Payers hold short-term financial view.	4		**C6.** Lemtrada® leads to cost savings on long term, but payers utilize a short-term perspective.
	30. High initial investment does not stroke with annual reimbursement	4		

Table 8. Conclusions drawn based on the interviews.

The answer to Q4 marks the first input for the value-based BMI framework. The six conclusions on Lemtrada's® BM can be mapped onto the upper vertical axis of the framework, as showcased in table 9. It also marks the end of this chapter. The next chapter will address the CARE-MS II data, in order to obtain the second input for the value-based BMI framework.

Find value absence: value potential that is not realized.		Find value missed: value realized that is not monetized.		
Distribution channels	Customer segments	Value proposition	Revenue model	Customer relationships
C4	**C3**	**C1 & C2**	**C6**	**C5**

Table 9. First input for the framework.

8. CARE-MS II results and analysis

With the first input for the value-based BMI framework provided, the second input can be addressed: the value of Lemtrada®. First, an overview of the data on which Lemtrada's® value is assessed is presented. After that, the problems with analyzing this data are discussed.

8.1 CARE-MS II data

The assessment of Lemtrada's® value is not based on primary data but on an existing set, due to obvious practical reasons. The CARE-MS II is a phase-three randomized, rater- and dose-blinded study that compared Lemtrada® to competing treatment Rebif ® (Interferon Beta-1a) in patients with RRMS who have relapsed on previous therapy. The study tracked and compared the outcomes of both treatments over the course of two years. The study was completed by more than 170 patients on Rebif® and over 460 patients who received Lemtrada® in its current dose. The data from this study provided the fundament for Lemtrada's® approval by the American Food and Drug Authority (FDA) and the European Medicines Agency (EMA).

Phase-three trials are complex, expensive and crucial for approval. They therefore have multiple research objectives, known as endpoints. These can be split up into two categories: efficacy and safety. Table 10 provides an overview of the endpoints of the CARE-MS II according to the EMA (2013).

Efficacy	
Primary endpoints	Time to 6-month sustained accumulation of disability measured by EDSS*.
	Annual relapse rate**.
Secondary endpoints	Proportion of patients who are relapse free** at year 2.
	Change from Baseline in EDSS*.
	Acquisition of disability as measured by change from Baseline in MSFC.
	Percent change from baseline in MRI-T2-hyperintense lesion volume.
Tertiary endpoints	Time to first relapse**.
	Proportion of patients with no MS disease activity (EDSS*, relapse**, MRI***).
	Time to sustained reduction in disability measured by EDSS*.
	Time to accumulation of disability measured by EDSS*, sustained over a 3-month period.
	Percent change from Baseline in MRI*** findings.
	The proportion of patients who have worsened, remained stable, or improved.
	Number of new or enhanced lesions.
	Change from baseline in health-related quality of life measures (HRQOL)****.
	Healthcare resource utilization.
Safety	
All endpoints	Adverse Events.
	Serious adverse events.
	Other significant adverse events.
	Changes in hematological parameters.
* EDSS	The EDSS has long been considered the standard for assessing disability in MS. It is an ordinal scale that ranges from 0 (normal neurologic examination) to 10 (death due to MS) in half-point increments.
** Relapse	Relapse is defined as new neurological symptoms or worsening of previous neurological symptoms with an objective change on neurological examination. The rate describes the average number of relapses per year.
*** MRI	Included MRI assessments: gadolinium-enhancing MRI, MRI-T2, MRI-T1.
**** HRQOL	HRQOL is assessed with the following patient questionnaires: EQ-5D, FAMS, SF-36.

Table 10. Care-MS II endpoints.

8.2 Analysis of CARE-MS II data

Clinical studies like the CARE-MS II are primarily conducted to obtain approval from authorities like the FDA and EMA. The objective is to prove that the efficacy and safety of the treatment are comparable or superior to existing treatments, or acceptable in case there are no existing treatments. Nearly all study endpoints are therefore clinical measures. Studies are designed to demonstrate that the treatment meets the minimal requirements for approval.

But approval does not necessarily mean that a treatment provides high value to patients, or that the product will be a commercial success. Let alone whether it holds significant value for a broader group of stakeholders such as care providers or the collective body of payers. So how does one determine value with this sort of data? Even though the CARE-MS II provides the most high-quality data available on Lemtrada®, it was not designed and conducted to determine the overall value of the treatment. It was therefore revealed that value cannot directly be extracted from the data. The following problems emerged during the initial analysis of the CARE-MS II data:

Sub-problem	Sub-problem description
Outcome definition	1. The endpoints are extensive, diverse and often independent. On top of that, one single endpoint can be measured in multiple ways.
Outcome integration	2. Outcomes of Lemtrada® are compared with Rebif® on each individual endpoint rather than used to determine the overall value of the treatment.
Cost integration	3. Costs of the treatment are excluded from the study.
Calculation method	4. The Lemtrada® treatment also has negative consequences for patients. That impact is assessed separately from the positive impact.
Value expression	5. The study reports individually on all endpoints, the same goes for the conclusions drawn remain sub-conclusions per endpoint.

Table 11. Problems in extracting value from the CARE-MS II data.

8.3 Limitations of current VBHC literature

Since Lemtrada's® value cannot be extracted from the CARE-MS II data, value must be determined by a different method. VBHC theory offers a perspective that can be used to determine the value of medical interventions .It has already been stated in chapter 2.2 that the abstraction of the theoretical value concept poses a barrier to the practical implementation of VBHC. The literature review of VBHC has provided some high-level direction on what value is and how it can be approached, but this is not detailed enough to be used in measurement. Table 12 shows that the theoretical answers of Q2 alone are not enough to solve the problems in table 11 and to determine a product's value. A solution to this problem must thus be designed and developed. Chapter 9 elaborates on this process.

Sub-problem	Sub-problem description
Outcome definition	ICHOM sets help define outcomes, but do not resolve how outcomes relate to each other and what their contribution to the overall value is.
Outcome integration	The outcomes hierarchy is useful in classifying different outcomes, but it is unclear how these tiers can be operationalized and combined.
Cost integration	ZiN has provided costing guidelines, but these are separate from outcomes.
Calculation method	There is no method for combining the different outcomes measured with different instruments into unifying value measures.
Value expression	There is no clear unit to express value in. The 'outcomes divided by costs' fraction has not yet been put into practice.

Table 12. Limitations of VBHC theory in determining value.

9. Tool development

For pharmaceutical suppliers to make BMI decisions based on value, it is critical that they understand what that value is. Value needs to be operationalized. The need for this value assessment is underlined by the fact that chapter 8 revealed that value cannot directly be derived from the CARE-MS II clinical trial endpoints. The second component of the approach must thus be developed: the tool. First, the several specifications required for the design are discussed after which the overall structure and functions of the design are presented. In the final section of this chapter, the design will be used to answer Q4 and Q6.

9.1 Design specifications

The design specifications in this thesis were derived from the empirical research. Additional specifications by the problem owners at Sanofi were included as well. The set of design specifications is structured and formulated in accordance with Van Aken et al. (2007). Table 13 shows the functional requirements and their origin in the research.

Purpose	Sub-solution	Functional requirements	Source
General	1. Tool understructure	The tool is a separate but complementary component to the framework.	Research objective
Input	2. Outcome definition	The tool unites different outcome measures and measurement instruments.	Chapter 8.3, table 12
	3. Outcome integration	The tool incorporates all six tiers to establish value.	Chapter 8.3, table 12
	4. Cost integration	The tool makes a link between outcomes and costs.	Chapter 8.3, table 12
Value assessment	5. Calculation method	The tool is able to combine the different outcomes into unifying value measures.	Chapter 8.3, table 12
	6. Value expression	The tool provides a unit for value.	Chapter 8.3, table 12
Decision support	7. Analysis	The tool can provide a detailed analysis of the different components of a product's value.	Chapter 8.3
	8. BMI suggestions	The tool suggests value-based BMIs that have been developed within the framework.	Research objective

Table 13. Functional requirements of the tool.

Some additional requirements and boundary conditions were formulated by the problem owners at Sanofi. The underlying idea behind these additional specifications is that the tool must within the current business and is universally applicable, as the problem owners intend to use the approach for more products other than Lemtrada® in the future.

User requirements:

- The tool allows for scenario building and modification.
- The tool is widely applicable for a wide array of pharmaceutical products.
- The tool is in line Sanofi employees' current knowledge and capabilities.

Boundary conditions:

- The tool can function independently, no connection to a data-base or internet required.
- The tool can be shared digitally amongst Sanofi employees.
- The tool works for different levels of data-aggregation.

9.2 Morphological analysis

Even with formulated requirements and specifications, the conceptual design of the tool is still undefined. There is a vast amount of options and potential designs that fit the requirements. So how does one make specific design choices when faced with many options and little certainty on which option works best?

A possible solution is to conduct a morphological analysis (MA). A MA is a method for studying multi-dimensional, non-quantifiable complex problems that provides a systematic approach for generating varieties of design. Especially in a situation in which sub-solutions to sub-problems need to be combined, solution analysis with a morphological matrix is suitable (Pahl & Beitz, 2013). The following general steps are involved in the construction of a morphological matrix: (1) listing of the design parameter, (2) listing of the values for each parameter, (3) construction of the matrix, and (4) morphology selection (Evbuomwan, 2013). These four steps will be individually described next.

9.2.1 Listing of parameters

When using a morphological matrix in design decisions, parameters are the individual sub-functions that the design must be able to perform (Pahl & Beitz, 2013). This way, the total design solution is divided into a set of sub-solutions. The required sub-functions for the VBHC tool are dictated by the eight design specifications listed in table 13. These parameters make up the vertical axis.

9.2.2 Listing of values

For each parameter, a range of values must be assigned. Values are possible conditions that each parameter can assume. They are potential sub-designs that can perform the sub-function of a parameter (Pahl & Beitz, 2013). The values that are possible for each parameter are limited by the design specifications of the problem owners. The values are mapped on the vertical axis of the matrix.

9.2.3 Construction of the matrix

By mapping the different parameters and values to a grid, the morphological matrix is realized (Table 14). The chosen values for each parameter are in green and will be addressed in the next section.

		Low	← Technical complexity →		High
Category	Parameter	Value 1	Value 2	Value 3	Value 4
General	1. Tool basis	Text-based framework	Excel model	'R' model	Digital application
Input	2. Outcome definition	Select one core measure	Combine without weights	Combine with open weights	Combine with defined weights
	3. Outcome integration	Separate components	Select on singe core measure	Integration of outcomes	
	4. Cost integration	Manual calculation	Assisted calculation	Automated calculation	
Evaluation	5. Calculation method	Rank order scaling.	Comparison of increase/decrease	Normalization of scores.	Regression of variables
	6. Value expression	Porter's value equation	Porter's outcome tiers	A newly developed unit	
Support	7. Analysis	Single product	Multiple products		
	8. Decision support	BMI matrix with web link	Decision tree with web link	Rules of inference with web link	

Table 14. Morphological matrix.

9.2.4 Morphology selection

A configuration of values for each parameter is known as a morphology. A morphology represents one possible design (consisting of multiple sub-designs). Theoretically, the matrix holds 4×4×3×3×4×3×2×3 morphologies, which means there are 10368 possible solution designs. This thesis only needs one, however. There are three general methods to use the matrix in deciding on a morphology (Pahl & Beitz, 2013; Evbuomwan, 2013).

- Pragmatic; define the morphology by finding the best value for each individual parameter.
- Pre-defined; compare a set of pre-defined morphologies on their different values.
- Cross-consistency; determine a set of feasible morphologies by eliminating all configurations that have inconsistent or incompatible values.

Given the fact that there are no pre-defined or exemplar designs that could be used to compare, the pre-defined approach is not appropriate. The cross-consistency method would probably be the most valid, but is rather complex. With 10368 morphologies, the process would require support from dedicated MA software. This combined with the time frame means that the first approach is preferred.

9.3 The VBHC tool

The eight designed sub-solution for each parameter in table 14 will now be discussed individually.

9.3.1 Parameter: tool basis

The ultimate design takes the form of a dynamic Excel file that can be used on a computer or tablet. A text-based framework was unlikely to be intuitive enough to work with. A more dynamic and guided approach was thus preferred. An application would have been useful, but limited resources and programming skills made this option unfeasible. Eventually it was decided to use Microsoft Excel as the basis for the tool, as most Sanofi employees are proficient with this program and this program works on a tablet, which makes it fit in with the one-device policy at the company. Figure 17 provides an overview of all components of the tool. The remaining three categories and seven parameters of table 14 are also included in the figure to indicate which tool components belong where.

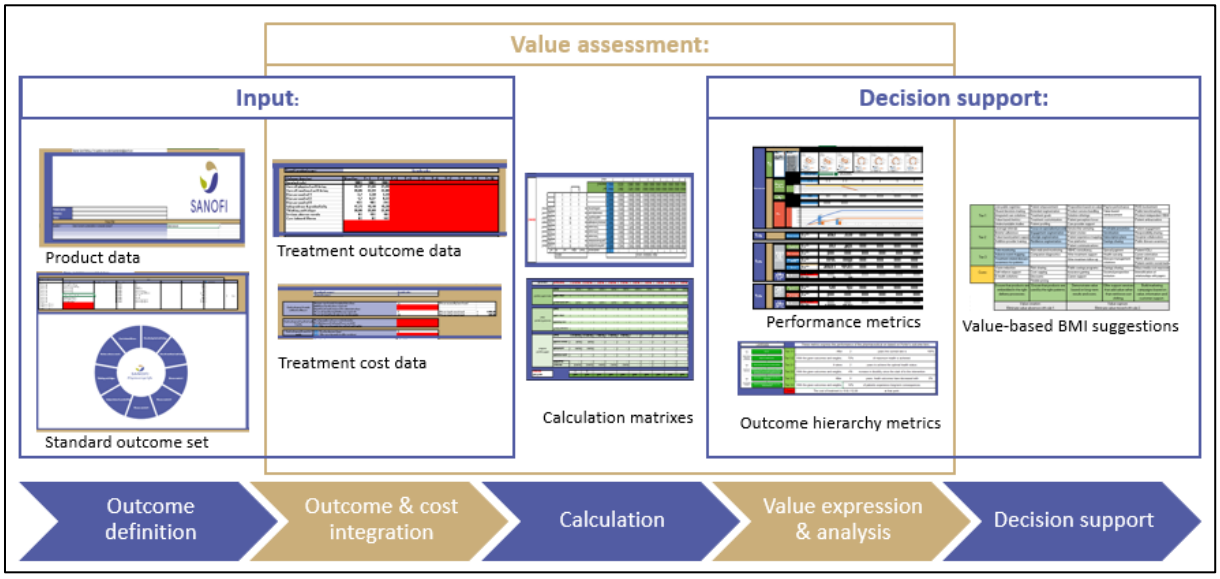

Figure 17. Overview of tool components.

9.3.2 Parameter: outcome definition

The first problem encountered in chapter 8 was the fact that there are multiple independent endpoints measures in the CARE-MS II. ICHOM advocates and supports the development of broad, patient-centric outcome sets, but does not explain how diverse outcome domains can be combined. Since outcomes are inherently condition-specific and multidimensional (Porter, 2010), it was decided to create an open input field in which up to 12 different outcome domains can be added. Different outcome domains hold different significance for different patients, that is why weights can be assigned to each different outcome. This way, patient preference profiles can be created. Because there is no prior data on outcome importance available, the default weight for each domain is set to 1.

9.3.3 Parameter: outcome integration

To determine each outcome domain's contribution to the overall value, the easiest option would be to assign an outcome domain to a tier and subsequentially measure each individual tier. This, however, would split value in different components. Another option would be to determine one core measure that indicates total value. But this conflicts with Porter's ideation. A new method of operationalization of the tiers was developed that would allow for integration. Table 15 describes the basic operationalization of each tier. With this realized, outcome data can simply be inserted into the tool.

Tier	Basic operationalization
1-1: Survival	Death is operationalized as the end of all outcome measurements. It is a meta variable.
1-2: Degree of health	Tier directly measurable through the combined performance on all outcome domains in Tier 1-2.
2-1: Time to recovery	Time-bound tier. Operationalized by measuring how long it takes to achieve the highest combined score on 1-2, 2-2 and 3-2.
2-2: Disutility of care	Tier directly measurable through the combined performance on all outcome domains Tier 2-2. Scores are inversed.
3-1: Sustainability of health	Time-bound tier. After the point defined by 2-1 has been reached, the decrease in health over time is measured.
3-2: Long-term consequences	Tier directly measurable through the combined performance on all outcome domains Tier 3-2. Scores are inversed.

Table 15. Global operationalization of the outcome tiers.

9.3.4 Parameter: cost integration

Even with the guidelines by ZiN, cost calculation is complex and time consuming. Simply referring users of the tool to the ZiN guidelines would discourage use of the tool. Fully automating the cost calculation process is to complex and inhibits scenario building. The middle road was therefore chosen. The guidelines of the ZiN have been condensed into separate components. The tool walks the user through these components by asking questions with pre-specified answers and broad cost estimates. If the user does not know the answer or does not want to include a certain cost aspect, it can be left blank.

9.3.5 Parameter: calculation method

Calculating the value of a product would have been a difficult task whichever option would have been chosen for the outcome definition parameter (9.4.2). However, the fact that the tool allows for the inclusion of multiple outcome domains belonging to multiple tiers made the process even more complex. How does one compare and relate MRI imaging results to patient questionnaires on emotional well-being, for example?

Rank order scaling would be the easiest solution. This method would also allow for large differences in outcomes to go by unnoticed. It was therefore deemed too simplistic to asses value. Comparing increases and decreases from baseline would be a simple and robust method, but the results of such a method of calculation would not be very insightful, as value either goes up or down. Regression analysis on the set of outcome domains might be considered in such situations. However, running these sorts of analyses on data in a healthcare setting without the support of biostatistical experts would be unthinkable. Normalizing the weighted scores thus seemed like the calculation method that would bring the most insightful results within realistic limits.

9.3.6 Parameter: value expression

Even with a method to calculate value, one must still be able to express it in a comprehensible way. VBHC theory provides two options: the value fraction and the outcome tiers, both proposed by Porter (2010). A third option would be to develop a new measure. Since it was feasible from Sanofi's point of view, all three options were explored and realized. The second, however, proved more useful.

Value fraction: Dividing outcomes by cost is useful in explaining and conceptualizing VBHC. Performing the calculation, however, leads to incomprehensibly small numbers with little meaning.

Outcome tiers: Assigning a measurement unit to each outcome tier is useful in demonstrating the total value delivered by a treatment while at the same time allowing for some more detail.

Newly developed unit: To better suit future adoption within Sanofi and the healthcare setting, a new value indicator was developed as well. Normalized data returns an elementary value between 0 and 1. This value resembles the utility value that is used to determine the quality-adjusted life years (QALYs) provided by pharmaceutical treatments. The 'VBHC-QALY' was therefore constructed.

9.3.7 Parameter: analysis

An expression of value should best be accompanied by additional descriptive statistics and analysis tools. An elaborate dashboard was therefore created. This dashboard allows for detailed examination of the product's value in different scenarios. To enhance the usability of the tool for Sanofi, the tool can hold and compare up to four different products at a time. This allows Sanofi to compare draw detailed comparisons of their product with those of competitors.

9.3.8 Parameter: BMI suggestions

The tool's purpose is to operationalize value and to guide the decision-making process on value-based BMIs. To be able to do the latter, a set of value-based BMIs had to be developed. Because the two components of the approach complement each other, the framework was used to develop possible BMI based on VBHC. This time, however, the lower side of the framework was used. These are not validated BMIs derived from empirical observations, but conceivable forms in which the supplier implications by Porter and Teisberg (2006) can be applied to pharmaceutical suppliers.

Of course, not all value-based BMIs are suitable for a certain product. It also would not be feasible to implement all potential BMIs at once. So how does one decide which BMIs are most suitable? Even though it is an essential part of the approach, a rather simplistic suggestion method was chosen. This has been done because the developed value-based BMIs have not been tested in practice yet. It was not deemed feasible to create highly intricate decision trees or inference systems if they lead to unfunded outcomes.

A more open method, in which the tool assesses the value of a product and proposes a set of BMI options, is used. Sanofi employees can then decide which BMI in the suggested set is most suitable. The lower side of the framework, that combines value on the vertical axis with the supplier implications by Porter & Teisberg and the formulated rules on the horizontal axis, creates a field in which value-based BMIs can be explored. The current matrix holds over 60 suggestions for pharmaceutical BM innovation that is based on VBHC. The largest portion is established by applying the supplier implications to the relevant BMs and the knowledge that has been developed so far. Others were derived from business-oriented publications on pharmacy (Ding et al., 2013; Stegemann et al., 214).

Based on the value of a product, the tool will highlight a set of value-based BMIs that technology managers of Lemtrada® can take into consideration (Figure 18). It is difficult to define the suggestions, as they must be specific enough to provide guidance while at the same time being universally applicable to support the use of the approach for a broad set of products. That is why for most value-based BMIs, a web link is added that leads to an exemplar situation of the value-based BMI. This example does not specifically have to be a VBHC initiative, as these are still rare, but should provide a picture of what the managers should be looking for.

Tier 1	Join public registries	Patient empowerment	Proposition based on value	Pay for performance	RWE involvement
	Shared decision-making	Extended segmentation	Product-service bundling	Value-based reimbursement	Public benchmarking
	Integrated care solutions	Treatment goals	Solution offerings		Product-independent VBHC
	Value-based metrics	Treatment customization	Patient perception focus		Patient ambassadors
	Understandable studies	Patient profiling	Care provider support		
Tier 2	Leverage referrals	Focus on specialized providers	Service line venturing	Profitable prevention	Patient engagement
	Bolster adherence	Engagement segmentation	Patient stories	Servitization	Responsibility sharing
	Value-based patient support	Lifestyle segmentation	Patient experience mapping	Subscription plans	Hospital collaboration
	Addition provider training	Resilience segmentation	Peer platforms	Savings sharing	Public disease awareness
			Patient communications		
Tier 3	Tele-monitoring	Risk-indicated monitoring	VBHC consultancy	Spread payment	Patient KOLs
	Adverse event mapping	Companion diagnostics	After-treatment support	Health warranty	Career orientation
	Treatment-related disease awareness for patients		After-treatmen follow-up	Disease management solutions	VBHC alliances
					Patient-centric social media
Costs	Waste reduction	Risk-sharing	Public savings programs	Savings sharing	Mass media cost exposure
	Self-reliance support	Cost capping	Insurance gaming	Societal perspective inclusion	Intensification of relationships with payers
	E-health solutions	Discounts	Career support		
		Flexible pricing			
	Ensure that products are embedded in the right delivery processes.	Ensure that products are used by the right patients.	Demonstrate value based on long-term results and costs.	Offer support services that add value rather than reinforce cost shifting.	Build marketing campaigns based on value, information and customer support.
	Value creation: Eliminate value absence with rule 1.		Value capture: Eliminate value missed with rule 2.		

Figure 18. Screenshot of the value-based BMI matrix in the VBHC tool.

The establishment of a pre-defined matrix of value-based BMIs for the pharmaceutical instrument marks the completion of the tool and therefore the completion of the approach. With both the framework for analysis and a tool that can operationalize value and provide BMI suggestions, the Lemtrada® case can be tackled. The full approach will be applied to the Lemtrada® case in the next chapter.

10. Applying the approach

With the tool developed and functional, both components of the approach are complete. This means that the full approach can be applied to the Lemtrada® case. First, the tool will be used to reassess Lemtrada's® value, as this could not successfully be done in chapter 8. This results in the second required input. With both inputs obtained, the framework will be used to find value absence and value missed in the current BM. Lastly, the decision-support function of the tool is used to find the most appropriate BM innovations.

10.1 Using the tool to determine value

Chapter 9 described the development of a tool that can operationalize value into actual metrics and provide BMIs based on those value metrics. In this section, the tool will be used for the former, in order to provide an answer to Q5a, Q5b and Q5. In that specific order.

10.1.1 An answer to Q5.a

Together with internal domain experts within the MS franchise, a standard set for RRMS was developed by emulating the standard ICHOM protocol on a smaller scale. The process and output structure of this session was validated by an ICHOM core group member (Appendix G) before they were supplemented and validated by a Dutch MS-specialized neurologist and an engaged Dutch patient representative who is also diagnosed with and treated for RRMS. The resulting standard set, together with correlating outcome tiers and a default relative weight of 1 is displayed in table 16. A more extensive description of the process and outcomes can be found in appendix H.

Medical condition:	Relapsing-remitting multiple sclerosis		
	Outcome domains	Weight	Outcome Tier
Outcome 1	Overall physical well-being	1	Tier 2-2
Outcome 2	Overall emotional well-being	1	Tier 2-2
Outcome 3	EDSS score	1	Tier 1-2
Outcome 4	Annual relapse rate	1	Tier 1-2
Outcome 5	Percentage with MRI activity	1	Tier 1-2
Outcome 6	Independence & productivity	1	Tier 1-2
Outcome 7	Thinking and fatigue	1	Tier 1-2
Outcome 8	Serious adverse events	1	Tier 2-2
Outcome 9	Care induced illness	1	Tier 3-2

Table 16. Developed standard set for RRMS.

10.1.2 An answer to Q5.b

Cost specifications defined by ZiN (2016) were obtained from the Lemtrada® cost-minimization study that was performed in the Netherlands and published in the Journal of Medical Economics (Piena et al., 2018). An elaborate cost estimation overview for a ten-year timeframe is provided in appendix I. The estimated total yearly cost is presented below (Table 17). Two comments are in place, however. First, the increase in informal care hours have been excluded from the calculation, since there were no estimates available on informal care consumption. Second, the acquisition costs have been derived from ZiN, which means that discounts given to hospitals are not included in the cost estimations.

Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	Year 8	Year 9	Year 10
€ 42.411,75	€ 25.779,47	€ 8.983,76	€ 5.908,48	€ 3.542,89	€ 835,45	€ 599,61	€ 418,19	€ 309,33	€ 309,33

Table 17. Yearly cost estimates for treating a patient with Lemtrada® in the Netherlands.

10.1.3 An answer to Q5

With all inputs complete, the tool can run the value analysis. Chapter 9.4.6 explained that all three options for value expression in the morphologic were realized. Porter's value equation did not prove to be informative. The 'VBHC-QALY' is an interesting measure as it allows for value-based cost-effectiveness analysis but provides limited detail. It was therefore decided to stick with Porter's outcomes hierarchy. As mentioned in chapter 9.4.3, the outcome tiers have been operationalized. They have also been translated into informative measures as well. Table 18 provides an overview of Lemtrada's® value expressed with Porter's tiers.

Tier 1-1	After	2	years the survival rate is	100%
Tier 1-2	With the given outcomes and weights,	75%	of maximum health is achieved.	
Tier 2-1	It takes	2	years to achieve the optimal health status.	
Tier 2-2	With the given outcomes and weights,	4%	increase in disutility since the start of to the intervention.	
Tier 3-1	After	0	years, healh outcomes have decreased with	0%
Tier 3-2	With the given outcomes and weights,	14%	of patients experience long-term consequences.	
Costs	The cost of treatment is	€ 68.191,23	at that point.	

Table 18. Value of Lemtrada® defined using Porter's outcome tiers.

The tool has only been populated with two years' worth of data. The outcomes would have likely been higher if another timeframe was used, but this cannot be supported at this point in time. The survival rate after 2 years is 100%, which is positive, but not uncommon in MS treatments. The second tier however, shows a high score. The performance on tier 2-1 and 2-2 are not very high. The sustainability of health, however, is very high. The tier 3-2, shows a very troublesome score, however. Around 14% of all Lemtrada® patients in the CARE-MS II dataset experienced negative long-term consequence that are related to the treatment. After two years, the costs of Lemtrada® are €68.191,23. This is relatively high but is known to decrease over time. Because of the high variability of costs over time, the variable will not be included into the value uncaptured analysis, as the results would not be representative.

10.2 Using the framework for BM analysis

With Lemtrada's® value on each tier obtained from Q5 (chapter 8.5.3) and a list of diagnosed problems in the BM elements that where identified in Q4 (chapter 7.6), the inputs for the value-based BMI framework are complete. This means that the input on both axes can be cross-referenced to find value absence and value missed in the framework.

The left side of the framework includes distribution channels and customer segments, the two BM elements in the framework focused on value creation. This side is used to identify value absence. By cross-referencing the conclusions on issues regarding these BM elements on the upper horizontal axis with a low value on the vertical axis, value absence is detected: unrealized value potential that can be materialized by making changes to the BM. Table 19 on the next page shows were value absence is identified in the BM.

The right side of the framework focuses on value capture, and includes the value proposition, revenue model and customer relationships. By cross referencing the conclusions the on issues regarding these three BM elements with high value on the vertical axis, value absence is detected: value that is created but not captured by the supplier. Table 19 shows were value missed is found in the BM.

		Find value absence: value potential that is not realized.		Find value missed: value realized that is not monetized.			
		Distribution channels	Customer segments	Value proposition		Revenue model	Customer relationships
		C4. Value primarily created and delivered to patients, but care providers are the primary distribution channel of value proposition.	**C3.** Value of Lemtrada® primarily created and delivered to patient rather than care provider, but care provider is the key decider.	**C1.** Value delivered by Lemtrada® to patient and society are not perceived as value by care providers.	**C2.** Lemtrada's risk-benefit ratio for care providers is not convincing.	**C6.** Lemtrada® leads to cost savings on long term, but payers utilize a short-term perspective.	**C5.** Lemtrada® is a complex but potent treatment, yet little is known about who receives the treatment.
Tier 1: Outcomes achieved	Tier 1-1: Normal value						
	Tier 1-2: **High value**				**(4) Value missed**		**(6) Value missed**
Tier 2: Recovery and disutility	Tier 2-1: Normal value						
	Tier 2-2: Normal value						
Tier 3: Sustainability of health	Tier 3-1: **High value**			**(3) Value missed**		**(5) Value missed**	
	Tier 3-2: **Low value**	**(1) Values absence**	**(2) Value absence**				
Costs	Excluded						

Table 19. Cross referencing the framework inputs to find value absence and value missed.

By applying the framework to the Lemtrada® case, table 19 revealed six areas of value uncaptured in the BM: two cases of value absence and four cases of value missed. The red and orange cells have been numbered. To further substantiate the found value uncaptured, each of the six areas of value uncaptured is supported with an interview quote. Table 20 holds the numbered cells of the found form of value uncaptured, the two inputs that were cross-referenced to find it and a quote from an interview participant.

Value uncaptured		Supporting quote
(1) Value absence		"At the [hospital] in [city], I have had this happen three times already, the patient tells the physician 'I want Lemtrada'. And the physician still sells the patient on something else, so they do not have to start with Lemtrada and initiate that trajectory, as they are afraid of thyroid conditions" (HAM).
Input 1:	**Input 2:**	
C4.	**Low value on Tier 3-2**	
(2) Value absence		"The benefit-risk ratio is best for patient who are treated in an early stadium. Also, because they better endure the adverse events. … But it makes sense that physicians prescribe Lemtrada to patients when they know 'this patient is doing so miserable, what do I have to lose?" (PM).
Input 1:	**Input 2:**	
C3.	**Low value on Tier 3-2**	
(3) Value Missed		"It is regarded as the most effective treatment, and the non-chronic treatment structure is also known by most. But often, the translation to what that means to the patient is not entirely clear to them. … You get your normal life back, and there is even the chance of functional improvement. And that proposition should be sitting more top-of mind with neurologists. Not just the efficacy, but also 'what does that mean for my patients?' KAM).
Input 1:	**Input 2:**	
C1.	**High value on Tier 3-1**	
(4) Value Missed		"That is when the risk profile makes an appearance. And it is ill suited to the physicians' needs. … It makes neurologists more cautious, especially since their own reputation is involved. Sometimes even more than the patient's interests" (PM).
Input 1:	**Input 2:**	
C2.	**High value on tier 1-2**	
(5) Value Missed		"They [Zorginstituut Nederland] have never seen the necessity of reviewing the cost-effectiveness of Lemtrada. … Personally, I would not have minded if they did research the cost-effectiveness, because it is a solid case. And until that happens, it will just be one's opinion against the other's" (MA).
Input 1:	**Input 2:**	
C6.	**High value on Tier 3-1**	
(6) Value Missed		"You are never able to directly ask the patient about his experience. Which always means that it is filtered. … Sometimes we ask the hospital to document the patient's experience, but they indicate that they don't have time for that. Maybe because we do not always ask that proactively. … I do see it as a limitation, especially since patients do discuss it amongst each other. Sometimes positive, sometimes negative. But often so with stories that are just erroneous or false." (KAM).
Input 1:	**Input 2:**	
C5.	**High value on Tier 1-2**	

Table 20. Supporting interview quotes for the identified value absence and value missed.

10.3 Using the tool for BM innovation

With value absence and value missed identified in the framework, the approach can be concluded by using the tool to address the problems. As mentioned in chapter 9.4.8, the tool provides a more open suggestion for BMI innovation to leave a little more freedom to the decision-maker.

10.3.1 An answer to Q6

The last sub-question of this thesis is 'which innovations should be implemented in Lemtrada's® BM to increase BM effectiveness?'. With the aid of the tool, the following six BM innovations are suggested to deal with the identified areas of value uncaptured (Table 21).

(1) Value absence: adverse event mapping
While the large majority of treatment-induced illnesses is treatable and well-manageable, the thought of giving patients an additional condition poses a huge barrier for Lemtrada prescription to care providers. Especially since many of these conditions are outside of the expertise of MS care providers. Sanofi should map the entire care delivery process and patient journey of those who receive treatment for these kinds of negative consequences. This might seem counterintuitive at first, but by documenting what these patients are going through, and how they are treaded for their conditions, Sanofi can take away the anxiety and 'fear for the unknown' from care providers that overrate the risks of Lemtrada treatment.
(2) Value absence: companion diagnostics
Developing and running companion diagnostics could improve the results from risk stratification based on a patient's own biology, thereby assisting in the selection of suitable patients and providing better insights into treatment risk factors. Companion diagnostics are complex, and often expensive, but can also lead to cost savings via better informed treatment decisions.
(3) Value Missed: after-treatment follow-up
Sanofi should create a clear overview of Lemtrada® benefits that occur after or outside of treatment. Real-world evidence on quality of life, employment and annual healthcare spending could be used to open the eyes of physicians that are normally only involved with MRI scans and relapse rates. A side-to-side comparison with competitors could also be made.
(4) Value Missed: proposition based on value
Currently, Lemtrada's® proposition is focused on efficacy. While this might be the most important factor from a rational point of view, emotional decision-making and the risks associated with Lemtrada® treatment lead to a perceived trade-off. By redesigning the value proposition around value, a 'total package' proposition can be employed rather 'benefits vs risk'. Lemtrada's® low financial strain and solid outcomes can be explicitly translated to care provider value with a value offer that takes the emphasis away from the associated risks without hiding or dismissing them.
(5) Value Missed: spread payment plans
To better suit the yearly budgets of hospitals and Dutch reimbursement practices, Sanofi should offer the option to split the cost of the vials over several years rather than lump-sum purchases. Such a solution will reduce Lemtrada's® strain on the yearly budget without the additional effort of legal complexities and measurement efforts of performance-based contracts.
(6) Value Missed: patient ambassadors
The first Lemtrada® patients in the Netherlands are now finishing their four years of mandatory monitoring, thereby marking the end of their active MS treatment. A third party should approach these patients to document their experience from start to end. This would bring physical clarity to Lemtrada's® positive effects on cognitive performance, career path and family life, but also to what it is like to receive additional treatment for a care-induced illness. Detailed and complete patient roadmaps that demonstrate both the positive and negative aspects can provide potential patients with the confidence to start the five-year Lemtrada® program while at the same time providing Sanofi with valuable patient insights.

Table 21. Suggested value-based BMIs to address value absence and value missed in Lemtrada's® BM.

11. Discussion

The final chapter of this thesis concludes Van Aken's (1994) reflective cycle. First, an answer to the central research question is provided. The separate sub-questions will not be discussed, since they have been answered in previous chapters. With the research question answered, two short sections are dedicated to the preliminary implementation and evaluation of the solution that were not included in the main text. After that, the research limitations and theoretical and managerial implications are discussed. The chapter is concluded with recommendations for future research.

11.1 Answering the research question

The central research question posed in this thesis was:

"How can value-based healthcare be used to innovate pharmaceutical business models?"

It is evident that the golden age of pharmacy is over. Developing and launching new technologies is no longer enough to achieve commercial performance as the demands of patients and care providers are escalating and national healthcare systems are succumbing to the rising costs. Pharmaceutical companies must take leave of the old blockbuster model in favor of more solution-centered BMs that provide value to a broader spectrum of stakeholders.

Value-based healthcare provides a novel and effective viewpoint for such efforts. It allows pharmaceutical suppliers to analyze and present their products in a completely new manner that better suits the changing market environment, while still being heavily supported by data and evidence. It also opens opportunities through which pharmaceutical companies can make innovative alterations and improvements to different components of their BMs benefit the patient, the payers and the business. The fact that it is currently prominent in healthcare policy and not yet embodied in the dominant logic of pharmaceutical firms adds to the allure of the opportunity and the urgency to start incorporating VBHC in the BM.

To provide insights on how pharmaceutical companies can use VBHC to innovate their BMs, a new approach has been developed. This approach consists of two separate but complementary components: a framework for value-based BMI and a digital VBHC tool.

Two literature reviews, one on BMs and BMI the other on VBHC, were performed to develop an understanding of the topics and to find suitable theoretical frameworks for analysis and BMI development. The two fields were then united through a comparison on overlaps, consolidation of differences and the introduction of the concept value uncaptured. The result is a framework for value-based BMI that serves two purposes: the upper side can be used to analyze BMs while the lower side can guide the development of BMIs.

Data from interviews and the CARE-MS clinical trial were obtained to serve as the two inputs for this framework. Analysis of both revealed that value cannot directly be extracted from the CARE-MS II data. In order to solve this problem, the VBHC should not only provide decision-support based on value but would have to be able to operationalize value as well.

The tool development process combined the developed theoretical knowledge with the design specifications dictated by the research findings and problem owners. A morphological matrix was used to record design options and decisions. The result of the design process is the 'Sanofi Digital VBHC Tool', a dynamic Excel tool that can both operationalize value and support BMI decision-making.

With both components realized and the value operationalization problem solved, the newly developed approach could be fully applied to the research case. An internally developed set for RRMS, CARE-MS II outcome data and Lemtrada® cost estimates were inserted into the tool to assess Lemtrada's® value.

With both inputs available, the framework was used to find value absence and value missed in the current BM. To address these value capture problems, the tool was consulted. Ultimately, six pharmaceutical BM innovations based on VBHC provided by the tool are suggested to be implemented by Sanofi.

The approach that emerged from this research process is more extended than was expected beforehand. The problems in extracting value from the CARE-MS II data and the resulting additional tool requirements added an extra component to the research objective. The diagram of the resulting approach (Figure 19) therefore is an expanded version of figure 5 in chapter 2.2.

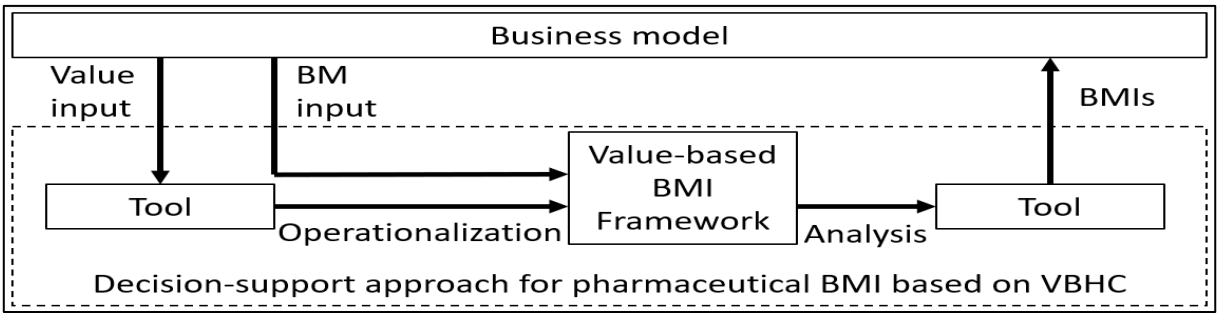

Figure 19. An approach for pharmaceutical BMI based on VBHC.

The first step of the approach for any firm wishing to engage in BMI is to define the current BM and identify issues in the five value-oriented BM elements to provide the first input for the framework. Once this has been done, the technology managers assess the value provided by a product in VBHC metrics. This entails three sub-steps:

1. Obtaining or developing a standard set for the medical condition that the product treats.
2. Acquiring outcome data that fits the outcome domains of that standard set.
3. Acquiring cost estimates that fit in with the guidelines of the authorities.

Once companies have obtained insight in their product's BM and patient value, they can start searching the BM for wasted value capture potential in the form of value absence and value missed. When uncaptured is found in the BM, the VBHC tool can be consulted to obtain a proposed set of new pharmaceutical BMIs grounded in VBHC principles and practices to address the problem. Once the selected BMIs are implemented, the entire process can be repeated. This way, value-based BMI becomes a continuous process rather than a stand-alone project

With a value-based framework of analysis for pharmaceutical BMs and a tool that can operationalize patient value and suggest value-based BMIs, pharmaceutical companies can use the concept of VBHC to drive BM innovation that leads to more effective value creation, delivery and capture for all stakeholders involved in the healthcare system.

11.2 Preliminary implementation and evaluation

In a typical case study that follows the reflective cycle, the created design is practically implemented in the case context. The implementation is then evaluated to assess its impact on the overarching business problem. Due to practical and time-bound restraints, this thesis research only performed the implementation and evaluation steps to a limited extent. While their roles in this research might be too thin to warrant a chapter in the main text, they do carry some interesting insights and implications that are worth mentioning.

11.2.1 Implementation

Even though the value-based BMIs remain a suggestion, the created design in the form of the framework and tool have been used to the full extent, signaling that the approach can successfully be applied in a practical setting. Together with the global access and Lemtrada biostatics team, a new initiative has been started aimed at obtaining 7 years' worth of data for Lemtrada®. Once this data is obtained, the implementation of the first suggested value-based BMI can be explored: a proposition based on value towards care providers and payers.

11.2.2 Evaluation

The final version of the approach was presented and compared to the design specifications that were dictated by the problem owners. Unfortunately, only one of the two original problem owners still was with the company at the end of the project. After going through the results, the remaining problem owner expressed contentment for the solution by signing off on the initial requirements document. Thereby indicating that all specifications have been met to a satisfying degree.

The contentment of the remaining problem owner led to a campaign in which the development results were presented to other Sanofi branches outside of the MS franchise. These sessions were used as additional evaluation moments for ascertaining the intention to use and collecting additional feedback and suggestions. Table 22 contains the addressed branches and responses. The approach was primarily met with positive reactions. It is planned to be fully implemented in three more franchises and to be adopted by the market access team for potential use in reimbursement and price negotiations and re-negotiations.

Branch	Outcome
Business operations & support	VBHC tool to be used as promotional vehicle.
Market access	Implementation initiated.
Finance	No practical application at his point in time.
Primary care	Implementation initiated.
Oncology	Implementation initiated.
Immunology	Implementation confirmed, not yet initiated.
Rare disease	No practical application at his point in time.

Table 22. Overview of internal campaign.

11.3 Research limitations

Serious effort and consciousness have been taken during the research and design processes to safeguard the research's integrity and quality. The standard limitations of case research nevertheless apply to this research, as well as some additional limitations that were revealed in the reflection process. While these bear legitimate limitations of the research, efforts have been made to reduce their impact on the thesis's relevance.

11.3.1 Limited generalizability of the research

The use of VBHC for effective pharmaceutical BMI has only been researched in a single case instance: Lemtrada®. In this specific case VBHC was deemed to be a promising concept for BMI. Other pharmaceutical products or companies might not benefit from innovating the BM with VBHC in the same manner, or might not benefit at all. To enhance the generalizability of the research findings and design, both the framework and tool were generically designed as to ensure that it can be used in a wider variety of contexts beyond the Lemtrada® case.

11.3.2 Validation of the standard set

Due to practical and budgetary restraints surrounding this thesis research, the ICHOM standard set development protocol had to be deviated from. The globally distributed surveys for VBHC experts, patients and physicians used by ICHOM were replaced with interviews. While these allowed for increased depth and revealed some interesting and helpful insights, the input from single respondents cannot be considered truly representative. That is why, for now, the input of these respondents is only used to assess the completeness of the set. Outcome magnitude preferences were not translated into the tool's analysis, as described in chapter 9.4.2. In future efforts, Sanofi might utilize its resources and extensive network to not only validate the outcome domains, but also gather outcome weighting preferences.

11.3.3 Preliminary implementation of BMI suggestions

The implementation of the solution is suspended at the point in which BMIs provided by the tool are suggested. For practical reasons, actual implementation of the proposed BMIs is beyond the scope of this thesis. While practical employment of (some of) the BMIs is currently being contemplated, it is unfortunate that the actual implementation and performance impact of the suggested value-based BMIs could not be put to the test. Practical implementation could have resulted in new and more specific design principles for value-based BMI in the pharmaceutical sector and could have contributed much to the calibration of the decision-support mechanisms.

11.3.4 Preliminary evaluation of the approach

The inability to perform a pre-test combined with the fact that one of the two involved problem owners left the organization halfway through the project made it difficult to perform a dependable evaluation. The design requirements were met, but these are only an indication of a minimum level of success. The remaining problem owner's satisfaction is highly subjective and is likely to be affected by the fact that this person was involved in the project himself. The internal presentation campaign initiated to measure the organization's intention to make use of the approach is an appreciated addition but lacks the potential to reveal shortcomings and future lessons. Hopefully, future application of the approach within Sanofi can lead to the identification of flaws and potential improvements.

11.4 Theoretical implications

The business problem described in chapter 2 was tackled via the consolidation of the theoretical fields of BMs and VBHC. As a result, theoretical implications have emerged for both.

11.4.1 Implications for the field of business model theory

Scholars have pointed out that current pharmaceutical BMs are out of touch with changes incurring in the healthcare landscape (Ding et al., 2013; Capo et al., 2014; Dierks et al., 2016). For pharmaceutical companies to remain successful, they must focus on justifying the value of newly developed products to healthcare payers and providers (EIU, 2012; Stegemann et al., 2014), and the individual patient in particular (Ding et al., 2013).

First and foremost, this thesis has elaborated current BM and BMI theory through the introduction of a new concept in the form of VBHC. Thereby providing a much-needed guiding theory for value-based BMI in the industry. By establishing common ground and reconciling conflicting interests, the first steps have been made in establishing VBHC for the supplying side of the equation.

In addition, this research has brought forward an approach for pharmaceutical BM innovation based on VBHC. The first component of this approach is a new framework for pharmaceutical companies to analyze their current BMs and to innovate them with VBHC initiatives. This framework was successfully applied to examine the case of Sanofi's Lemtrada® product and make substantiated suggestions for BMIs, which means that the framework has passed an initial test of validity and research applicability.

The second component makes a contribution to BM(I) theory by proposing a set of newly developed value-based BMIs that can help companies in the pharmaceutical sector seize the market opportunity created by the rise of VBHC in healthcare systems. This research has provided an initial insight on how BM and VBHC interests can be united in a way that is beneficial to all relevant stakeholders.

11.4.2 Implications for the field of value-based healthcare

Theoretical implications for the field of value-based healthcare have also emerged. Many conceptual issues and theoretical gaps still exist (Mkanta et al., 2016; Raspe, 2018). They lead to discussions on what can be regarded as 'real' VBHC and impede the successful integration of VBHC and the advantages it promises.

The most significant contribution made to the field of VBHC is the operationalization of the value concept. This quantitative interpretation and analytical approach should be regarded as a true novelty in a field that is currently still planted in conceptual abstraction. This step not only progresses VBHC from the ideological to the measurable, but also creates a common language through which care providers, payers, patients and pharmaceutical suppliers can engage in meaningful discussion and policy that accelerate the shift towards VBHC.

The second contribution to VBHC stems from the perspective of the pharmaceutical company that this thesis takes. Until now, VBHC has almost exclusively been examined from the perspective of the care providers. By adopting the much-ignored viewpoint of a supplier some early direction is provided to the role that this essential party will play in the evolution towards value-based care.

11.5 Managerial implications

The primary managerial implication of this research stems from the developed framework consisting of the value-based BMI framework and the VBHC tool. Technology managers who are interested in reaping the opportunity created by VBHC are no longer limited to 'talking the talk' but are also able to 'walk the walk'. The managerial implications of the research can be broadly captured in four domains.

First, technology managers have been provided with an instrument that helps them to better understand the true impact that the existing portfolio has on the life the patients who receive treatment. More effort should be invested in development of a deeper understanding of what the treatments that these companies provide can actually mean for a patient, aside from global efficacy figures and safety data.

Second, the value-based approach for assessing and expressing the value has opened new possibilities in market access processes like approval, and more importantly, reimbursement. With the developed tools, insights and framework, these increasingly difficult procedures can be supported from a VBHC perspective that many care providers and insurance companies have already adopted.

Third, the understanding that is developed and captured by the research should also be employed in marketing activities for the existing product portfolio. The concept of value can be used as novel means to communicate a product's benefits and to justify its price. Treatments that show superior patient value or that incorporate value-based elements in their BM can capitalize on the current popularity of VBHC with payers, policy makers and care providers.

Finally, demonstrating serious engagement in VBHC should function as a starting point for dialogue with other parties in the healthcare system. Pharmaceutical companies should drop their wait-and-see attitude and proactively contribute to the shift towards VBHC, as it is in their own interest. While VBHC is still in its early stages, commitment to VBHC projects can be used to demonstrate good will and competence to other parties and might lead to new partnerships.

11.6 Future research directions

The suggestions for future research predominantly stem from the research limitations described in chapter 11.4. First of all, it would be interesting to see how the proposed value-based BMIs affect the BM effectiveness, as this research did not see them implemented in practice. Doing so might reveal new BM aspects that should be taken into the decision-making process. Additionally, it would be interesting to study what kind of products or market environments are more suitable for VBHC and how pharmaceutical suppliers can use this in their own advantage as well as the advantage of patients, care providers and payers.

Lastly, it is my believe that further exploring the quantitative approach towards VBHC can reveal incredible new insights that can benefit the bottom line of pharmaceutical companies as well as the overall quality of care. The VBHC tool opens a range of new possibilities for systematic VBHC research. Examples are the comparison of patient value for different kind of patient architypes, the performance of value-based cost-effectiveness analysis with the VBHC-QALY and the comparison of value between treatment alternatives.

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Appendices

Appendix A. Case of Lemtrada®

A-1. Introduction

Lemtrada is an innovative prescription infusion medicine used to treat adults with relapse-remitting multiple sclerosis (RRMS). It was approved for MS treatment by the European Medicines Agency in 2013, meaning that it can be marketed and prescribed since that year. The primary working compound in Lemtrada is known as alemtuzumab, which is a humanized anti-CD52 IgG1 monoclonal antibody that depletes CD52-expressing cells from the circulation. In non-medical terms, Lemtrada® depletes the aggressive T and B cells of the immune system that are damaging the brain. After depletion, the cells are repopulated in a more balanced arrangement with the regulative cells. This effectively 'resets' the immune system, thereby restraining the disease. An illustration that exemplifies this mechanism is provided in figure 2. This process provides an explanation, at least in part, for the sustained disability improvements in alemtuzumab-treated patients (Jones et al., 2010). At the current moment, Sanofi is the only party allowed to market alemtuzumab for MS treatment.

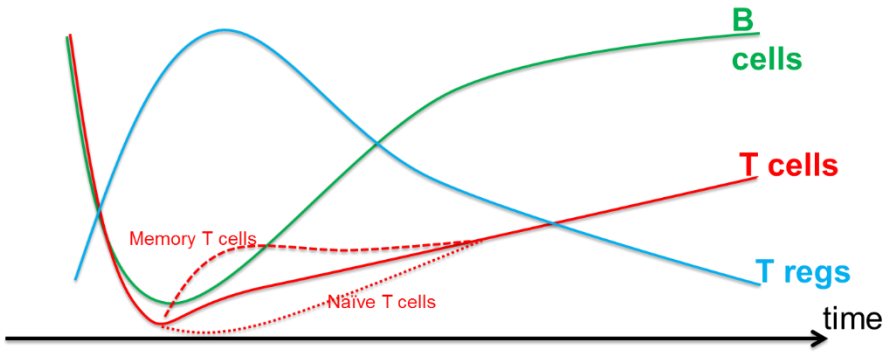

Figure 1. Depletion and repopulation of T and B cells.

A-2. Multiple Sclerosis

Multiple Sclerosis is a chronic neurological disorder and is the leading cause of disability in young adults in developed countries (Nederlandse Vereniging voor Neurologie, 2012). In the Netherlands, MS occurs in 1 person per 1000 inhabitants (Nederlandse Vereniging voor Neurologie, 2012). Of all MS cases, 80-90% start in the form of relapsing-remitting multiple sclerosis (RRMS), which is characterized by episodes of clearly defined attacks of new or increasing neurologic symptoms known as relapses, followed by partial or complete recovery (Zorginstituut Nederland, 2015). A visual representation of the development of the disease is presented (in Dutch) in figure 3. The figure shows how residual levels of impairment permanently remain after each relapse. Early, effective treatment can prevent irreversible increase in disability and progression of the disease.

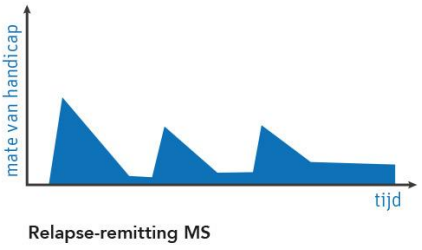

Figure 2. Progression of RR-MS. (LevenmetMS.nl).

A-3. Clinical value

Lemtrada® is a prescription infusion medicine currently available and reimbursed in the Dutch healthcare system. It is categorized as a disease-modifying therapy (DMT) and is generally given in second-line treatment, when earlier (lower-risk) treatment has provided unsatisfactory results. Based on reviews on quality, safety and efficacy, the risk-benefit balance of Lemtrada in the treatment of adult patients with relapsing remitting multiple sclerosis has been deemed favorable by the European Medicines Agency in 2013. Lemtrada® is recommended as a treatment option by the National Institute for Health and Care Excellence (2014) and Zorginstituut Nederland (2015).

Lemtrada® significantly reduces the relapse-rate as well as the risk of disability for RRMS patients in comparison with both placebo and first-line DMT treatment (NICE, 2014). In addition to high efficacy rates, clinical studies on patients treated with Lemtrada have even suggested reversal of pre-existing disability (EMA, 2013). This improvement of pre-existent disability has later been supported with Class I (topmost-level) evidence (Giovannoni et al., 2016). Long-term (eight year) data shows that 70% to 78% of the included patients had stable or improved disability scores (Comi et al, 2018; Singer et al., 2018).

Like most second-line RRMS treatments, Lemtrada® has a higher risk profile than first-line treatments. The major adverse effects of Lemtrada® treatment are the development of secondary autoimmune disorders, with one-third of all treated patients developing thyroid disorders and less than 1% of all treated patients developing immune thrombocytopenia or nephropathy (Lemtrada® therapy guide, 2014). These adverse effects, however, are detectable and manageable with proper monitoring (Gonzáles et al., 2017). Nevertheless, the high risk – high efficacy characteristics of Lemtra® have resulted in physicians reserving Lemtrada® treatment for situations in which earlier treatment(s) did not provide satisfying results. Postponing effective treatment is not without risks however, since relapses and disease activity occurring in the meantime will often result in an irreversible increase in disability.

A-4. Cost effectiveness

Like several other RRMS treatments, Lemtrada® is administered through an infusion. Unlike other RRMS treatments, Lemtrada® is only administered in two short treatment series, with one recovery period in between. As revealed by the latest summarizing article on the CARE-MS II clinical study (Alroughani et al, 2018), most patients will only receive these first two treatments, after which no more treatment is deemed necessary. A fragment of the treated patients might receive additional treatments in consecutive years (Figure 4). The most common reasons for additional treatment are: relapses, MRI activity or both relapses and MRI activity. Table 1 provides an overview of the amount of additional treatments that patients have received in clinical trials.

Figure 3. Lemtrada® administration scheme.

Number of additional Lemtrada® treatments	% of patients in CARE-MS II trial
1 additional treatment	29 %
2 additional treatments	16 %
>2 additional treatments	6 %

Table 1. Additional Lemtrada® treatments given in CARE-MS II trial study.

The uncommon treatment structure inherent to Lemtrada® treatment results in a similarly unusual cost structure for MS treatment standards, where in the first years of treatment costs are high. After this period, no more treatment is performed, which drastically reduces cost. This is in stark contrast to competing first-line and second-line RRMS pharmaceutical treatments, where perpetual treatment is given until the disease progresses from RRMS into a more severe stadium. Not only has Lemtrada® been deemed cost effective and therefore appropriate for reimbursement (Zorginstituut Nederland, 2016), cost-effectiveness analyses have shown that Lemtrada® dominates comparators using a 5-year horizon (Piena et al., 2018), a predictive 20-year horizon (Chirikov et al., 2019) and the QALY-standard (NICE, 2014; Hartung, 2017). While this might seem as a strong value proposition at first glance, contemporary costing and reimbursement policies make this cost-effective pharmaceutical RRMS treatment unappealing to hospitals and pharmacists. The main reasons being the annual budgeting system and the differentiation between intramural and extramural medication in the Dutch healthcare system. Short-sighted and inflexible policy inhibits the adoption of pharmaceuticals with innovative treatment and costing characteristics, and reinforce unsustainable medical and financial actions by doing so.

A-5. Potential of VBHC for Lemtrada®

Whether or not VBHC will prove to be the much needed solution to world-wide quality and financial sustainability issues in healthcare remains unclear, and will only become apparent over time. And while the rise of VBHC in healthcare policy could be perceived as a threat for pharmaceutical companies (Larsson et al., 2015), this certainly does not need to be the case per se. A broader perspective on, and definition of, patient outcomes combined with a long-term orientation might facilitate the adoption of Lemtrada® within the Dutch healthcare system. Especially since the short-sighted reimbursement system and the inconsistent risk-benefit perception of Dutch physicians are suspected to be the cause of the limited adoption of the treatment in the Netherlands. Lemtrada's® high efficacy, potential to curtail the progression of disability and low financial strain in the long-term seem well-suited for the vision of VBHC. On the next page, a figure is presented that illustrates how widespread Lemtrada® application can facilitate in achieving three different objectives: a public objective (reducing the financial burden of MS treatment in Dutch healthcare spending, a societal objective (reducing the number of Dutch RRMS patients that are in need of treatment), and a private objective (increasing the sales of Lemtrada® for Sanofi Genzyme in the Netherlands).

A-6. Potential of VBHC for Lemtrada®

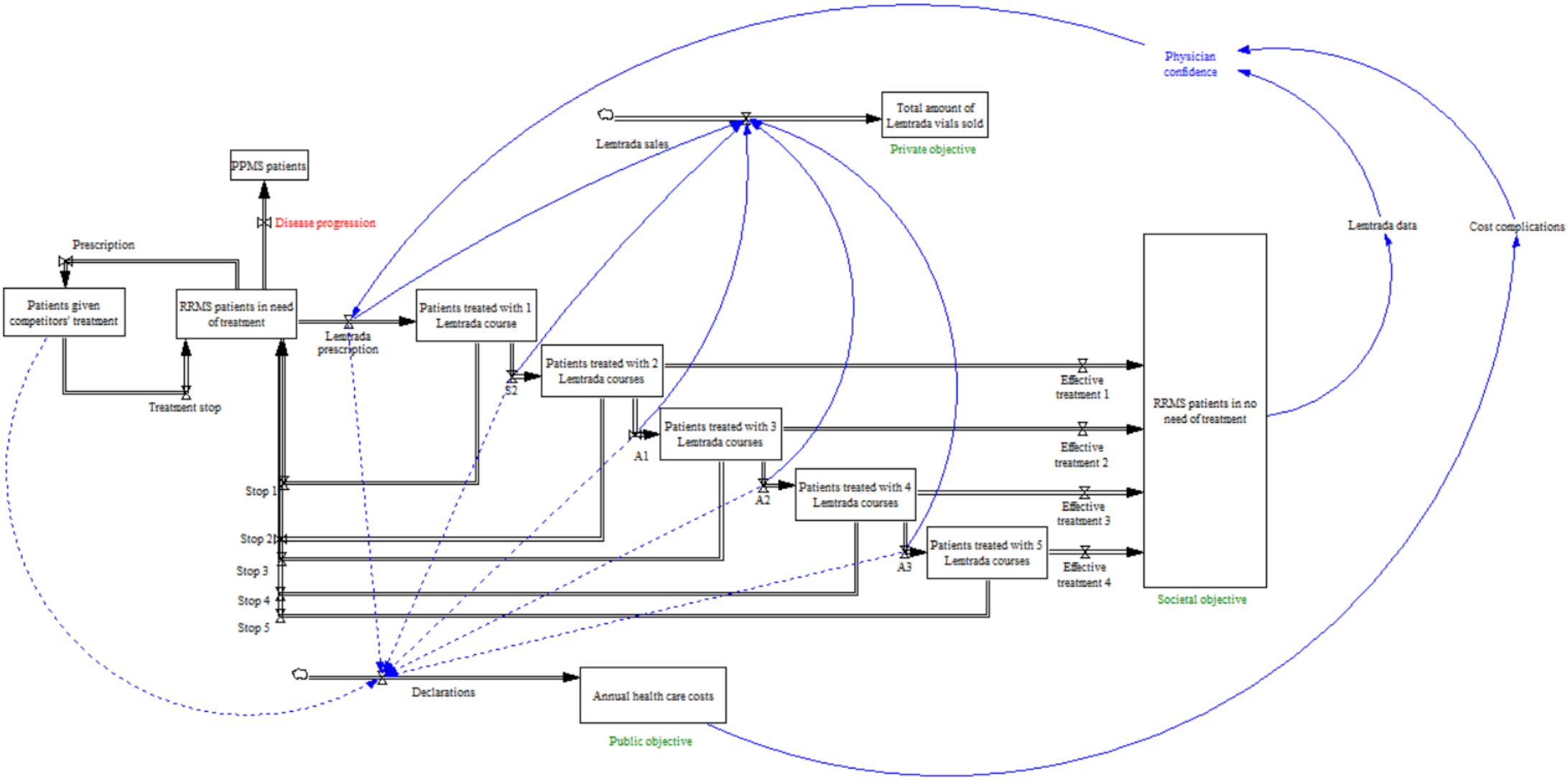

Figure 4. Potential benefits of increased Lemtrada® prescription.

A-7. References

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Appendix B. ICHOM literature study

In many cases, ICHOM combines the publication of a standard set with the publication of an article that describes the development process. These publications have been analyzed in order to synthesize a method and framework for standard set development. As of this moment, fourteen articles have been published.

B-1. List of reviewed ICHOM articles

	Authors	Title
1	Morgans et al., (2015).	Development of a Standardized Set of Patient-centered Outcomes for Advanced Prostate Cancer: An International Effort for a Unified Approach.
2	Clement et al., (2015).	A proposed set of metrics for standardized outcome reporting in the management of low back pain.
3	Salinas et al., (2015).	An International Standard Set of Patient-Centered Outcome Measures After Stroke.
4	McNamara et al., (2015).	Standardized Outcome Measurement for Patients With Coronary Artery Disease: Consensus From the International Consortium for Health Outcomes Measurement
5	Mahmud et al., (2015).	A Proposed Minimum Standard Set of Outcome Measures for Cataract Surgery.
6	Allori et al., (2016).	A Standard Set of Outcome Measures for the Comprehensive Appraisal of Cleft Care.
7	Rolfson et al., (2016).	Defining an International Standard Set of Outcome Measures for Patients With Hip or Knee Osteoarthritis: Consensus of the International Consortium for Health Outcomes Measurement Hip and Knee Osteoarthritis Working Group.
8	Rodrigues et al., (2016).	Defining a Minimum Set of Standardized Patient-centered Outcome Measures for Macular Degeneration.
9	De Roos et al., (2017).	A Consensus Set of Outcomes for Parkinson's Disease from the International Consortium for Health Outcomes Measurement.
10	Martin et al., (2017).	Defining a Standard Set of Patient-centered Outcomes for Men with Localized Prostate Cancer.
11	Ong et al., (2017).	A Standard Set of Value-Based Patient-Centered Outcomes for Breast Cancer The International Consortium for Health Outcomes Measurement (ICHOM) Initiative
12	Zarillo et al., (2017).	An International Collaborative Standardizing a Comprehensive Patient-Centered Outcomes Measurement Set for Colorectal Cancer.
13	Oude Voshaar et al., (2018).	The International Consortium for Health Outcome Measurement (ICHOM) Set of Outcomes that Matter to People Living with Inflammatory Arthritis.
14	Akpan et al., (2018).	Standard set of health outcome measures for older persons.

B-2. General composition of an ICHOM publication

It is advantageous that the ICHOM utilizes standard guidelines for both the creation of the sets and reporting on the process. On their website, ICHOM provides additional documentation on their processes. The following characteristics of were present in all 14 publications as well as the additional content.

Concept:	Details:
Background	The relevant medical condition poses a significant burden on patients and the healthcare system. However, no internationally acknowledged universal set of outcome measures has been defined, which complicates outcome measurement and comparison. Thereby limiting the implementation of value-based healthcare.
Objective	To develop a global minimum standard set of outcomes relevant for a certain medical condition (or group of conditions) with the aim to facilitate monitoring, comparing and improving health outcomes that matter to patients.
Standard set components	The resulting standard set entails recommendations on the following components: 1. **Outcomes:** The patient-centered outcomes that represent true success in managing the specified medical condition. 2. **Case-mix variables:** Factors that will affect the outcomes above, but which we cannot control as part of management of the condition. We measure these to build risk-adjustment models that ensure fair comparison of outcomes. 3. **Measurement tools:** Scientifically validated instruments that are used to measure the outcomes and case-mix variables. 4. **Data sources:** These can be administrative, clinician-reported or patient-reported. 5. **Time points:** Specified time points for data collection
Method	A modified Delphi method is used in combination with teleconferences to reach consensus. The set is developed in 6 to 8 sessions. During the voting sessions, the inclusion cut-off point is determined at variably 67% or 70%, depending on the work group.
Process	In general, the following process is employed: 1. **Initial literature study and concept development:** The leading project group assembles a set of potentially relevant items (i.e. conditions/domains/time points/risk-adjustment variables) that are identified in a series of literature reviews and/expert consultation. 2. **Refinement by domain experts:** During the conference calls, these items are discusses and expanded on or revised based on the input of the different domain experts within the full working group. 3. **Validation by patients and healthcare professionals:** Patients are asked to rate the importance of the outcomes selected by the work group. Healthcare professionals are asked to rate the relevance of the domains, the feasibility of implementation and te appropriateness of risk-adjustment and time points for assessment. 4. **Open review:** Representatives from key stakeholders are invited to participate in the open review for additional feedback.

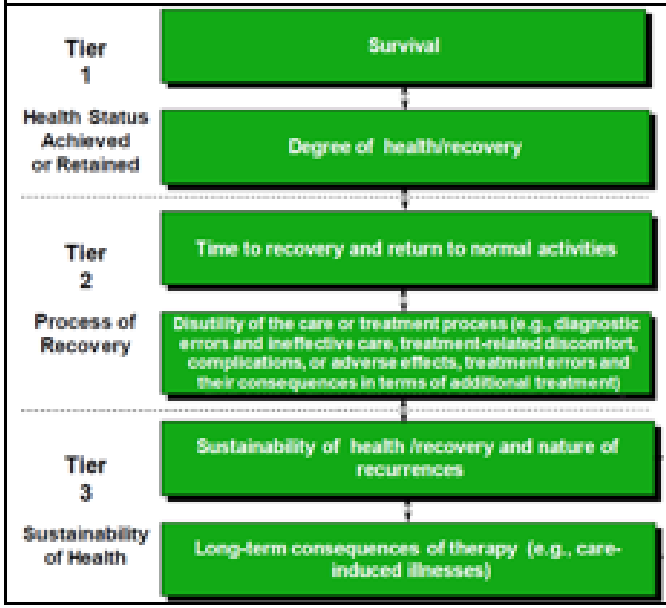
B-3. Characteristics per publication

Fortunately, the standard set development process has been standardized to a fair extent. The same holds for the reporting style of the publication. Sadly, not all articles share the same length or depth. Articles ranged from 7 to 28 pages. Some included additional documentation such as the voting outcomes, meeting notes, detailed participant descriptions, complete list of selected outcome and case-mix items. It could be the case that the characteristic belongs to that process, but that it simply was not included in the publication.

Standard set components	Relevant criteria	Details	Present in articles:
1. Outcomes	Outcome selection criteria	The Working Group selected outcomes based on 4 criteria: (1) the frequency of the outcome; (2) its impact on the patient; (3) the potential to modify the outcome; and (4) the feasibility of "capturing" the outcome in clinical practice.	4, 6, 7, 8, 9, 13
		Guiding principles for inclusion included emphasizing or prioritizing (1) pragmatism over idealism; (2) completeness in data collection over breadth of areas surveyed; (3) measures that can also be collected through retrospective abstraction; (4) instruments that are perpetually freely available and ideally with a digital platform; (5) instruments made of modular subunits that permit recombination of elements; and (6) measures robust to comparison in both low- and high-income countries and with available cost utility values to calculate measures of cost-effectiveness.	3
		Not provided.	1, 2, 5, 10, 11, 12, 14
2. Case-mix variables	Case-mix selection criteria	Case-mix-adjustment variables were selected based on the following three criteria: (1) the potential relevance (strength of the causal linkage between the risk factor and the outcome), (2) the risk factor independency, and (3) feasibility of measurement.	4, 6, 7, 9, 13
		Not provided.	1, 2, 3, 5, 7, 8, 10, 11, 12, 14
3. Measurement tools	PROM selection criteria	PROM tools were researched based on the outcome coverage, psychometric quality, clinical interpretability, and feasibility to assess and implement the PROMs in daily practice.	2, 4, 8, 11, 12,
		Understandability, cost and time to complete were all assessed to determine the feasibility of implementing specific PROMs.	13
		Not provided.	1, 2, 5, 6, 7, 9, 10, 14

4. Data source	Data source selection criteria	A consistent effort was made to simplify the set of outcomes and associated data, especially the information requested from physicians in order to boost compliance.	2, 3, 7, 11
		Not provided.	1, 4, 5, 6, 8, 9, 10, 12, 13, 14
5. Time points	Time-point selection criteria	Three predominant factors contributed to the selection of time points for the standardized data collection: (1) typical treatment periods, (2) stages of growth and development, and (3) potential burden of data collection on a team.	6, 9, 12
		Not provided.	1, 2, 3, 4, 5, 7, 8, 9, 10, 11, 13, 14.
Framework used		Derived from outcomes hierarchy (Porter, 2010)	3, 7
		Fully based on outcomes hierarchy (Porter, 2010)	11, 13, 14
		Degree of health, survival and disease control, disutility of care	1, 4, 10, 12,
		Disease specific	2, 5, 8, 9, 6
Adverse effect selection criteria		While no objective criteria were used, the working group aimed to include complications and adverse events that are relatively frequent, severe, avoidable, and feasible to capture.	2, 7
		Not provided.	1, 3, 4, 5, 6, 8, 9, 10, 11, 12, 13, 14

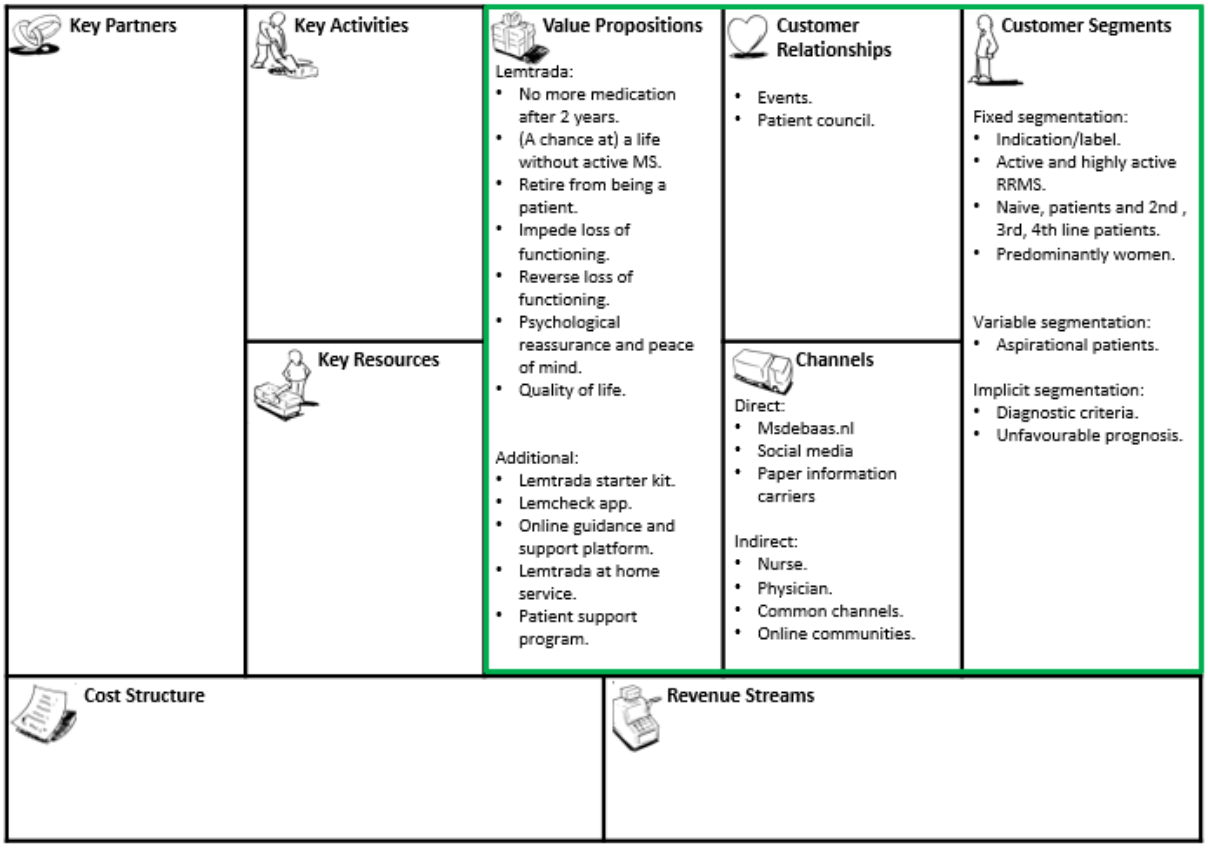
B-4. Framework for standard set formulation

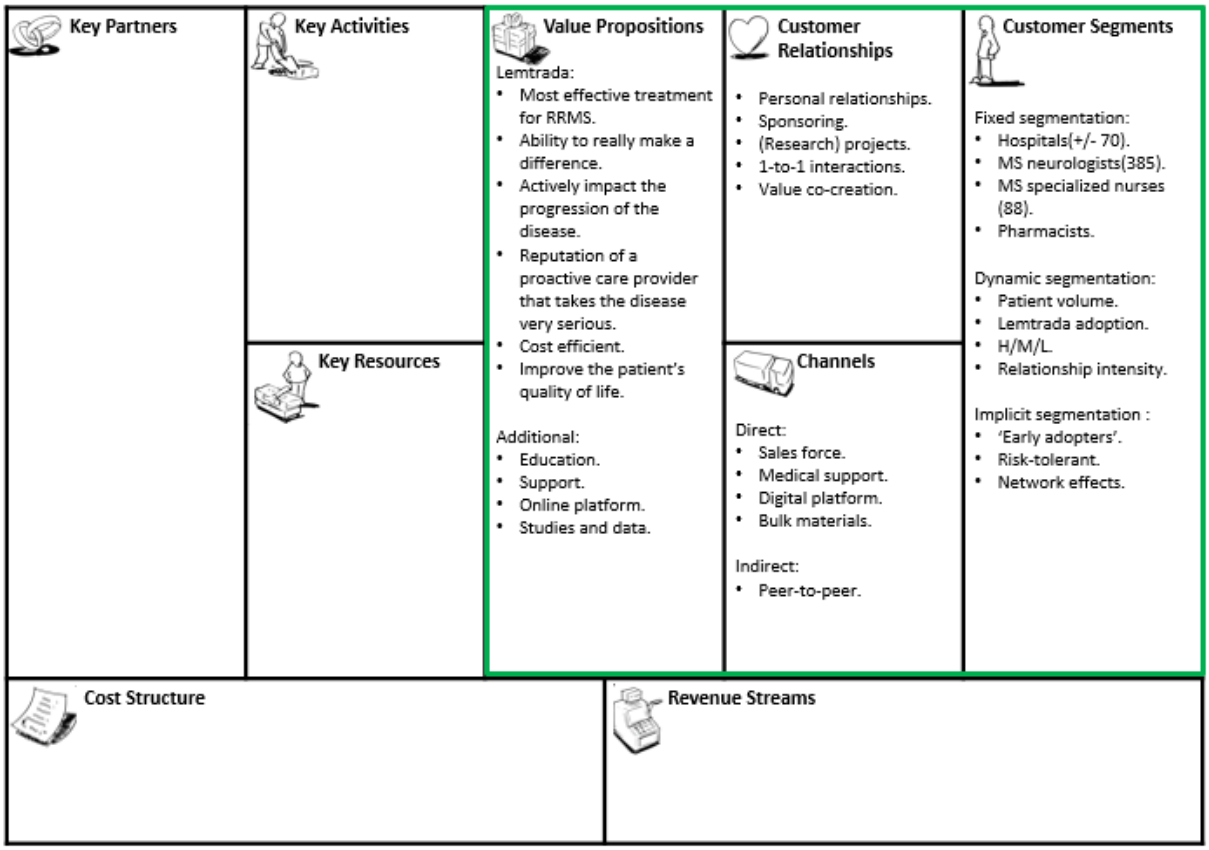
Framework	Standard set components				
Outcomes hierarchy (Porter, 2010).	1. Outcome	2. Case – Mix variable	3. Measurement tool	4. Data source	5. Time points
	Selection criteria: 1. Frequency of the outcome. 2. Impact on the patient. 3. Potential to modify the outcome. 4. Feasibility of "capturing" the outcome in clinical practice.	Selection criteria: 1. Potential relevance. 2. Risk factor independency. 3. Feasibility of measurement.	Selection criteria: 1. Outcome coverage. 2. Psychometric quality. 3. Clinical interpretability. 4. Feasibility to assess and implement the PROMs in daily practice.	Selection criteria: 1. Low complexity. 2. Low dependency on information from physicians.	Selection criteria: 1. Typical treatment period(s). 2) Stages of growth and development. (3) Potential burden of data collection on a team.
					

Appendix C. Comparison of ZiN and VBHC costing principles

Step	Zorginstituut Nederland	Value-based healthcare
1. Perspective definition	For economic evaluation, ZiN adheres to the 'societal point-of-view'. This includes all actors in the society. All costs must be included, regardless of who incurs them.	"Costs, like outcomes, should instead be measured around the patient" (Porter, 2010, p. 2481). "CEA generally considers costs and benefits from the societal or health care sector perspectives, whereas VBHC is intended to adopt the patient perspective" (Tsevat et al., 2018, p. 329).
2. Time horizon specification	The societal point-of-view implies that all consequences that are related to the intervention can be incorporated into the analysis. Long-term costs, when applicable, are assessed using econometric or statistical models.	"Reimbursement should cover a period that matches the care cycle… The relevant cost of care for determining value is the cost of the full set of interventions taken together" (Porter, 2010, appendix 1, p. 4).
3. Cost categories	From the societal point-of-view, three cost categories can be distinguished: (1) costs within healthcare, (2) costs of patients and family and (3) costs in other sectors.	"Costs borne by patients and their families in supplementing their care should be part of the cost […] The same holds for costs currently borne by patients' employers, such as lost work time and sick days" (Porter, 2010, appendix 1, p. 12).
4. Cost unit identification	In identifying the individual cost units, all costs must be included. This means that aside from the costs of initial treatment, additional costs incurred due to adverse effects, complications and follow-up must be included.	"Costs should reflect the full array of resources involved in caring for the patient's condition, including inpatient, outpatient, and rehabilitative care, along with all associated drugs, devices, services, and ancillary equipment" (Porter, 2010, appendix 1, p. 2).
5. Units of measurement	Healthcare consumption data are based on primary and secondary data obtained from clinical trials, case reports and provider surveys.	"Valid costs for patient care provide the common data for clinicians and administrators to collaborate on improvement… We must assign clinical and administrative resources for the projects and shared their process maps and costing data" (Kaplan et al., 2014, p. 403).
6. Valuation of cost units	Preferably, cost analyses are performed on established reference prices, to enhance interpretability and comparability. When not available, the researchers must calculate their own estimates.	"Practical considerations, such as the availability of data and cost of information gathering, will also play a role in the measures selected. For example, billing data are often more easily accessible than data from chart reviews or new data entry, and measures calculated from billing data can be the place to start as information systems are improved" (Porter, 2010, appendix 2, p.4).
7. Uncertainty	In economic analysis, measurement error is assumed. When data indicates spread in cost estimates, statistical methods are used to calculate the averages and standard errors.	"Calculate total and average costs for any category or subcategory of patients while still capturing the detailed data on individual patients needed to understand the sources of cost variation" (Kaplan & Porter, 2011, p. 52).

Appendix D. Business model canvas for Lemtrada®.





Business Model Canvas – **Common areas**

Key Partners

Primary partners:
- Neurologists treating MS.
- Nurses treating MS.

Secondary:
- Zorginstituut Nederland.
- Ministry of Health, Welfare & Sport.
- Ad agencies..
- Market researchers.
- Distributors.
- Health insurance companies.
- Partners of patients.
- Hospital pharmacists.

Key Activities

Primary activities:
- Influencing behavior.
- Providing information and product message.
- Gather product and customer feedback.
- Gather market insights.

Support:
- Developing marketing and medical materials.

Key Resources

- Sales talent.
- Product knowledge.
- Medical knowledge.
- Relationships.
- Budget.

Value Propositions

Customer Relationships

Channels

Customer Segments

Cost Structure

- Franchise: personnel costs.
- Operations: projects, materials, consultancy and patient care.
- Cost shifting: administration, check-up and adverse effects.

Revenue Streams

- 100% sales Lemtrada vials.
- Hospital places and pays orders, insurer provides hospital with reimbursement.
- Proposition → Z-index list price→ individual price negotiations.

Appendix E. Extensive business model ontology of Lemtrada

E-1. Product

The MS franchise of Sanofi controls two major products:
(1): Aubagio® (Teriflunomide), a first-line oral RRMS medication that has to be taken on a daily basis.
(2): Lemtrada® (Alemtuzumab), a first-line and second-line infusion DMT that is administered as a non-chronic treatment course.

Both main products have different features and multiple additional offerings included aside from the pharmaceutical product. Both products, therefore, provide a substantially different value proposition to the customer. The focus of this research, however, is on Lemtrada®.

The value proposition of Lemtrada® consists of multiple offerings, and can be split into two major categories: the first consisting only the Lemtrada® vials and the second consisting all additional products and services.

As mentioned in the main text, the value offer and customer interface are separately performed for patients and healthcare providers, as recommended by Osterwalder and Pigneur (2010), because of the multi-sided characteristics of the healthcare system.

E-1.1a Value proposition 1 to patients: Lemtrada® vials.

This value proposition can be decomposed into seven different features:

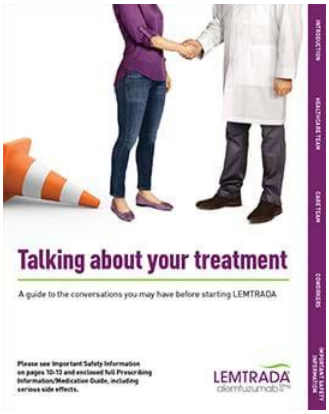
- *No more medication after 2 years:* once the treatment course has been completed together with additional the 4 years of monitoring, the patient no longer requires treatment or medication.
- *(A chance at) a life without active MS:* the results of the treatment differ per patient. However, in clinical trials, 53%–60% of patients achieved no evidence of disease activity (NEDA) in each year through Years 2–8; 15% achieved NEDA sustained over Years 3–8 (Singer et al., 2018). For treatment naïve patients, these numbers are even larger.
- *Take one's leave of being a patient:* once a patient has shown no evidence of disease activity for a sustainable period of time, can he or she still be considered a patient?
- *Impede the loss of functioning:* Lemtrada effectively stops the deterioration of individual functioning and stabilizes the patients EDSS.
- *Reverse loss of functioning:* In some patients, EDSS even significantly improves. While this does not happen for all patients, the mean EDDS change in clinical trials over the course of 8 years actually is positive.
- *Psychological reassurance and peace of mind:* In the unfortunate case that Lemtrada does not provide adequate results, a patient is still able to say: 'I have done everything that I could have done to face this terrible condition'.
- *Quality of life:* Lemtrada® has an easy and patient-friendly treatment plan that encompasses low complexity and involvement of the patient. Drug adherence is no major risk in Lemtrada® treatment.

An important side note on product features here, is the price that is paid for Lemtrada®. While it is free in a monetary sense, it is not costless from an economic point of view, as Lemtrada® incorporates notable health risks for the patient as well.

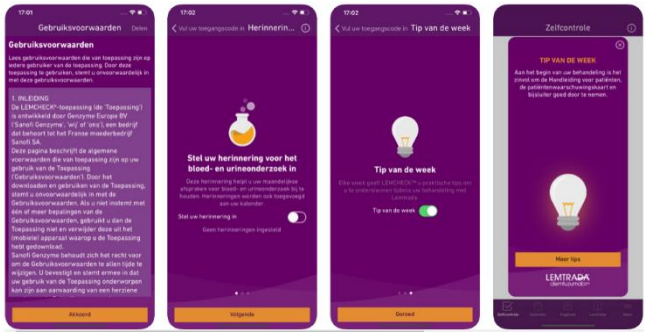
E-1.1b Value proposition 2 to patients: additional products and services.

This second value proposition is made up of the following set of offerings:

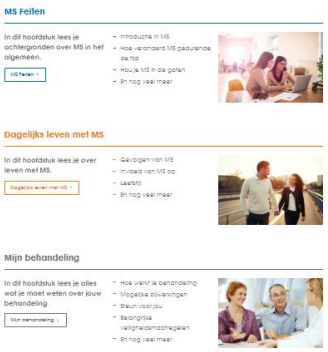
- *Lemtrada® starter kit:* each patient starting on Lemtrada® receives a small kit including an information guide, instructions, package leaflet and warning card.



- *Lemcheck app:* this app reminds patients to self-examine for adverse effects, sends reminders for the monthly blood and urine check-up and provides additional information to the patient.



- *MSbegeleidingsprogramma.nl:* a platform for RRMS patients on Lemtrada® that provides information on RRMS, has tips for daily life with RRMS and provides insights in the patient's treatment process.



- *Alcura 'Lemtrada at home' service:* a national pharmacist will visit patients at a location of their preference to collect the blood and urine samples of the patient, who then no longer needs to visit a hospital or clinic.

- *Alcura patient support program:* a national pharmacist has a package of offerings that a patient can subscribe to. The offerings include:
  - Informational e-mails.
  - Magazines with real-life patient stories.
  - Supportive text messages.
  - Check-up phone calls from a trained nurse.

As discussed before, a different value proposition can be described for healthcare providers. It is important to make this distinction, as it forces one to face Lemtrada's problem from a new perspective. This persistent problem is sharply phrased by the franchise head as:

"A persistent discussion surrounding the Lemtrada® case is 'what is in it for the doctor?'.

Tables 1.C and 1.D provide an extensive overview of with each offering, the reasoning, the price and the payer.

E1.1.2a Value proposition 1 to healthcare providers: Lemtrada® vials.

For physicians, value proposition can be decomposed into the following features:

- *Most effective pharmaceutical against RRMS:* at this point in time, Lemtrada® is the most effective treatment for combatting RRMS for both naïve patients and patients who have relapsed on previous treatment.
- *The opportunity to truly make a difference:* it allows healthcare professionals to make a substantial positive change to the life of the patient they are treating.
- *Effectively affect and stop the progression of the disease:* Lemtrada® allows healthcare providers to actively influence the medical condition of the patient, rather than managing the symptoms.
- *The reputation of a proactive professional who takes RRMS seriously:* currently, most physicians that prescribe Lemtrada® are regarded as innovators who are willing to take personal risks when it benefits the patients.
- *Cost effectiveness:* by prescribing Lemtrada®, healthcare providers can decrease the budget pressure on their clinics and the national healthcare system.
- *Improve quality of life:* Lemtrada's efficacy and treatment course combined with Sanofi's 2018 explicit strategy to make life as easy and comfortable for the patient allow healthcare providers to maximize the quality of life for patients that have to live with RRMS for the rest of their lives.

Again, a side note must be made for Lemtrada's® risk and effort characteristics. Due to Lemtrada's® risk profile and the inherent follow-up policy mandated by European law, Lemtrada's® adverse events portfolio significantly reduces the total risk and effort benefits.

Hospital account manager:
"I know some physicians out there who consider the administrative implications of these mandatory check-ups as such a hassle … that it is an outspoken barrier for them against prescribing Lemtrada®."

E-1.2b Value proposition 2 to healthcare providers: additional products and services.

This second value proposition is made up of the following set of offerings:

- *Education:* the MS franchise offers extensive education and training to healthcare providers that prescribe Lemtrada®.
- *Support:* healthcare providers are actively and passively supported by Sanofi in order to maximize their potential and the outcomes for RRMS patients receiving Lemtrada®.
- *Access:* healthcare professionals are granted access to extensive information and data.
- *Online platforms:* Sanofi offers healthcare providers that are treating RRMS with Lemtrada® online platforms on which they can acquire information, ask questions and communicate.
- *Studies and research:* Lemtrada® and RRMS are constantly being researched by Sanofi. These studies are in collaboration with healthcare providers who benefit from these new research results and insights.

E-2. Customer interface

This section addresses all customer-related issues of Lemtrada's® business model. The customer interface describes which target customers are addressed, through which channels it addresses them and what relationships in maintains with customers. One more, the customer interface is addressed separately for patients and healthcare providers.

E-2.1a Patient segments

Below, a list is provided of patients segments and a description of each segment.

Fixed segmentation:

- *Indication:* Lemtrada® has been approved with a label for certain indications. In Lemtrada's case, this indication is adults between 18 and 55 years old who are diagnosed with active or highly active RRMS.
- *Treatment history:* Lemtrada® has been approved for treatment naïve patients as well as patients who have reached insufficient results from earlier treatments. The distribution of patients is not equal. Below, a table is provided with insights in Lemtrada® patient treatment histories for a sample of anonymous Dutch patients.

Naive	Previous treatment			
11%	89%			
	2nd Line	3rd Line	4th line	Non-naive, treatments unknown
	30%	7%	18%	34%

- *Sex:* (RR)MS is a disease that is more prominently diagnosed in woman then in men. Roughly two out of every three patients is female, the other third accounts for male patients.

Variable segmentation:

- *'Aspirational' patients:* Lemtrada® is most appropriate for patients who still possess high functionality. Therefore, patients that have more to lose and are willing to take risks to minimize their loss are most suitable patients.

E-2.1b Healthcare provider segments

Fixed segmentation:

- *Hospitals:* there are roughly 70 hospitals in the Netherlands in which MS is treated.
- *MS neurologists:* there are 385 Dutch neurologists who treat patients with MS.
- *MS specialized nurses:* there are 88 Dutch nurses specialized in MS treatment.
- *Hospital pharmacists:* these purchase Lemtrada® in name of the hospital and to the order of the treating neurologist or nurse.

Dynamic segmentation:

- *Patient count:* healthcare providers are categorized based on to amount of MS patients they treat on a yearly base. Categories are 'Low' (1 to 20), 'Medium' (21 to 40) and 'high' (50 >).
- *Adoption:* care providers are categorized by the extent to which they have adopted Lemtrada® in their arsenal of treatment options. Categories go from 1 (Not aware of Lemtrada®) to 6 (Lemtrada® ambassador).
- *Relationship intensity:* an additional object of segmentation is the intensity of the personal relationship that is maintained between the care provider and Sanofi.

E-2.2a Patient channels

Table 1.e provides more detailed insights into the patient channels. They can be split up in two different groups: those channels of which Sanofi can directly control the flow of information, and those in which it can only indirectly control the flow of information (or not at all).

Direct channels:

- *MSdebaas.nl.*
- *(Social) media platforms.*
- *Leaflets, brochures and other paper information carries* (distributed through clinics and hospitals).

Indirect channels:

- *Nurses.*
- *Neurologists.*

Hospital account manager:
"Of course their consideration is to provide objective information, but how should I put this … they translate this information based on their own personal insights."

- *Public channels* (deliver quality content when possible).
- *Online communities.*

Franchise head:
"There are these online communities surrounding Lemtrada. Which, again, we have little influence or control over, but are very important for the decision that people make. … And doctors are able to subscribe to these communities as well. … They are another example of one of those things that we have very little control over, but that have quite a big impact on your product reputation".

Therapeutic area manager:
"There is a lot of garbage and misinformation on the internet … As [colleague] mentioned, we have very little control on what is posed on these online communities"

- *Patient support.*

E-2.2b Healthcare provider channels

Table 1.f provides more detailed insights into the patient channels.

Direct:

- *Sales force.*
- *Medical support.*

Franchise head:
"Face-to-face, education, both with the sales people as well as a medical consideration, are the most important channels".

- *Digital platforms.*
- *Bulk materials.*

Indirect:

- *Peer-to-peer (education).*

E-2.3a Patient relationships

Due to thorough and active legislation, it is nearly impossible for Sanofi, or any other pharmaceutical company, to maintain relationships with (potential) patients. All interaction with patients is shares these common characteristics:

1. *Incidental:* these interactions are discontinuous, often sparked by projects and events.
2. *Formal:* these interactions have a clear purpose and defined responsibilities.
3. *One-sided:* the roles between both parties cannot be perceived as equal.
4. *Anonymous:* interactions take place not with persons, but with patients.

Due to these characteristics, it is hardly possible to perceive a 'World MS day' or one-time patient advisory board as relationships. As the therapeutic area manager mentioned:

'Given the common definition of a relationship as an interaction that goes beyond a transaction and is maintained over time, I honestly wonder if we maintain any relationships at all with our patients'.

The Benelux head of the franchise reiterated that statement, saying:

'It is transactional, discontinuous and there is no feedback whatsoever … Besides, they are anonymous relationships. How can one maintain a relationship with a patient who is anonymous?'

Therefore, relationship with RRMS patients are regarded to be non-existent for Lemtrada®.

E-2.3b Healthcare provider relationships

Fortunately, the rules that restrict relationships with patients are not applicable to healthcare providers. It is perfectly acceptable to interact with a person with a professional career as a care provider. Naturally, there are rules and guidelines in place to ensure that no unfair power balance or conflict of interest can arise. But aside from these rules, meaningful and mutually beneficial relationships can be maintained between a pharmaceutical company (employee) and a healthcare professional. Even on a personal level.

As a hospital account manager noted:

"I have a couple of neurologists, who are delighted to have a lunch meeting with me, and have done so for years. Just like that, a consultancy lunch, without reimbursement."

And

"They like these casual moments in which we mutually share information. But we share personal matters as well. They just highly appreciate that."

With regard to healthcare providers, a following set of relationships can be defined. A more detailed overview is provided in table 1.G.

Relationships

- *Personal contact and interaction.*
- *Sponsoring.*
- *(Research) project cooperation.*
- *1 to 1 consultancy.*
- *Co-creation and development.*

E-3. Infrastructure management

This pillar is conceptualized the company's value creation processes. It describes what abilities are necessary to provide the value propositions and maintain the customer interface. Because the firm's internal infrastructure is fixed, and not dependent on the different customer segments, it will not be mapped separately for patients and healthcare providers. This internals aspect will be considered as one coherent entity.

E-3.1 Key capabilities of the Benelux MS franchise

In order to make Lemtrada's® business model work, the following key capabilities are performed on a daily basis.

Key capabilities:

- *Behavior and decision impact:* the combined efforts of the entire franchise are aimed at influencing patient and healthcare provider decision making, with the ultimate goal to influence prescribing behavior. The main resource required in order to maintain this capability is human capital.

Maintaining and further developing a highly motivated and qualified team is therefore one of the key focus areas specified in 2019's MS brand plan, with Sanofi Genzyme having the second best skilled and competent representatives compared to all competitors.

- *Accurate, extensive and up-to-date knowledge base:* to effectively persuade care providers to prescribe Lemtrada® and to optimally support providers and patients during and after treatment, it is important that there is a vast body of knowledge that can be consulted. While information and data can be stored and easily shared, it is practically useless without trained and educated agents, ranging from medical liaisons to patient support specialists.

According to a hospital account manager:
"That is for physicians essential. And when you want to continue to be a good conversation partner, a valuable conversation partner, who knows what is happening in the landscape, you have to stay well-informed".

- *Network and relationships:* shared value creation, customer acquisition and innovation and opportunity development have become necessities for pharmaceutical companies that want to be successful in the modern landscape. In order to keep up with environmental developments and the accompanying threats and opportunities, the MS franchise maintains a strong and diverse network of relationships and partners, making it their most important intangible asset.

- *Budgetary power:* the franchise's extended activities, staff, (sponsor) projects and materials require a strong financial backbone, especially since these activities consume a lot of resources, but do not directly create revenue. Their only benefit to the company is that they might have a positive effect on the amount of Lemtrada® prescriptions. In order to execute such a strategy over a sustained period of time, large budgets and persistent investment are needed.

E-3.2 Value configuration of the Benelux MS franchise

The value configuration describes the main activities that the MS franchise performs on a daily basis in order to fuel their business model and make the value proposition possible. Activities are reliant on capabilities and their fundamental resources.

While a value configuration contains a set of activities, it can also be categorized as one of three configuration architypes: the value chain, the value shop or the value network.

And while the MS franchise in the Netherlands is centered on marketing & sales and service, it does only partly qualify as a value chain in and of itself. Rather, it forms the final components of a larger value chain controlled by Sanofi Genzyme. The MS franchise can also be perceived as more service oriented that production oriented. Its value creation logic is resolving customer problems, thereby qualifying as a value shop.

Primary activities:

- *Influencing behavior.*
- *Delivering information and message.*
- *Gathering patient and healthcare provider feedback.*
- *Gathering intelligence on market and customer developments.*
- *Creating and delivering marketing and medical materials.*

Table 1.H. provides an extensive overview of these activities and their activity categorization.

E-3.3 Benelux MS franchise partner network

The MS franchise relies on a diverse partner network. Different partners provide different value to the franchise. According to the franchise head, the partnership purpose and intensity is often strongly related to the product's life cycle.

Primary partners:

- *Neurologists who treat MS patients.*
- *Nurses who treat MS patients.*

MS franchise head:
"Care providers are our most critical partner. … Of course there are those physicians who regard us merely as suppliers of a therapeutic solution, a manufacturer and vendor. Fortunately, a far bigger group of physician do regard us as partner. They trust us to have the most extensive knowledge on our pharmaceutical product, and feel that they can count on us to provide them this knowledge".

Secondary partners:

- *Zorginstituut Nederland*
- *Ministerie van Volksgezondheid, Welzijn en Sport.*
- *Ad and marketing consultancies.*
- *Market intelligence agencies.*
- *Distributors.*
- *Health insurance companies.*
- *Partners of MS patients.*
- *Hospital pharmacists.*

Table 1.I. provides an extensive overview of the partners and their strategic relevance.

E-4. Financial aspects

Finally, the financial aspects for Lemtrada® will be discussed. Cost and financing structures of pharmaceutical companies are a complex and much debated topic, both in academic and public media. Lemtrada® has been developed, tested and approved for RRMS treatment over the course of many years. This process has cost hundreds of millions of dollars in R&D, clinical trial research, market access and infrastructure development. These costs, however, are sunk costs. Lemtrada® has been developed and approved. What remains securing accessibility and adoption. For that reason, we will only look at Lemtrada's costs and revenues in relation to the Benelux MS franchise from a post-market perspective.

E-4.1 Revenues

Lemtrada® provides exactly one revenue model to the franchise: revenues from selling vials. The vials provide 100% of monetary income.

Therapeutic area manager:

"For Lemtrada® we rely on a single source of revenue: the vials. Aside from the vails, money only flows out".

While pricing policies are complex, heterogeneous and disclosed, they all follow a similar path:

1. Once a pharmaceutical product has been approved for the Netherlands, the Minister of Health, Welfare & Sport is empowered by the Pharmaceutical Pricing Law to determine a maximum price. It is then illegal for the supplier to offer, sell or supply the product at a price that is higher than the maximum price.
2. In agreement with regulating authorities, the pharmaceutical company will then provide its own proposed price. This price will be listed in the so-called 'Z-index', and is then often referred to as the 'list price'.
3. Very often, however, hospitals and pharmacists are not willing to pay the list price. Discounts, rebates and alternative pricing structures can then be negotiated with different purchaser.

The average price for a single Lemtrada® vial in the Netherlands is, according to Zorginstituut Nederland, set at €7.630,- per vial. One should keep in mind that a standard Lemtrada® treatment case requires 5 to 8 vials over the course of 2 to 3 years.

Both the franchise head and the therapeutic area manager confirmed that there exist individual price agreements with different purchasing organs. Currently, no alternative payment schemes, such as maximum spending caps or pay-for-performance systems are in place. This however is not for a lack of trying. During Lemtrada's® launch, back in 2014, such an initiative was started. Back then, however, the response from future potential purchasers was unenthusiastic.

MS franchise head:

"In the early days of Lemtrada, we did extensively explore such possibilities. But in the end, it turns out that that is so complicated and troublesome to set up and implement, that back then they all said 'let's just settle on a fixed discount'". "Such systems introduce noise in their cost and reimbursement processes with the insurance company, which is unwelcome. So they prefer a simple fixed discount."

This argument was also supported by the market access lead for Lemtrada®, who back then was responsible for this initiative.

E-4.2 Costs

Lastly, costs are addressed. As mentioned before, R&D and operational costs related to the production of Lemtrada® are not included, as they are not performed by the MS franchise in the Netherlands. What is important to keep in mind that these costs are sunk costs. The sole purpose of the MS franchise is to recoup these costs and secure a profit via sales.

MS franchise cost:

- *Wages:*
  The Dutch MS franchise comprises of:

Franchise head	Therapeutic area manager	Medical manager	Medical science liaison	Hospital account manager	Project manager	Product manager	Patient support lead
1x	1x	1x	2x	5x	2x	2x	1x

- *Operations:*

Projects	9%
Sales	3%
Marketing & consultancy	41%
Patient care	47%
Market access	0%

Cost shifting:

- Lemtrada® is an inpatient pharmaceutical, meaning that it is administered in the hospital. For the patient's safety, he or she is held at the hospital for the entire duration of a treatment course. As a result, the hospital has to take in a patient for at least 8 full days, which is an additional expense for the hospital. These costs are estimated at €500,- per administration.

- Due to Lemtrada® notable risk profile, patients require blood and urine samples to be tested every month, for a period that lasts to four years after the last infusion. These check-ups are performed by the hospitals, resulting in extra work and costs on their account.
  These costs are estimated at €1700,- per patient per year, and run for at least five years.

- Lemtrada's® adverse effect profile is also a consideration, as it is addressed by the hospital.

• Adverse event	Annual probability	Cost (€)[1–3]
Alemtuzumab		
Respiratory infection	29.43%[4]	124.43
Herpes infection	8.62%[4]	160.64
Urinary tract infection	10.67%[4]	156.09
Autoimmune thyroid-related adverse events:		
- Hypothyroidism	1.69% - 5.35%[8*]	259.52
- Hyperthyroidism	1.59% - 6.67%[8*]	645.16
- Graves' disease	1.19% - 6.11%[8*]	645.16
-Thyroidectomy	3.21%[8**]	4570.00[10]

• Adverse event	Annual probability	Cost (€)[1–3]
Alemtuzumab		
Iodine ablation	2.97%[8**]	1,515.00[10]
Immune thrombocytopenia:	0.4%[4], of which:	
- Observation only	13.33%[4]	1,111.12
- Steroids only	46.67%[4]	1,149.88
- Steroids and immunoglobulin	13.33%[4]	8,426.20
- Steroids and rituximab ±immunoglobulin	20.00%[4]	10,055.11
- Steroids and splenectomy	6.67%[4]	2,672.76
- Good pasture's syndrome	0.0001%[4]	7,827.28

Table A. Value proposition of Lemtrada® to patients.

Value offer to patients						
	General	**Reason**			**Price**	
	Name	**Use**	**Risk**	**Effort**	**Price scale to patient**	**Payer**
Value proposition 1: Lemtrada®						
Feature 1	No more medication after 2 years.				**Free** **There are, however, considerable adverse effects inherent to Lemtrada® treatment. The patient risks the chance to incur one or more of these adverse effects.**	**Hospital buys vials, insurance company reimburses the hospital.**
Feature 2	(A chance at) a life without active MS.					
Feature 3	*Take one's leave of being a patient.*					
Feature 4	*Impede the loss of functioning.*					
Feature 5	*Reverse loss of functioning.*					
Feature 6	*Psychological reinforcement and peace of mind.*					
Feature 7	*Quality of life*.					
Aggregated						

Table B. Value proposition of additional products and services to patients.

Value offer to patients						
	General	**Reason**			**Price**	
	Name	**Use**	**Risk**	**Effort**	**Price scale to patient**	**Payer**
Value proposition 2: additional products and services						
Offer 1	Lemtrada® starter kit				**Free**	**Sanofi Genzyme**
Offer 2	Lemcheck app				**Free**	**Sanofi Genzyme**
Offer 3	MSbegeleidings programma.nl				**Free**	**Sanofi Genzyme**
Offer 4	Alcura 'Lemtrada at home' service				**Free**	**Sanofi Genzyme**
Offer 5	Alcura patient support programme				**Free**	**Sanofi Genzyme**

Table C. Value proposition of Lemtrada® to healthcare providers.

Value offer to healthcare providers						
	General	**Reason**			**Price**	
	Name	**Use**	**Risk**	**Effort**	**Price scale to healthcare provider**	**Payer**
Value proposition 1: Lemtrada®						
Feature 1	*Most effective pharmaceutical against RRMS*				**€7000 per vial (8 to 11 vials needed)** **€1500 post monitoring costs per year (5 to 6 years needed)** **There are considerable adverse effects inherent to Lemtrada® treatment. The care providers shares the responsibility for these effects.**	**Vials are reimbursed** **Costs included in yearly budget**
Feature 2	*The opportunity to truly make a difference*					
Feature 3	*Effectively affect and stop the progression of the disease*					
Feature 4	*The reputation of a proactive professional who takes RRMS seriously*					
Feature 5	*Cost effectiveness*					
Feature 6	*Improve quality of life*					
Aggregated						

Table D. Value proposition of additional products and services to healthcare providers.

Value offer to patients						
	General	**Reason**			**Price**	
	Name	**Use**	**Risk**	**Effort**	**Price scale to care provider**	**Payer**
Value proposition 2: additional products and services						
Offer 1	*Education*				**Free**	**Sanofi Genzyme**
Offer 2	*Support*				**Free**	**Sanofi Genzyme**
Offer 3	*Access*				**Free**	**Sanofi Genzyme**
Offer 4	*Online platforms*				**Free**	**Sanofi Genzyme**
Offer 5	*Studies and research*				**Free**	**Sanofi Genzyme (among others)**

Table E. Channels for patients.

Patient channels					
	Channel name	**Awareness**	**Evaluation**	**Purchase**	**After sales**
Channel 1	MSdebaas.nl	Information on all RRMS treatment options	Objective information on all treatments		Information and passive support
Channel 2	Social media platforms	Information on all RRMS treatment options			Emotional support
Channel 3	Paper information carries		Objective information on Lemtrada®		Information and passive support
Channel 4	Nurses	Information on all RRMS treatment options	Expert's assessment of all treatments	Prescription decision	Regular check-ups
Channel 5	Neurologists	Information on all RRMS treatment options	Expert's assessment of all treatments	Prescription decision	Periodical check-ups
Channel 6	Public channels	Information on all RRMS treatment options			
Channel 7	Online communities	Information on all RRMS treatment options	Informal experience sharing and influencing		
Channel 8	Patient support			Objective information on treatment course	Active support

Table F. Channels for healthcare professionals.

Healthcare provider channels					
	Channel name	**Awareness**	**Evaluation**	**Purchase**	**After sales**
Channel 1	Sales force	Visits, messages and updates about Lemtrada® and MS	Objective but commercially driven information on Lemtrada®		Check-ups and general interaction
Channel 2	Medical support	Answering questions, problem solving and medical data provision	Objective information on Lemtrada		Answering questions and problem solving
Channel 3	Digital platforms	Information and experience sharing	Information and experience sharing		Information and experience sharing
Channel 4	Bulk materials	Information on Lemtrada®			
Channel 5	Peer-to-peer		Information and experience sharing		

Table G. Relationships with healthcare professionals.

Healthcare provider relationships				
	Mechanism name	**Mechanism function**	**Mechanism objective**	**Also a channel?**
Mechanism 1	Personal contact and interaction	Personalization: individual attention is provided to a healthcare provider's work-related and personal matters.	Retention	Yes: sales force.
Mechanism 2	Sponsoring	Overwritten: part of value offer		
Mechanism 3	(Research) project cooperation	Personalization: (financing) research on care providers' focus areas Trust: focus area outcome results reinsure healthcare providers	Acquisition	No
Mechanism 4	1 to 1 consultancy	Personalization: information exchange centered on a healthcare provider's personal information need.	Acquisition / retention	Yes: sales force.
Mechanism 5	Co-creation and development	Overwritten: part of value offer		

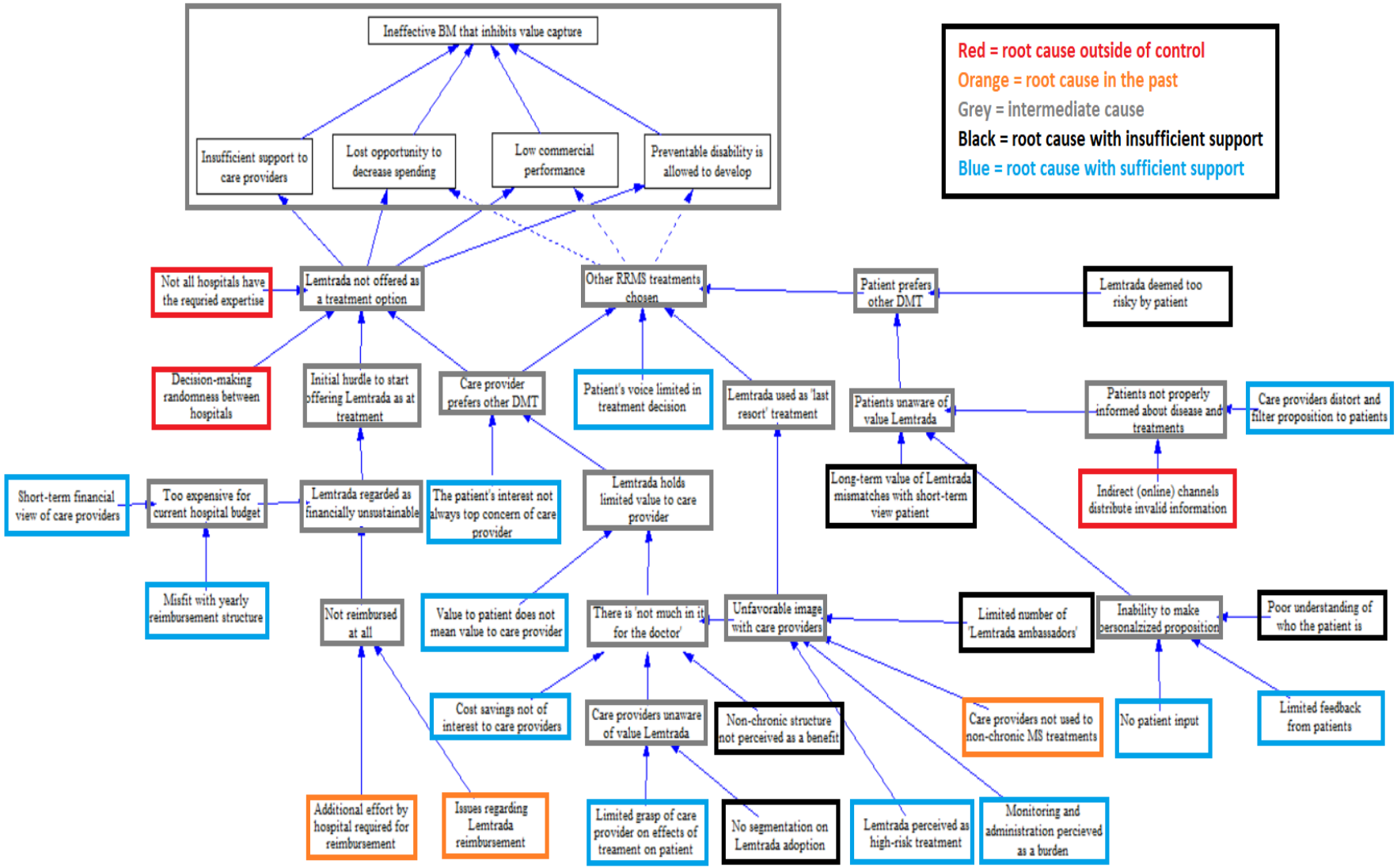
Table H. MS franchise value configuration

Value configuration					
	Name	**Description**	**Activity nature in value chain**	**Activity nature in value shop**	**Activity level**
Key activity 1	Influencing behavior	Influence patient and healthcare provider decision making, with the ultimate goal to influence prescription behavior.	Marketing & sales	Choice	Primary
Key activity 2	Delivering information and message	In order to be included in the decision options, information relevant to the patient and the care provider must be delivered at the right the time, together with arguments for why Lemtrada® is the right choice.	Service	Problem-solving	Primary
Key activity 3	Gathering patient and healthcare provider feedback	Due to the restrictions on patient communications, it is important that the franchise staff uses indirect channels to acquire customer insights, experiences and feedback.	Support activity	Control and evaluation	Support
Key activity 4	Gathering intelligence on market and customer developments	Acquiring knowledge on the market environment and customer segments, and developing strategies and initiatives that ensure Lemtrada's® relevance in the healthcare landscape.	Support activity	Problem-finding and acquisition	Support
Key activity 5	Creating and delivering marketing and medical materials	It is important that the arguments and solutions offered by representatives and medical liaisons is supported by attractive and scientifically relevant materials for patients and care providers. Developing these materials is complex, and due to the constant developments within healthcare, time-bound.	Marketing & sales / service	Choice	Primary

Table I. Partnerships

Partnerships							
	General			Strategic relevance (0 – 5)			
	Name partner	**Description**	**Reason** (use/risk/effort)	**Importance**	**Competition**	**Integration**	**Substitutability**
Agreement 1	Neurologists	Constant partnership	Use	**5**	**0**	**3**	**0 (group level)**
Agreement 2	Nurses	Constant partnership	Use	**4**	**0**	**3**	**2 (group level)**
Agreement 3	Zorginstituut Nederland	Approval and reimbursement	Use	**3 (only during launch)**	**0**	**2**	**0**
Agreement 4	Ministerie VWS	Approval and reimbursement	Use	**2 (only during launch)**	**0**	**1**	**0**
Agreement 5	Consultancy	External capabilities	Use	**3**	**1**	**1**	**4**
Agreement 6	Intelligence agencies	External knowledge	Use	**2**	**0**	**2**	**2**
Agreement 7	Distributors	Logistics	Use	**4**	**2**	**3**	**2**
Agreement 8	Health insurance companies	Market access	Use	**3**	**0**	**2**	**2**
Agreement 9	Partners of MS patients	Patient care collaboration	Use	**2**	**0**	**1**	**3**
Agreement 10	Hospital pharmacists	Market access	Use	**3**	**0**	**3**	**1**

Appendix F. Current reality tree



Appendix G. Statement of approval by ICHOM core group member

I hereby declare that the standard set for relapsing-remitting multiple sclerosis which was presented and developed by Jelle Walraven is of satisfactory quality and to the best of my knowledge can be considered as useful and practically applicable.

The process in which the standard set came to be successfully emulates the process of authentic ICHOM sets. Sufficient preparation and effort seem to have been invested in order to create the final product. The chosen outcome domains and measurements seem logical and appropriate for the intended use.

I deem this standard set to be suitable for outcome measurement as described in the various value-based healthcare whitepapers and standards.

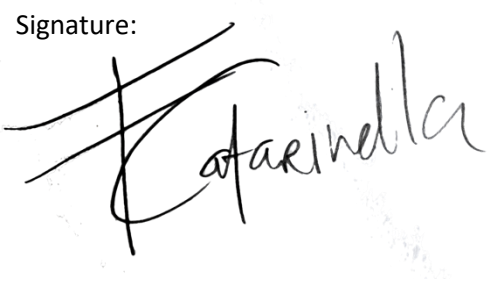
Name: F.S. Catarinella, MD

Profession/specialty: Research associate, Department of Vascular Surgery, Amsterdam UMC.

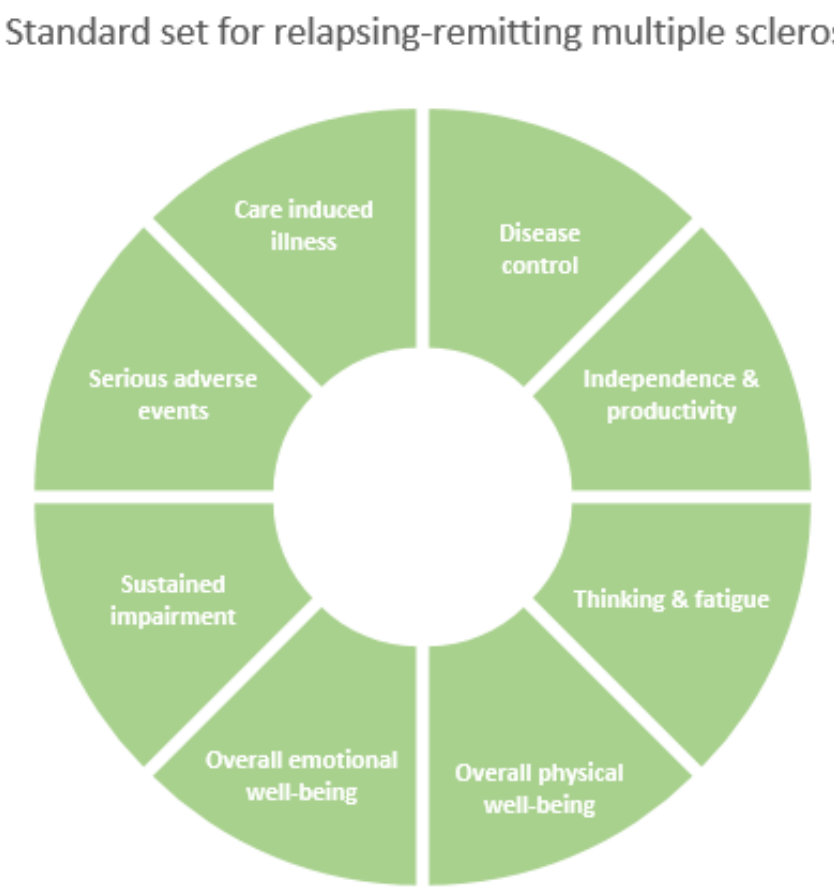
Core group member of ICHOM set for: Deep venous obstruction

Date: 19-08-2019

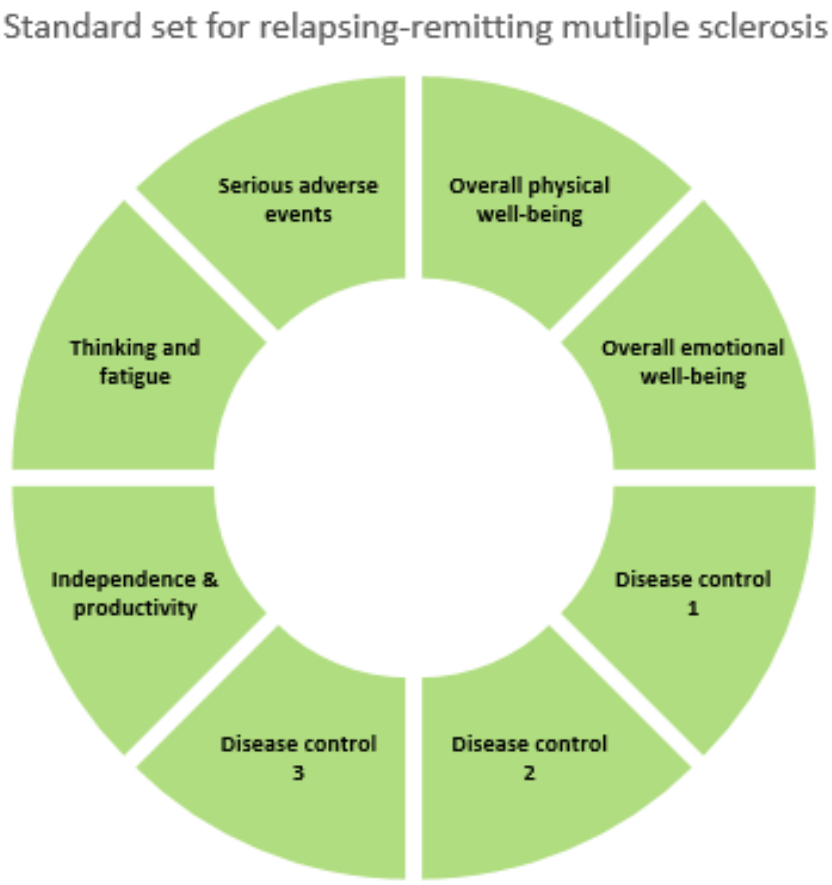
Signature:



Appendix H. Revised and validated version of internally developed standard set for RRMS



Initial standard set developed in NGT session.



Ultimate standard set validated by ICHOM member, neurologist and patient.

Outcome Tier	Outcome domain	Standard set components				
Outcomes hierarchy (Porter, 2010).	**Standard set, self-developed.**	**1. Outcome**	**2. Case – Mix variable**	**3. Measurement tool**	**4. Data source**	**5. Time points**
Tier 1-1: Survival		• Vital status	Demographics: • Sex • Age Clinical status: • Baseline EDSS • Baseline MRI marking • Baseline BMI • Biomarkers • Comorbidities • Relapses in the past 12 months • Psychological status • Cognitive status • Vitamin D level Life style: • Smoking • Alcohol consumption	• Clinical	• Clinical	• Continuous
Tier 1-2: Health retained	1. Disease control 1	• Disability		• Expanded Disability Status Scale (EDSS)	• Clinical	• 3-month interval
	2. Disease control 2	• Relapses		• Annual relapse-rate	• Clinical	• Continuous
	3. Disease control 3	• MRI activity		• % of patients	• Clinical	• 12-month interval
	2. Independence & productivity	• Ability to work & learn • Ability to live a 'normal life' • Ability to join in family life • Independence in basic tasks and maintenance • Mobility		• FAMS (MOB)	• PROM	• 12-month interval (preferably more frequently)
	3. Thinking & fatigue	• Fatigue • Cognitive performance		• FAMS (T & F)	• PROM	• 12-month interval (preferably more frequently)
Tier 2-2: Disutility of care	4. Overall physical well-being	• Medication sickness • General well-being • Pain • Adverse events		• FAMS (S)	• PROM	• 12-month interval (preferably more frequently)

	5. Overall emotional well-being	• Anxiety • Depression • Overall happiness	Background: • Previous treatment • Previous medication • Adherence • Year of diagnosis	• FAMS (E W-B) •	• PROM	• 12-month interval (preferably more frequently)
Tier 3-2: Long-term consequences	7. Serious adverse events	• Malignancies • Sustained disability		• % of patients	• Clinical	• Continuous
	8. Care induced illness	• Several • Depression		• % of patients	• Clinical	• Continuous
Tier 2-1: Time to return to activities		Measured by tracking time to achieve the outcomes of Tier 1-2.				
Tier 3-1: Sustainability of health		Measured by tracking the stability of the outcomes of Tier 1-2 over time.				

Appendix I. Costs incurred with Lemtrada® treatment in the Netherlands

I-1. Category 1: Costs within care

				Timeline:	**T= year 1**	**T= year 2**	**T= year 3**	**T= year 4**	**T= year 5**	**T= year 6**	**T= year 7**	**T= year 8**	**T= year 9**	**T= year 10**
				Probability:	100%	100%	29%	16%	6%	0%	0%	0%	0%	0%
		Drug acquisition:												
			Primary treatment:											
				First Alemtuzumab 12 mg	35000									
				2+ Alemtuzumab 12 mg		21000	21000	21000	21000	21000	21000	21000	21000	21000
			Pre-medication:											
				Methylprednisolone 1000mg	150	90	90	90	90	90	90	90	90	90
				Aciclovir 400 mg	10	10	10	10	10	10	10	10	10	10
				Ranitidine 150 mg	0,2	0,12	0,12	0,12	0,12	0,12	0,12	0,12	0,12	0,12
				Tavegyl 1 mg	1,4	0,84	0,84	0,84	0,84	0,84	0,84	0,84	0,84	0,84
		Administration:												
				Hospital admission	2780	1668	1668	1668	1668	1668	1668	1668	1668	1668
				Regular preperation	60	36	36	36	36	36	36	36	36	36
				Total:	38002	22805	22805	22805	22805	22805	22805	22805	22805	22805
Total				Actual (total x probability):	€ 38.001,60	€ 22.804,96	€ 6.613,44	€ 3.648,79	€ 1.368,30	€ -	€ -	€ -	€ -	€ -
		Monitoring:												
					100%	100%	100%	100%	100%	29%	16%	6%	0%	0%
				First administration:	2558									
				Annually after year 1		1701	1701	1701	1701	1701	1701	1701	1701	
Total				Actual (anuallly x probability):	€ 2.558,00	€ 1.701,00	€ 1.701,00	€ 1.701,00	€ 1.701,00	€ 493,29	€ 272,16	€ 102,06	€ -	€ -
		Adverse events:						Probabilities accounted for in 'cost calculation adverse event' sheet						
				Respiratory infection	36,49	36,49	36,49	36,49	36,49	36,49	36,49	36,49	36,49	36,49
				Herpes infection	13,79	13,79	13,79	13,79	13,79	13,79	13,79	13,79	13,79	13,79
				Urinary tract infection	16,65	16,65	16,65	16,65	16,65	16,65	16,65	16,65	16,65	16,65
			Autoimmune thyroid-related adverse events:											
				- Hypothyroidism	7,79	7,79	7,79	7,79	7,79	7,79	7,79	7,79	7,79	7,79
				- Hyperthyroidism	24,12	24,12	24,12	24,12	24,12	24,12	24,12	24,12	24,12	24,12
				- Graves' disease	18,64	18,64	18,64	18,64	18,64	18,64	18,64	18,64	18,64	18,64
				-Thyroidectomy	146,70	146,70	146,70	146,70	146,70	146,70	146,70	146,70	146,70	146,70
				-Iodine ablation	45,00	45,00	45,00	45,00	45,00	45,00	45,00	45,00	45,00	45,00
			Immune thrombocytopenia:											
				- Observation only	0,01	0,01	0,01	0,01	0,01	0,01	0,01	0,01	0,01	0,01
				- Steroids only	0,02	0,02	0,02	0,02	0,02	0,02	0,02	0,02	0,02	0,02
				- Steroids and	0,04	0,04	0,04	0,04	0,04	0,04	0,04	0,04	0,04	0,04
				- Steroids and rituximab ±immunoglobulin	0,08	0,08	0,08	0,08	0,08	0,08	0,08	0,08	0,08	0,08
				- Steroids and splenectomy	0,01	0,01	0,01	0,01	0,01	0,01	0,01	0,01	0,01	0,01
				- Good pasture's syndrome	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
Total					€ 309,33	€ 309,33	€ 309,33	€ 309,33	€ 309,33	€ 309,33	€ 309,33	€ 309,33	€ 309,33	€ 309,33
Full tot.					€ 40.868,93	€ 24.815,29	€ 8.623,77	€ 5.659,13	€ 3.378,63	€ 802,62	€ 581,49	€ 411,39	€ 309,33	€ 309,33

I-2. Category 2: Patient and family

Travel expenses:												
Administration		Probability:	100%	100%	29%	16%	6%	0%	0%	0%	0%	0%
	Inpatient administration		5	3	0,87	0,48	0,18	0	0	0	0	0
Follow-up (excluding AE's)		Probability:	100%	100%	100%	100%	100%	29%	16%	6%	0%	0%
	Neurologist consult		5	4	4	4	4	1,16	0,64	0,24	0	0
	Nurse consult		4	4	4	4	4	1,16	0,64	0,24	0	0
	Monitoring		13	12	12	12	12	3,48	1,92	0,72	0	0
Total trips to hospital:			27	23	20,87	20,48	20,18	5,8	3,2	1,2	0	0
Total x cost (5,66):			€ 152,82	€ 130,18	€ 118,12	€ 115,92	€ 114,22	€ 32,83	€ 18,11	€ 6,79	€ -	€ -

I-3. Category 3: Other sectors

Method 1: Friction				Adjust with progression of EDSS score									
			Yearly absence da	**5**	**3**	**0,87**	**0,48**	**0,18**	**0**	**0**	**0**	**0**	**0**
			Days after ZiN cut-off	5	3	0,87	0,48	0,18	0	0	0	0	0
Zorginstituut		**8**	Hours per day	8	8	8	8	8	8	8	8	8	8
Nederland	**Specify gender**	**Unknown**	Total:	1390	834	241,86	133,44	50,04	0	0	0	0	0

I-4. Total cost

		Timeline:	T= year 1	T= year 2	T= year 3	T= year 4	T= year 5	T= year 6	T= year 7	T= year 8	T= year 9	T= year 10
Category 1 - Costs within care												
	Acquisition & administration		38.001,60	22.804,96	6.613,44	3.648,79	1.368,30	-	-	-	-	-
	Monitoring		2.558,00	1.701,00	1.701,00	1.701,00	1.701,00	493,29	272,16	102,06	-	-
	Adverse events		309,33	309,33	309,33	309,33	309,33	309,33	309,33	309,33	309,33	309,33
Category 2 - Patient and family												
	Travel expenses		152,82	130,18	118,12	115,92	114,22	32,83	18,11	6,79	-	-
Method: **Manual inputation * ZiN**	Informal care		-	-	-	-	-	-	-	-	-	-
Category 3 - Other sectors												
Method: **Zorginstituut**	Productivity loss		1.390,00	834,00	241,86	133,44	50,04	-	-	-	-	-
	Total		42.411,75	25.779,47	8.983,76	5.908,48	3.542,89	835,45	599,61	418,19	309,33	309,33