Exploring the Integration of Evidence-Based Medicine, Quality of Life Considerations and Health Economics for Rare Diseases

A Thesis submitted by

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Abstract

This thesis is expected to contribute to the practice of treatment of rare diseases by integrating the three perspectives Evidence Based Medicine (EBM), Quality of Life (QoL) and Health Economics (HE) considerations into a comprehensive framework. Rare diseases have low prevalence but combined affect approximately up to 10% of the overall population, posing unique challenges across all three perspectives. Multiple stakeholders exert influence and drive decisions based on different and sometimes conflicting criteria and objectives, resulting in controversies and real or perceived suboptimal outcomes and deployment of resources which affect the well-being of patients. EBM, QoL and HE are not directly linked with one another and most often not considered together in all relevant decisions. Agency theory is utilized as an underlying theoretical framework. Both previous research and current empirical evidence have identified some gaps which are consistents with the double agency theory framework and, in addition, with the missed opportunity to fully integrate the three perspectives. This thesis aims to confirm and possibly close some of these gaps, broaden the scope and applicability of the theory, attempting to offer an integrated approach that mitigates the current empirical observation that each approach is taken independently forces on the other stakeholders' suboptimal results. A deductive research method was selected and both qualitative and quantitave research was pursued. This thesis reports on research that focuses on Hereditary Angioedema (HAE) as an example for rare diseases, using a combination of a broad survey with treating physicians, a search on social media and a meta-analysis of scientific articles and research on the condition and its relevant aspects. The chosen methodology allowed for a broad scope of sources and perspectives, consistent findings and strong conclusions, and the identification of potential gaps and misalignments. The research confirmed patients, the physicians and the payers as the most important stakeholders. It also provided insights on the variables leading to diagnosis and treatment decisions, which included specific aspects of the condition, behaviors by patients, caregivers and physicians, alternative treatment options and objectives, with their corresponding implications on clinical outcomes, QoL and costs. The different components of the research mapped into the themes identified in the literature search, reinforcing the application of the theoretical framework and extending its application into the area of rare diseases. While answering the RQs and substantiating the application of the double agency theory as an underlying theoretical framework, the thesis was able to prove the interrelation of the different variables, possibly setting the groundwork to develop an algorithm or a formula which would allow to optimize the outcome of the treatment and the funding decisions. However, current constraints such as high variability and lack of sufficient data would probably cause such an algorithm to be cumbersome and of limited use in real life. On the other hand, the prioritization and quantification of the variables, may be instrumental and could contribute to building bridges across the stakeholders patients, physicians and payers, enabling the sharing of knowledge and augmenting its impact through the integrated approach, offering a more robust instrument to enhance the impact of their action.

Certification of Thesis

This Thesis is entirely the work of Andreas C. Amrein except where otherwise acknowledged. The work is original and has not previously been submitted for any other award, except where acknowledged.

Principal Supervisor: Prof. Jeffrey Soar

Associate Supervisor: Prof. Peter A. Murray

Student and supervisors signatures of endorsement are held at the University.

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Glossary

Angioedema	Swelling of the area beneath the skin, similar to urticaria, or hives, but different as urticaria affects only the top layer of skin. Angioedema affects the deeper layers, including the dermis, subcutaneous tissue, the mucosa, and submucosal tissues
Appendicitis	Inflammation of the appendix, that causes pain in your lower right abdomen
C1-inhibitor	C1 esterase inhibitor
DALY	Disability-Adjusted Life Year, a time-based measure that combines years of life lost due to premature mortality and years of life lost due to time lived in states of less than full health
EBM	Evidence based medicine
Epidemiology	Study of distribution, determinants and control of health-related states and events in populations
ER	Emergency room
Erythema marginatum	Redness of the skin or mucous membranes involving pink rings on the torso and inner surfaces of the limbs which can manifest over several months.
FDA	Food and Drug Administration
HAE	Hereditary angioedema
HCP	Healthcare professional
HE	Health economics
HRQoL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio, to compare two treatments, divides difference in cost by the difference in effect
ICU	Intensive care unit
Incidence	Epidemiological measure that takes into account the time when a new disease or a new case of a known disease occurs among members of a population. Captures the dynamic of the disease in a particular population.
Intussusception	Serious condition in which part of the intestine slides into an adjacent part of the intestine. This "telescoping" often blocks food or fluid from passing through
IV	Intravenous
LTP	Long term prophylaxis
Mesenteric lymphadenitis	Inflammation of the lymph nodes which are in a membrane that attaches the intestine to the abdominal wall

NRCT	Non-randomized clinical trial
RCT	Randomized clinical trial
RWE	Real world evidence
QoL	Quality of life
QALY	Quality-adjusted life year, the number of quality years of life that would be added by an intervention. One QALY is equal to one year of life in perfect health. Often measured in terms of the person's ability to carry out the activities of daily life, and freedom from pain and mental disturbance.
SC	Subcutaneous
Strangulation ileus	Loop of the small intestine caused by abnormal adhesion
Thyroiditis urticaria	Chronic skin condition characterized by recurrent attacks of itchy hives that may vary in size, number and distribution, that patients experience daily for more than 6 weeks
YPLL	Years of potential life lost, by reference to the number of years between a subject's age of death and his/her corresponding life expectancy.

1 CHAPTER 1 - INTRODUCTION

1.1 Overview

Healthcare systems profess to have the patient at the center, yet it is healthcare professionals and payors that do most of the therapeutic decision making on behalf of the patient (Szasz, 1997) and few are involving the patients or even adjust care to the patient's preferences (Couet, 2013). Applying agency theory, patients are the principals, while physicians and payors are agents (Tofan, 2012). Using healthcare systems over time, physicians have developed and are using Evidence Based Medicine (EBM) as a decision-making tool to optimize the clinical outcome for the patients (Greenhalgh, 2014, Sackett, 1997). They are looking for efficacy. Payors (healthcare authorities, insurers) on the other hand pursue Health Economics (HE) and need to allocate limited resources across an ever-increasing number of patients with costs of drugs and healthcare services surging at the same time. They are looking for effectiveness (Eis, 2012) and use Real World Evidence (RWE) to determine it. Patients, on the other hand, are living with the condition, the symptoms, the co-morbidities (other coexisting conditions), and the burden of the disease which impacts their Quality of Life (QoL). The different stakeholders have different skills, priorities, incentives and most often are not communicating with each other on each case. This causes a disconnect between stakeholders as the three perspectives are not considered in a holistic way when making treatment and funding decisions. Each approach taken independently forces suboptimal results on the other stakeholders. This disconnect between the approaches is a source of controversy and misalignment between patients, physicians and payors (Fuchs, 2011) although there have been attempts to involve patients towards EBM in order to lead to more efficient decision-making (Greenhalgh, 2014). This thesis first analyzes the different perspectives and then their dependency, differences and gaps, aiming to provide a more comprehensive evidence-based decision-making framework which improve the alignment of all stakeholder needs and priorities and which may support the achievement of improved and more cost-effective healthcare solutions. The rare disease Hereditary Angioedema (HAE) was chosen as a sub-segment of medicine, as it allows focus while meeting a strong need because the challenges of diagnosis, treatment, QoL and associated costs are high.

1.2 Background

1.2.1 Healthcare systems and drivers

In physics a mechanical system of three bodies subject only to the force of gravity is already known to be “unstable”: there is no combination of position and movement that ensures equilibrium. In a similar way, healthcare systems have more than three independent forces (or stakeholders) which interact and which affect the clinical outcome, the QoL and the economic aspects of a treatment. Similarly as in physics, no healthcare system appears to be in equilibrium, or even recognized by all stakeholders for offering the best possible solution. Different processes and incentive systems for the different stakeholders generate different forces with varying degrees of negotiating power. Even a regulator backed by government and law is not omnipotent and will be forced to change when the political power shifts. Supremacy through information asymmetry, for example, healthcare professionals recommending over-sophisticated expensive treatments to naïve, unaware and intimidated patients, can only go so far. Patients do not get necessary treatment when they cannot afford to pay or when payers (insurance companies and reimbursement agencies) put in place budgetary blocks based on real-life health outcomes combined with a measure in monetary terms. Willingness to pay is influenced and sometimes limited by the ability to pay. If a disease can be treated by a low-cost generic, payers may not see the need and pay extra for the drug with a new mechanism of action with apparently no superior efficacy. If the disease can be treated effectively with an injection, why should the payer pay much more for an oral formulation and its increased convenience (Insight, 2016)? Should a part of the budget be used for a severe need of a few or rather for a medium or moderate need of many more? How much of the budget size and allocation is influenced by advertising and lobbying?

1.2.2 Current challenges and opportunities

The “freedom of therapy” (or ”clinical autonomy” (Britten N. , 2001)) enjoyed by doctors until recently, may be coming to an end. Scientific progress translated into consensus on therapy standards, improved transparency, increased exposure to malpractice suits, augmented pressure from insurers and payers to reduce spending, the introduction of AI for diagnostics and therapeutic decision making and more, might be limiting the available choices, while at the same time enable more efficient decisions which should produce better outcomes. New technologies such as Watson, AI and machine learning have been developed or are being developed for use in healthcare mainly to support the management of large quantities of data. During the writing of the thesis, the use seems still not to be firmly or consistently established. While the situation is evolving, it can be observed that even healthcare systems which are very advanced and which have some of the largest healthcare spending per inhabitant as a percentage of GDP and in absolute terms (Reinhardt, 2004), can be facing a reduction in life expectancy (NCHS, 2017). Despite better education, better drugs, better diagnostics, more available funds and better data, suffering and morbidity are increasing (Anderson, 2003). Morbidity increases with lifestyle choices on diet and physical activity. Yet, in addition, such outcomes can be explained by a combination of suboptimal utilization of scientific knowledge, infrastructure, information, funding and faulty decision

making driven by specific processes and incentive systems which do not drive the right therapeutic behaviors as required (Davis, 2007; Starfield, 2000).

1.2.3 Implication for rare diseases and rationale for this thesis

While above holds true for practically all areas of medicine across therapeutic areas and healthcare systems, it is especially true for patients afflicted by rare diseases who suffer the most. Rare diseases are mostly debilitating and life-altering, wrong therapeutic decisions have a significant impact in terms of health outcomes and quality of life (Schieppati, 2008). The gaps between what is theoretically and practically possible today and what truly happens in real life, can in many cases not be explained by lack of solutions, lack of funding or even lack of policy or goodwill. The main goal of this thesis relates to how fully integrated evidence-based decision making would provide important benefits to patients, healthcare providers and payers. Comprehensive real-world data can provide the evidence in a way that clinical trials cannot, for example, that increased patient convenience leads to improved long-term outcomes (through better compliance) and thus justifies the higher cost.

1.2.4 Decision-making challenges in healthcare

The healthcare industry is a complex system of stakeholders with widely differing objectives, incentive systems, depths of knowledge, experience, criteria for decision making and personal exposure to the consequences of the decisions made. The road to the ultimate goal of universal, optimal and affordable health coverage for all is paved with challenges and inefficiencies (Evans, 2013), and still a long way off into the future (Shaikh, 2017). At the center of healthcare is the patient who has a medical need. The prescribing doctor performs a diagnosis, prescribes treatment and assesses the outcome (Couet, 2013, Szasz, 1997). While this basic process is followed around the globe, it is also burdened by complexity and conflicting forces.

In the recent past, the term EBM was coined to describe and promote the process of systematically finding, appraising and using contemporaneous research findings as the basis for clinical decisions (Rosenberg, 1995; Straus, 2019). This approach factors in the clinical outcome of the therapy (also expressed as efficacy). After two decades of enthusiasm and significant improvements, a set of challenges surfaced, such as distortion of the evidence brand, an unmanageable plethora of evidence, increasingly marginal gains, overemphasis on following algorithmic rules, and a poor fit for multimorbidity (Greenhalgh, 2014). More research is needed to incorporate all available evidence, address the newly identified challenges and improve the treatment approaches for the well-being of the individual patient (Hoffmann, 2014), while maximizing the effectiveness within the larger socio-economic context. A society governed by the laws of economics, i.e. with limited resources and funding, needs to make choices and set priorities on which treatment to offer one or more individuals and at what cost, in order to maximize the health outcome of the whole population. Payers already have to make these decisions with the support of bodies dedicated to evaluating healthcare excellence (NICE, 2018). Some drugs and treatments are not reimbursed for everybody or at any price (Goodall). Such decisions often are controversial,

especially for the affected individual patient (Donnelly, 2015) and are or should be the result of clinical, ethical and economic considerations.
This thesis set out to analyze the current decision-making process, drivers, incentives and impact of the key stakeholders on the treatment of rare diseases.

1.3 Motivation for the thesis

1.3.1 Challenges specific to rare diseases

Rare diseases pose a number of additional and unique challenges that have a direct impact on the well-being of the affected individuals, their families, their workplace, social environment and, by aggregation, to society. Awareness concerning rare diseases is low due to the extremely low prevalence of these conditions. Relative lack of experience and education frequently are reasons for no diagnosis or misdiagnosis (Shen, 2017). For several rare diseases, patients are diagnosed only after years, decades, and sometimes never (Knight, 2006, Zanichelli, 2015). The identification of patients through classical screening programs is economically and logistically not viable given the low probability of finding patients when the prevalence is less than 1:10,000. Innovative approaches using big data, social media and medical record data mining, bio markers and more, are required to provide the diagnoses for rare disease. These approaches are also required in some cases to discover the patients, and for evidence-based decision making in the course of action. Rare diseases are mainly genetic, frequently hereditary, but they can also result through genetic mutations. In almost all cases they are debilitating and cannot be cured, except with gene therapy which is in its infancy (Schieppati, 2008). The only options for people living with a genetic disease are drug therapies which aim to mitigate the symptoms and allow for a better quality of life. Rare diseases often increase their devastating impact on patients through co-morbidities (other coexisting conditions) which impede normal life. Education, professional development and career opportunities are significantly affected causing stigma, as the patients tend to fall behind in their professional development, refrain from participating in social activities, and are perceived or perceive themselves as not being “normal”.

1.3.2 Expected contribution of this thesis

This thesis was expected to contribute to the decision-making process in regards to optimize the use of resources to help affected patients. Drugs that treat rare conditions are called orphan drugs. Their discovery and development costs are approximately the same as for mass-market conditions, but the small number of diagnosed and treated patients allow for only a fraction of the drug consumption. Thus, there is a significantly reduced volume base to recoup the investments made in orphan drug discoveries. For this reason, treatment costs are significantly higher and, in most cases, not affordable by the individual. Regulatory bodies and payers cannot apply the same criteria for approvals and reimbursement as for the more classical treatment methods. From a utilitarian perspective, it would be considered unethical to invest substantial amounts of resources to develop treatments for rare conditions, as it is not maximizing society’s benefits, even more so when considering

opportunity costs (Gericke, 2005). On the other hand, society has the moral obligation not to abandon individuals that are affected by severe conditions, as rare as they might be.
While in many cases scientific knowledge, drugs and even funding do exist to mitigate the condition, in real life only a minority of patients benefit. A comprehensive and fully integrated evidence-based decision-making protocol for healthcare systems could provide economically viable and acceptable relief to people affected by these conditions and with a significant unmet medical need.
The focus of this thesis relates to the effectiveness - the extent to which an intervention does more good than harm when provided under the usual circumstances of healthcare practice - vs. efficacy - the extent to which an intervention does more good than harm under ideal circumstances such as within a trial. To evaluate the efficiency and the cost efficiency of therapies, clinical trials need to be supplemented with RWE, and this thesis builds heavily on performing meta-analyses by consolidating a body of knowledge built over the recent years for HAE.

1.4 Thesis aims

The thesis aimed to first understand and describe in a structured way existing decision-making processes, variables and criteria used by the different stakeholders involved in therapeutic decision making and funding. Agency theory was used as an underlying theoretical framework and as a basis for understanding better the connectedness of a healthcare system. The thesis aimed to validate its mechanisms and some of its gaps, like the complication that within healthcare systems there are multiple agents for the same principle, that they influence one another, that there are different information asymmetries which can be in either direction. This was expected to be achieved with an analysis of new data that has become only recently available thanks to the soaring digitalization, the diffusion of databases, and the advent of complex analytics. The objective was to integrate the increasingly granular and longitudinal RWE and relevant socio-economic data into one framework which could subsequently be used to drive decisions which maximize both health and quality of life outcomes at the individual level and within healthcare systems as a whole. The full integration of all known considerations is key to achieving a more comprehensive evidence-based decision-making framework. By applying agency theory, it was envisaged that such a framework would be explained in such a way that a network of relationships could be better articulated between health providers, payors and end-users within the healthcare space.
This thesis focuses on rare health conditions, specifically a potentially fatal condition, or HAE, where the burden of the disease, impact of drugs and economic implications are stronger than for comparable mass market and specialty ailments (Angelis, 2015). Further, this segment of the healthcare space has been going through a rapid transformation which is raising new challenges to all stakeholders (Schieppati, 2008). This is the case for health care providers and payors who face unmet medical needs combined with economic constraints, ethical dilemmas (Gericke, 2005) and unclear and incomplete data (Hughes, 2005, Picavet, 2011).

In this thesis, a theoretical framework and some of its gaps are validated. With the newly accessible data, possible extensions in scope have been explored, aiming to develop a more comprehensive framework. This framework is expected to describe and guide through an improved and optimized collection, interpretation and leverage of evidence which can then be utilized by the various stakeholders to produce better health outcomes. Beyond the principles, possible solutions and improvements have been developed for systems, processes, decision-making criteria, incentive systems, behaviors and communication by and between the different stakeholders. While the point of "perfect equilibrium" can probably not be reached, there is room for significant improvement, which was translated into more cost-effective, rapid and impactful healthcare. Optimized healthcare finds a balance between five closely interrelated dimensions (Groves, 2013) including (1) healthy living with individual lifestyle choices that maximize health and prevent disease, (2) appropriate care providing timely and appropriate treatment, (3) qualified healthcare provider performing the adequate activity to achieve the outcome, (4) appropriate resourcing ensuring cost-effectiveness while eliminating fraud, waste and abuse, and (5) appropriate innovation to drive further development.

2 CHAPTER TWO - RESEARCH QUESTIONS AND THEORETICAL FRAMEWORK

2.1 Problem Statement 1

EBM alone does not explain all therapeutic decisions made by physicians. Multiple stakeholders around the patient influence and drive therapeutic decisions based on different and sometimes conflicting criteria and objectives, resulting in controversies and real or perceived suboptimal outcomes and deployment of resources. The issue is further accentuated for rare diseases with far fewer patients, facing significantly higher treatment costs, and less information and experience available to drive decisions. The vast majority of rare diseases are genetic and cannot be cured. A few high-cost treatments exist, but they can only mitigate the impact on the quality of life of patients exposed to life-altering and debilitating symptoms.

RQ 1.1: How do different stakeholders and decision-makers have an impact on patients with rare diseases?

RQ 1.2 Are diagnosis and treatment decisions made with EBM, QoL, HE and RWE considerations in mind?

2.2 Problem Statement 2

The three perspectives EBM, QoL and HE/RWE are not linked and most often not considered together in all relevant decisions. The three key groups of stakeholders HCPs, patients and payers do not share objectives, decision-making criteria and not systematically communicate with each other neither on policy nor on the treatment of individual patients. This results in suboptimal clinical results, conflicts and missed opportunities of cost-effectiveness.

RQ 2: How can the decision-making process and the available and potentially available data be combined to allow the stakeholders to make economically more efficient therapeutic decisions with better health and QoL outcomes?

2.3 Theoretical framework

2.3.1 Agency theory

The thesis builds on the agency theory, which describes systems with principals and agents. "Agents" are persons or entities who are able and expected to make decisions on behalf of other persons or entities ("principals") and where the outcomes are the consequence of the agents' actions (Bandura, 2001). Dilemmas arise in circumstances where the agent is motivated to act following other interests that are different or even contrary to the ones of the principal. These dilemmas are called moral hazard. In its original form, agency theory argues that in the modern corporation, managers decide and act in their own interest, which leads to different activities and lower shareholder returns, compared to if the owners exercised control. (Pratt, 1985, Jensen, 1976). Another problem highlighted by agency theory is the problem of risk sharing, when principal and agent have different attitudes towards risk. These problems generate so-called agency loss which results from the asymmetry of information (Tofan, 2012) and misaligned incentive schemes. Agency theory has also developed mechanisms to reduce agency loss. (Eisenhardt, 1989, Dwyer, 2012). The basic idea of agency theory is illustrated in Figure 2.3.1.

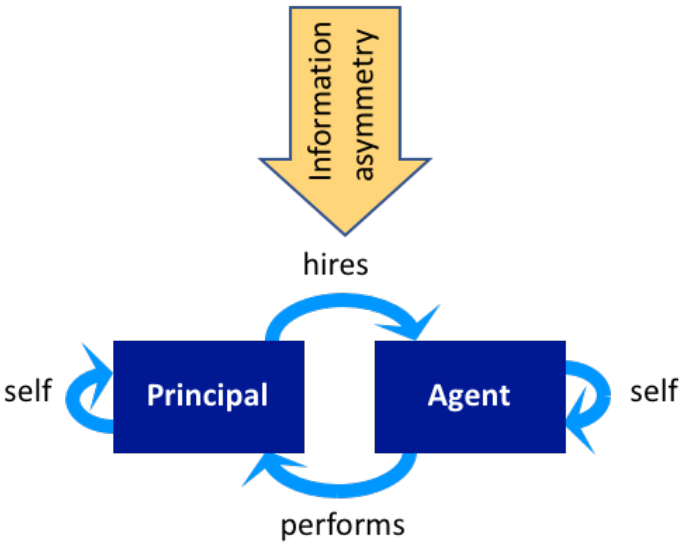

Figure 2.3.1- Agency theory

2.3.2 Agency theory adaptation to healthcare systems

The agency theory has been adapted from the business world to the healthcare space, with the aim to describe the mechanism, challenges and potential dilemmas (Langer, 2008, Gafni, 1998). Previous scholars have already identified the doctors as double agents, accountable to both the patients and the payors (Tofan, 2012, Angell, 1993), as illustrated in Figure 2.3.2.

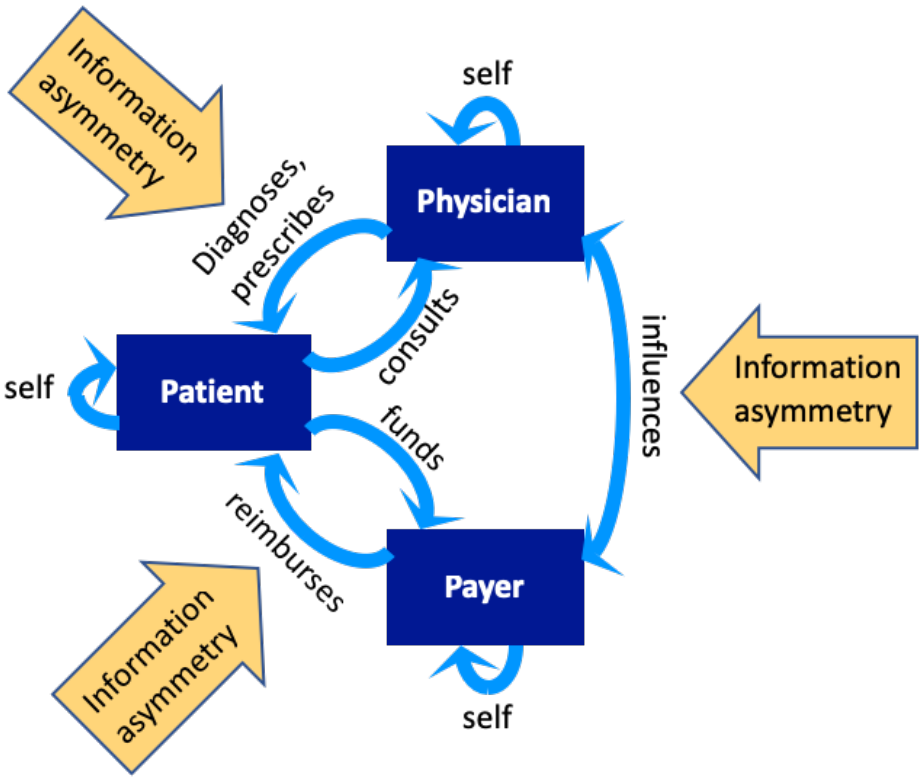

Figure 2.3.2 - Possible adaptation of agency theory to healthcare systems

Reality seems to require a more comprehensive and complex adaptation of agency theory: there are multiple interdependencies between all three parties and further complications producing information asymmetry, which can run in opposite ways across all stakeholders. Despite the complexity, the theory is expected to describe the mechanisms that lead to suboptimal outcomes and possible solution paths (Shortell, 1998, Scott, 2003, Stavropoulou, 2012).

This thesis is expected to observe and potentially confirm the real-life implementation of governance approaches in the area of modern treatment of rare diseases, which has been partially discussed in more generic settings by previous research (Vick, 1998). It will attempt to observe and confirm the governance devices in place to alleviate the agency problems between patients and physicians and then possibly contribute to the expansion of the theory with an integrated framework which can offer real-life results through better clinical outcomes, improved quality of life and increased cost-effectiveness.

3 CHAPTER THREE - LITERATURE REVIEW

The literature search was conducted through a systematic search by relevance (variables, rare disease, HAE, less than seven years) but also extended its scope beyond HAE and rare diseases to ascertain transferability of concepts. The literature search analyzed and extracted data from a selection of articles in Medline and Embase filtered for duplication and relevance based on the presence of relevant keywords. Articles were searched based on selected keywords such as EBM, QoL, health economics, diagnosis, treatment, clinical outcome, on demand treatment and other technical terms relevant to the treatment of medical conditions. These were subsequently combined with each other and with the terms “rare disease”, “genetic disease” and “hereditary angioedema” to ensure all literature pertinent specifically to the slected condition are also included. All references cited in the literature were also followed to include the original sources and the the sampling of articles was performed based on publication date (priority on articles after 2010) and availability of numerical data and quantitative analysis.

3.1 Evidence Based Medicine (EBM)

3.1.1 History of EBM

Florence Nightingale wrote in her book (Nightingale, 1863) about 150 years ago that “In attempting to arrive at the truth, I have applied everywhere for information, but in scarcely an instance have I been able to obtain hospital records fit for any purpose of comparison. If they could be obtained, they would enable us to decide many other questions. They would show subscribers how their money was being spent and what good was really being done with it.” In contemporary society, we still face the challenge of deciding how to use limited funds to decide on treatments relative to each other in terms of efficacy and cost-effectiveness.

In the 1980s the concept of Evidence Based Medicine (EBM) was coined at McMaster Medical School in Canada as a process to turn clinical problems into questions and then systematically locating, appraising, and using contemporaneous research findings as the basis for clinical decisions. The approach was triggered by the limitation of most doctors having a narrow perspective, limiting themselves to their own experience and that of a relatively few colleagues with whom they exchange views. This sometimes led them to make erroneous conclusions while also failing to search for evidence which might cause them to reach a different conclusion or allow them to come to a more balanced decision (Grahame-Smith, 1995). The physician’s personal experience can in most cases be characterized as anecdotal, ungeneralizable and not the best basis to make scientific decisions with the patient’s health as an objective (Green, 1998), yet still today it appears to be a most powerful persuader and driver, more so than scientific publications. All too often physicians, in their daily work, are unaware of the available clinical and scientific evidence and/or fail to apply it (Guyatt, 2004). Their values differ from the patients, who sometimes are not involved in the decision-making process (Couet, 2013).

3.1.2 Role of Randomized Controlled Trials in EBM

Randomized Controlled Trials (RCT) are the 'gold standard' for establishing efficacy and required to seek regulatory approval to market a drug, but they draw their data in an idealized environment and can only measure efficacy in limited populations. As such, compared to real-life data, they cannot provide a true indication of a drug or a treatment's effectiveness. (Annemans, 2007). Results are obtained in a highly controlled environment, over a small set of subjects, over a short period of time, across a handful of highly dispersed clinical trial centers. Regulatory bodies ask questions about the sole dependence on randomized clinical trials and the lack of real-life supporting evidence by pharmaceutical companies on the efficacy and effectiveness of new drug treatments (Saha, 2015). Subjects and patients are often highly selected (e.g. younger, stronger) raising questions on the representation of "all patients in the world". Further not every clinically important question can be addressed through clinical trials be it for recruitment challenges, ethical constraints, or other limiting factors. Real-life data needs to be sourced outside of the scope of a clinical trial and includes, for example, epidemiology, compliance, adherence and cost insights (Dangi-Garimella, 2017). An interesting side effect and reality check would be that real-world adherence is lower than in a clinical trial setting.

3.1.3 Use of evidence in EBM

EBM is the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients. The approach integrates individual clinical expertise with the best available external clinical evidence from systematic research (Sackett, 1996). Computer power (hardware and software) theoretically permits to rapidly locate any relevant evidence that would make it easier for busy clinicians to make best use of the published literature. (Rosenberg, 1995). With the invaluable skill to appraise critically publications of all types, it is possible to close the gulf between good clinical research and clinical practice (Rosenberg, 1995), especially to overcome the human trait of over-interpreting experiences with individual patients. EBM claims that experts are more fallible in their treatment recommendations than evidence from sound systematic observation, presuming further that in most cases basic science alone does not provide valid and practical guidance (Brian Haynes, 2002).

Hence the EBM approach is used across all steps from diagnosis, prognosis, treatment, quality of care, and health economics, with this latter still demanding most of the work and research.

3.1.4 Introduction of EBM into clinical practice

Historically medicine was based on the physician's authority, his personal experience, and a component of tradition. Few people understood the work of a medical doctor (Hoffmann, 2014). The basic assumption that led to EBM was that evidence from sound systematic observation enables better healthcare and better care for patients. The objective of EBM is to augment the individual clinical experience of healthcare practitioners, not to just replace their experience (Brian Haynes, 2002). On this pursuit, physicians, practitioners, health care managers, policy makers and patients follow up and integrate the best findings from research

that are both scientifically valid and applicable for treatment. In order to reach this improved state, practitioners in general had and still have to accept that the bases for therapeutic decision-making can change, they have to accept that some decisions made in the past are not valid anymore, and they have to embrace these evidence-based changes, sometimes admitting to them and explaining them to their patients.
In the more of two decades since its inception, the concept of EBM has delivered numerous successes, yet there is still a wide variation in its implementation, which is cause for challenges (Greenhalgh, 2014). Pharmaceutical and medical device companies have an economic interest which sets their strategic agenda. They decide on the drugs that will be pursued, the tests and treatments that will be compared, and frequently also the measures and the values which define both what is the condition and what is considered to be success in its treatment.

3.1.5 Current state of affairs of EBM

For some conditions with a high prevalence affecting a large share of the population and where significant clinical progress has been achieved, the volume of evidence available has increased exponentially. The volume of relevant data has become such that making it available and keeping the clinicians up to speed has posed a new hurdle (Greenhalgh, 2014). Conditions that have been at the center of attention for a longer period of time have been thoroughly researched and EBM is providing only marginal gains. Rare diseases that have been identified relatively recently appear to be subject to comparatively large investments, strong progress, and therefore surge in the available evidence.
Widespread use of EBM has made it a tool also for institutional control and healthcare policy, hence it has assumed a political component. As a consequence, changes and funding of medical practice have political, legal and medical implications which requite the attention and endorsement by the respective institutions (Greenhalgh, 2014).
Rare conditions have a dominantly genetic cause and often multimorbidity. Clinical trials aim to have a narrow scope to enable isolation of cause and impact, using or defining algorithmic rules. Subsequently, both the evidence and the algorithmic rules have a constrained spectrum of applications, which limits their usefulness in complex multimorbid patient situations.

3.1.6 EBM applied

Following the diagnosis of the patient, the clinician evaluates all available evidence in the form of articles, with a set of questions the reflects common sense, but is not always obvious (Rosenberg, 1995), for example

- Are the results valid?
- Was the assignment of patients to treatments randomized?
- Were all patients who entered the trial properly accounted for and attributed at its conclusion?
- Was follow up complete?
- Were patients analyzed in the groups to which they were randomized?
- Were patients, health workers, and study personnel blinded to treatment?

- Were the groups similar at the start of the trial?
- Aside from the experimental intervention, were the groups treated equally?
- What are the results?
- How large was the treatment effect?
- How precise was the treatment effect?
- Will the results help me care for my patients?
- Can the results be applied to my patient care?
- Were all clinically important outcomes considered?
- Are the likely benefits worth the potential harms and costs?

While the evidence would not automatically dictate patient care, it does provide a broader and more robust factual basis on which decisions can be made, compared to previous personal and more limited experience of the health practitioner. EBM takes all aspects of patient care into consideration and can subsequently be utilized directly in a patient's care or further, to develop team protocols or even hospital guidelines (Rosenberg, 1995).

3.1.7 EBM requirements

EBM demands a willingness to admit uncertainty, to encourage skepticism, and to be flexible, but with the advantage to accommodate new evidence which may contradict previous assumptions and practice (Rosenberg, 1995). This indicates that its potential for improving continuity and uniformity of care across health systems through the common approaches and guidelines developed by its practitioners is the basis of the ultimate objective of this thesis: broadening the scope to include healthcare effectiveness including wider and deeper socio-economic considerations.

3.1.8 EBM advantages

EBM offers a range of advantages: external clinical evidence invalidates previously accepted diagnostic tests and treatment and replaces them with new ones that are more powerful, more accurate, more efficacious, and safer (Sackett, 1997). It allows clinicians to routinely upgrade their knowledge base, improve their understanding of research methods and makes them more critical in using data, improves their confidence in treatment and management decisions. Clinical teams benefit from a framework for group problem solving, for teaching and for juniors to contribute usefully to the team. Most important is that patients benefit from more effective use of resources and a better understanding and communication about the rationale behind treatment decisions (Rosenberg, 1995).

3.1.9 EBM challenges

To complete the picture, EBM also poses a number of challenges: it takes time both to learn and to practice. Inevitably, it exposes gaps in the evidence, but this additional rigor and transparency forces research and development to higher standards of quality. While technology has become a strong enabler, electronic databases used for finding relevant evidence could still be not comprehensive, nor always well indexed, nor contain the information needed to avoid litigation (Sackett, 1996; Straus, 2019). Authoritarian clinicians may see EBM as a threat. It may cause them to lose face by potentially exposing their current

practice as obsolete or occasionally even dangerous (Rosenberg, 1995). Despite the use of much broader, validated and stronger evidence, the inherent bias of journals and authors towards positive results stays: they are not so interested in negative conclusions; things are much more interesting if they turn out positive (Grahame-Smith, 1995). Some critics argue that at best, EBM is a heuristic method for a lower level of partial abstraction (Sackett, 1996) not giving justice to its strengths when fully applied. Another potential risk could be that taken in isolation, better data can lead to additional activity without improving overall patient outcomes (e.g. unnecessary screening to amortize expensive equipment or resources). Additional evidence would need to come together with more transparency, improved scrutiny and realigned incentive systems to prevent such abuse. The primary challenge with real-world data and true evidence is to ensure quality and the right incentives at the point of care to extract relevant information (Dangi-Garimella, 2017). The use of real-world evidence could introduce new sources of bias which can completely distort the results: different degrees of severity of a condition are often treated with different drugs which makes some treatments look more or less effective than what they really are or than what would be visible in an observational study. Ultimately, a practical limitation may need to be considered: most busy prescribing doctors simply lack the time or the skills to track down, absorb and integrate the evidence into their daily routine (Davidoff, 1995). To help the physicians with their treatment and to ensure a consistent approach across patients and healthcare systems, clinical guidelines are being used.

3.1.10 Purpose of clinical guidelines as an execution instrument for EBM

Clinical guidelines have been introduced and are a widespread and essential tool to ensure high-quality medical practice. They deal with clinical conditions or symptoms, health care providers and clinic managers use them in their daily patient management (Woolf, 1999) through health care policy, planning, delivery, evaluation, and quality improvement. They consolidate and bridge the gap between EBM, policy, local contexts and patient choice (Kredo, 2016). Clinical guidelines are transparently constructed, and continuously updated evidence-informed approaches integrated with expert opinion and patient values (Grilli, 2000).

Guidelines can be developed by representative groups of specialists, or also by official institutes like the National Institute for Health and Clinical Excellence (NICE) in the UK. NICE produces clinical guidelines, quality standards, public health and health technology appraisal guidance for the National Health Services. In its function, the institute commissioned the National Clinical Guideline Centre (NCGC) to produce clinical guidance and quality standards on patient experience in adult NHS services. Such a process showcases the important role that guidelines have in ensuring high-quality, effective and appropriate health care to the population (Staniszewska, 2014).

3.1.11 Application of clinical guidelines in medical practice

Clinical guidelines assist physicians and patients when making therapeutic decisions about appropriate health care for specific clinical circumstances (Graham, 2011). In practice, clinical guidelines are recommendations intended to optimize patient care, built on a systematic review of the evidence and an assessment of the benefits and harms of alternative care options. In addition to recommendations on specific drugs to be prescribed, they may offer concise instructions on which diagnostic or screening tests to perform, how to provide medical or surgical services, how long patients should stay in the hospital, or other details of clinical practice (Woolf, 1999). Other frequently used descriptions are protocol and care pathways. Protocols are sets of rules or instructions about how to do a particular process explicitly, and without error (Campbell, 2003). Care pathways describe series of evidence-informed steps, which lead the journey of care of patients following a particular diagnosis (Rotter, 2010).

The adherence by physicians and patients to guidelines improves effectiveness and quality of care, decreases variations in clinical practice and decreases costly and preventable mistakes and adverse events (Kredo, 2016).

3.1.12 Clinical guidelines as a means to reduce complexity and costs

A few decades ago, for most conditions, there was a single class of drugs built on a single mechanism of action, with a few primary drugs with similar profiles that could all be prescribed. Science and medical knowledge have increased exponentially and today, for the same condition, several biochemical processes are addressed by multiple classes (for some oncologic conditions there can be at least seven or eight primary drugs that in addition can freely be combined between them (Frank, 2007)). Healthcare costs are rising rapidly, driven by an ageing population with increased demand for care which includes more and more expensive technologies.

The concomitant cognitive burden faced by many physicians can cause wrong or delayed decisions, additional costs, and suboptimal health outcomes for the affected patient. In addition to the complexities driven by scientific progress, physicians are exposed to other sources of complexity as well. Globalization has caused many countries to become more diverse in terms of cultures, races, ethnicities, with consequently different attitudes and levels of experience towards illness and responses to treatment. Healthcare systems appear to have stratified with more fragmented insurance arrangements. Physicians are serving patients covered by different insurance plans with each plan possibly having different prices, coverage and constraints on utilization of care and prescribing.

Such complexities and diversity can cause variations in service delivery among providers, hospitals, and geographical regions. A likely result would be that at least some of this variation stems from inappropriate care and the overuse or underuse of services. Healthcare professionals desire and are bound by agency to offer the best care possible and therefore clinicians, policy makers, and payers see guidelines as the instrument to make care more consistent and efficient (Woolf, 1999). Guidelines, protocols, pathways on what physicians and health care professionals should do in particular situations are instruments in the effort to improve quality of care and its cost-effectiveness (Shortell, 1998). The consensus and the

therapeutic execution based on updated guidelines would reduce complexity, close the gap between what clinicians do and what scientific evidence supports, providing solutions that timely and effectively benefit the majority of all stakeholders in a consistent manner. In short, clinical guidelines improve efficiency through standardized care and optimized value for money.

3.1.13 Clinical guidelines vs. customization

Customization of medical care drives four types of costs (Frank, 2007): (1) Communication costs: Communicating with patients to determine their symptoms, histories, and preferences take time and effort. More and more patients seek information on the Internet or have already been influenced by friends or family members, by direct to consumer advertising or by the popular press. Frequently the treating physicians need to correct or complete wrong or misleading perceptions developed by nonprofessionals and persuade or negotiate the following of the correct treatment (Groopman, 2007). (2) Cognition costs: Effort and time required by a physician to absorb, comprehend and factor in all information from different sources (including patients and clinical evidence) necessary to decide on treatment and to follow up based on outcomes. (3) Coordination costs: Moving away from consensus treatment paradigms and guidelines, physicians possibly need to involve other stakeholders either for advice or for approval for decision and execution of treatment. (4) Capability costs: To provide customized medical care, physicians need to have the right capabilities to understand and be able to prescribe different therapies or combinations thereof. Such specialization requires upfront one-time investments and normally also continuous medical education to stay up to date with scientific progress.

3.1.14 Limitations of guidelines

Despite their known benefits, studies have shown that guideline implementation is complex and challenging. The different stakeholders (patients, physicians, health institutions, healthcare systems, and more) are often subject to misaligned or even competing drivers and incentives (Liang, 2017). In areas undergoing rapid scientific advancements and progress, guideline developers and implementers may find it harder to stay updated or even aware of the latest and most relevant theories and results among the multitude available, when choosing or tailoring medical interventions.

Guidelines are by definition designed for an effective health impact on broad classes of patients. Individual patients might be exposed to unique circumstances and the optimal treatment might not be aligned with the guidelines and in addition entail costs of coordination and cognition, which takes the treatment approach back to how it was done historically (Frank, 2007). Rigorously following the guidelines may lead to wrong recommendations for individual patients or groups of patients.

More fundamentally, concerns have increased on the quality, reliability, and independence of practice guidelines. It has to be remembered that scientific evidence about what to recommend can still be lacking, misleading or misinterpreted. The guideline development groups additionally influence the content of the guidelines through opinions, different experience or other parameters affecting individual members differently. Guidelines also do

not require unanimous endorsement to become effective. Studies have been conducted on the quality of guidelines measured in terms of whether they reported the type of professionals and stakeholders involved in the development process, the strategy to identify primary evidence and how recommendations were graded according to the quality of supporting evidence. The majority did not meet the criteria indicating that basic improvements need to still be made, including the setting up of explicit methodological criteria for the production of guidelines (Grilli, 2000; Kung, 2012; Shaneyfelt, 2012; Ruan, 2015).

3.1.15 Evaluation of healthcare

The evaluation of health care depends on the criteria used by every stakeholder. Overall it has been advocated at a relatively early stage that in aggregate three criteria should be used: clinical effectiveness, economic efficiency and social acceptability (Doll, 1974). This thesis aims precisely to measure the impact of the different stakeholders and the roles of the different perspectives in the decision making and execution of alternative therapies, with the objective in the second phase to explore the combination of all in order to attain superior outcomes in a more cost-effective way. Social acceptability plays a key role, as Doll (1974) already noted, “there is no point providing a health service that is clinically effective and economically efficient, but no-one wants”.

3.1.16 EBM and shared decision making

EBM is defined as the explicit, judicious, and conscientious use of current best evidence from health care research in decisions about the care of individuals and populations (Brian Haynes, 2002). Once a diagnosis of the condition is confirmed, ideally patients and healthcare provider decide together on the course of action based on the available and known evidence. The treatment decision by the physician should not only build on research and clinical evidence, but also reflect the patient’s values, preferences, circumstances and local context. (Hoffmann, 2014). Patients and clinicians would-be partners and such a partnership would presume that the treating physician facilitates patient involvement and is open to adjusting the treatment to the preference of the patient. Studies have shown that patients are unable to fully partner during the clinical encounters, and at the same time, physicians do not like their patients to engage (or interfere) in the decision-making process (Couet, 2013). Lack of time, skills, knowledge, mutual respect and effective communication processes pose barriers to effective shared decision-making (Staniszewska, 2014). It appears that a large portion of doctors believe they know how much the patient wants to be involved and even what therapy the patient would prefer, if he or she had full access to and ability to fully interpret the clinical data. With this approach, EBM could turn into forcing evidence and measures onto a not fully engaged patient resulting in suboptimal adherence and clinical outcomes.

The ideal working solution is best described as shared decision-making, where both clinician and patient jointly assess options with their benefits and harms, and together decide, incorporating the patient’s values, preferences, and circumstances (Hoffmann, 2014). High-quality patient experience demands a few additional attributes from the interaction with the

physician: the patient is an active participant, the physician is responsive with his or her services, he or she offers an individualized approach, provides a lived experience that includes continuous care and relationship, and lastly offers timely communication, information and support (Staniszewska, 2014).

3.2 Randomized Clinical Trials (RCT)

3.2.1 RCTs

EBM had been mainly defined by scientifically validated evidence generated through RCT (randomized clinical trials). Increasingly there is awareness and belief that the patient's experience of the condition, as well as the real-life implications, should be included in all EBM considerations (Greenhalgh, 2014). RCTs are designed to demonstrate under ideal and controlled conditions the causality between the use of a specific drug or treatment and the intended and unintended effects on the health of the study subjects. RCT generate results from a small set of patients in a highly controlled environment, across a handful of highly dispersed clinical trial centers over a short period of time (Saha, 2015).

RCTs follow a few key concepts (Gerss, 2010). They need to be externally valid, which is achieved through the recruitment of representative samples and the use of inductive statistical analyses, where the results can be generalized from the sample to the total population. To assess the effect of the studied treatment, internal control groups are assigned to receive a control intervention which can be a placebo, a reference treatment (if a head to head comparison is the goal), or the same treatment with different dosing administration quantities, or scheduled, or no treatment at all. Internal validity across patient groups is obtained through randomization and both subjects and trial personnel are kept blinded, which coined the name "double blinded", to remove bias. Primary and secondary outcomes are pre-specified before the trial starts, and carefully defined to satisfy criteria of validity, to measure what is intended, to eliminate or minimize bias, to be reliable, sensitive to change and realistic. The analysis has to be pre-specified to ensure validity is obtained, and that basic null- and alternative hypotheses are specified. Scientific evidence is achieved by statistical significance, which defines the sample size based on the upper bound of false positives that is considered acceptable, which usually is set at 5%. When publishing results, it is expected that the researchers reveal the level of scientific evidence and the limitations of the trial and its conclusions.

3.2.2 Limitations of RCTs

RCT narrow down the scope to highly selective populations which as a result cannot be compared with or are not representative of the more heterogeneous populations in real life where patients show varying genetic make-ups, present different comorbidities and/or are already under treatment with other medications. The majority of RCTs fail to achieve their initial enrollment projections and delays in patient recruitment can disable the trial and potentially halt the whole R&D program (Davis, 2017). RCTs are not the only source of good quality, reliable evidence. For rare diseases, in particular, meta-analyses of individual

trials can help address the challenge of individual low powered clinical trials (Day, 2010). Another approach is Real World Evidence (RWE).

3.3 Real World Evidence (RWE)

3.3.1 RCTs vs. RWE

RCTs are required by regulatory bodies as a mechanism to evaluate the efficacy of new drugs. RCTs cannot be replaced as controlled environments are needed to separate the impact of medical interventions. RCTs presume data being generated by a given probability distribution curve whereas different causes and effects are being tested. To evaluate the cost-efficiency in absolute terms and in relation to other treatments, RCTs need to be supplemented by RWE (Saha, 2015). Increasingly regulatory bodies such as the FDA expect from pharmaceutical companies additional real-life supporting evidence on efficacy and effectiveness of new drug treatments. The differences are, that in RCTs patients are randomized to the treatments; physicians, and patients' choices are not considered for selection of the treatment, non-adherent patients are taken out of the analysis and the experiment is based on an artificially created homogeneous treatment group. The purpose of RCTs is to establish the efficacy of the medication/therapy. With RWE on the other side, therapy or medications to patients are determined by doctors' choices as per standard practice, non-adherent patients can switch the treatment and in such a case are likely to remain included. RWE contains heterogeneous patient populations reflecting realistic scenarios which are likely to indicate the effectiveness of the drug/therapy under various conditions. Real world data for RWE enables to better understand the full impact of a condition at a much larger scale than is possible with RCTs: it can enable researchers to observe and understand the patient's experience across millions of patients versus the few thousand that are part of a typical RCTs. (Davis, 2017). RWE is the intersection between the structured rigor of RCTs, and the clinical exposure a treatment receives in real-life practice (Looney, 2016). RWE covers the whole patient journey through the treatment cycle and enables the learning of how the treatment performs in a wider variety of populations and practice settings. Observing how drugs are dosed and applied in clinical practice and how patients adhere to the prescribed therapies, would allow for a definition of more realistic clinical practice standards and guidelines. Under every scenario, RWE should substantiate the findings and the conclusions generated in more controlled settings, while also contributing to the generation of hypotheses to identify new drug targets, drug labels or new patient populations that may benefit. RWE is expected to generate insights that can be leveraged to affect decisions from R&D through commercialization, through the entire product life cycle. For rare diseases, it is often not possible to recruit an adequate sample size to attain statistical significance and test treatments following accepted and robust study designs for hypothesis testing (Hughes, 2005). This reality would further support the use of RWE for such conditions.

In connection with RWE, the expresssion real-world data is also frequently used. The two terms real-world data ad RWE are used interchangeably but are in fact different (Elton, 2015): Real world data provides patterns of information that allow clinicians to make

appropriate treatment decisions. RWE is the next step: the data is used to generate insights utilizing a rigor of analysis comparable to randomized and controlled clinical studies. As such it becomes representative and timely, complements traditional sources, validates clinical trials and becomes the foundation for pricing linked to therapeutic value and health outcomes as a whole for health systems. Real-world data is observational data which can be categorized into four types: (1) Patient claims data (available typically with payer, prescriptions, procedures, demographics, diagnoses, etc.); (2) Patient registries (available with provider and payer, demographics, diagnosis, prescriptions, laboratory tests results, outcomes, etc.); (3) Electronic health records (EHR/electronic medical records (EMR)), demographics, family histories, hospitalization details, etc.); (4) Web/social data (sentiments, dialogues). Real-world data can have a broad range of applications and is of immense value, yet it may not be a replacement for RCTs which, for the foreseeable future, appear to continue being the "gold standard" for demonstrating safety and efficacy.

3.3.2 Big Data, AI and machine learning

In the recent years technological progress in the information technology sector has brought substantial innovation opening possibilities to work with large amounts of data. The rapid surge of information thanks to the digitization has coined the term Big Data: not only for its sheer volume, but also for its granularity, complexity, diversity and timeliness. Researchers and practitioners can now mine the data to see what treatments are most effective for particular conditions, assess side effects, and increasingly important, assess and compare the socio-economic impact, from the costs to the quantification of QoL parameters (Lumry, 2018). This has been a hot topic for some years and there is a wave of research and attempts at applications, but reality suggests challenges in execution and conversion of the concept into execution (McAfee, 2012; Mayer-Schönberger, 2013). Focusing on healthcare, Big Data paves the way for huge potential, applications like Watson by IBM, which are built on solid research and state of the art visionary technology (Groves, 2013) however the outcomes so far have been below expectations. The tipping point seems imminent, and yet elusive. Not only new tools and applications are necessary to take advantage of the new insights, but also new mindsets, system changes, and safeguard policies to protect the privacy of the patients. The full value will also come by changing the paradigm from data analytics and interpretation to predictive modeling and simulation of outcomes, which have never been used in a scale of this magnitude. Combinations of data systems and pools multiply the quantity and quality of insights compared to individual sets (for example combining treatments, clinical outcomes, behavioral data and costs) (Groves, 2013). Complexity and amount of data appear to require game-changing technologies and the use of AI (Artificial Intelligence) and ML (Machine Learning) appears to be the enabler.

3.3.3 The influence from and on daily reality

This broader approach on EBM needs to be effectively executed and therefore take into consideration the daily reality of the users, their routines, belief system, behaviors, expectations, time, and ability to absorb and act on information (Bates, 2003). Key requirements are workflow integration, EBM must fit into the users' processes and systems,

when addressing behaviors and beliefs in real-life settings. Today's technology and leverage of networks enable "on the spot" accessibility of information/evidence, which can be real-time and possibly predictive and normative: EBM can even anticipate the needs of the treating physicians and the affected patient. On the downside, such an enabled and possibly wide-ranging approach can lead to information overflow, which needs to be managed as well as how accountability is to be managed. Discussions and decisions have to take place in regard to how difficult it should be made for physicians to overrule EBM based on possibly outdated information, limited experience or erroneous beliefs.

The healthcare industry is lagging behind and reluctant to change, as healthcare professionals are used to making decisions independently and leveraging their own personal experience and clinical judgement. Due to privacy and ethical concerns, it is still not easy to share data, and the link or measure of a universal good, health, to economic values, appears to still be a taboo to many. Better clinical outcomes combined with cost pressures (e.g. already in 2009 healthcare costs in the US represented 17.6% of GDP) will be the main drivers to fully leverage what is technically possible in terms of both data and tools. Optimizing both may allow health care to take a leap, and with this thesis, we aim to contribute by describing a broader and deeper evidence-based approach.

This thesis builds on the broadly accepted EBM concepts and extends it by pooling currently fragmented and dispersed data pools and insights, which combined are expected to be strengthened in content and depth.

3.3.4 RCTs/RWE and meta-analysis

RCT remains the ideal and most credible instrument for scientifically funded conclusions on treatment effectiveness, but they have logistic and ethical challenges (Richesson, 2010), which are even more dominant for rare diseases. As it becomes difficult to recruit sufficient patients for large RCTs, the question to ask is if a "large" study or a meta-analysis of two (or more) smaller studies leads to stronger results. Previous research suggests that every trial probably has some degree of bias inherent in it. While the investigators aim for an unbiased RCT, bias cannot be fully excluded, as small and inconsequential as it might be (Day, 2010). Further, it cannot be said how significant it, or even in which direction it skews the results. Avoidance of bias is one of the most critical features of any study and the original primary reason for randomizing. Two or more trials might reduce any possible bias, especially if these RCTs are executed by different organizations in different regions and possibly different patient populations. The results of such meta-analysis would be statistically stronger compared to those of a single study, even if the number of subjects was the same. This thesis builds on meta-analysis combining RCTs and RWE.

3.3.5 From efficacy and effectiveness to RWE

Efficacy is the extent to which an intervention does more good than harm under ideal circumstances, while effectiveness is the extent to which an intervention does more good than harm when provided under the usual real-life circumstances of healthcare practice. When improving and funding healthcare, payers focus on the cost-effectiveness of treatments in a real-world environment and therefore RCT needs to be supplemented by

RWE. The disparity between the therapeutic efficacy of treatment observed in a tightly managed RCT and the effectiveness in a real-world setting is called the "efficacy-effectiveness gap." (Makady, 2017). RWE provides insights, foresight and predictive findings on diseases, products and patient populations based on observational data in real-life settings. While RCTs focus on the lenses of the clinician and the patient, RWE patient outcomes incorporate also the perspectives of the payer, the drug or device manufacturer, and more (Looney, 2016).

3.3.6 Sources for RWE

RWE is typically generated from secondary analysis of observational non-interventional data provided by the health care system and the patients themselves, for example through digital health applications. These data sources reflect or measure the consumption of drugs or the use of medical devices by a mix of individuals in real-world settings, as opposed to controlled clinical trials. Sources include claims data from insurers and government health programs, clinical data from medical records, patient registries, laboratory results data, survey, social media, mobile technologies (health apps). Electronic health records are introduced into healthcare organizations worldwide to improve patient safety, healthcare quality and efficiency (Yu, 2018). RWE data such as for example the consumption of drugs and the impact of the treatment on daily life, can be collected in non-RCT settings, in non-interventional/non-controlled settings or in non-experimental settings. There is the possibility of above-mentioned existing data-sources, but also to purposefully design studies that generate real-world data such as observational studies or pragmatic trials. Patient-reported outcomes are commonly used in many areas of clinical research and have been proven useful when studying effectiveness when comparing alternative interventions, when monitoring changes in health status over time, or when predicting relevant clinical events through analysis of prodrome (Rajmil, 2010).

Effective utilization of the multiple data sources would require increased transparency, standardization of data formats and definitions, advanced analytics, and linkages between disparate data types. Strong support in the form of collaborations across health systems, patient advocacy groups and digital health providers are key enablers and accelerators. As RWE does not involve random assignment of subjects to treatments, the researcher may need to additionally deploy advanced matching and statistical techniques to control for potential bias (Malone, 2017). The effort is warranted as stakeholders recognize the value of RWE in providing or reinforcing the evidence on the effectiveness of medications (Makady, 2017).

3.3.7 Patient registries

Patient registries are programs that collect, store, retrieve, and disseminate clearly defined set of data on identifiable individuals. The definition goes beyond a simple database to include also the systematic collection and use of the data stored in the registries. Besides patient details, registries also collect information about the condition, patient characteristics (family history, genetics), the treatment provided, and health measured taken over the course of the treatment (e.g. blood pressure, blood sugar, number of attacks). The objective of

registries is to count and describe health and disease characteristics within a sampled population and consequently draw conclusions that can be extrapolated for a larger population or a population in a different healthcare system.
Patient registries are being used for public health surveillance and for research inquiry. They are particularly important for tracking trends and understanding rare diseases, as they provide consistent streams of data for defined populations that can be shared for research and health policy purposes. The data can cover prevalence, incidence, treatments, outcomes and spending over time (Richesson, 2010). The value of the registry to a user is directly linked to its quality which depends on how completely each patient case is recorded and how valid each data point is.

3.3.8 Challenges of patient registries

Each registry can be subject to bias if it is linked to a specific center, a region or organization, whereas bias manifests in a mistaken estimate of a measure due to any systematic error in the design, conduct or analysis of a study. Registries may be affected by selection and information biases, with selection bias due to distortions the selection of subjects in the registry or from factors that influence participation or inclusion (Rothmann, 2008) and information bias due to systematic errors in the measurements (Richesson, 2010). Another type of bias could be lead-time bias, which results from advances in testing that enable earlier identification of the disease. The number of detected cases can be inflated when innovative technologies that can identify diseases non-invasively or earlier in the course of the disease are applied. This creates the false impression that the incidence of the disease is increasing. (Richesson, 2010). Combining different registries allows the validation of each while at the same product more rigorous statistical data. The longer and broader a registry has been in existence, the more consistent data collection, documentation and quality control have been, the more reliable it becomes, and the stronger the epidemiological findings and conclusions become.
Another challenge arises when too much data is being collected or measured. Important funding, effort and time can be consumed for data of secondary importance instead of broadening the scope, which would enable stronger findings. Each variable included for measurement should have an operational definition and be standardized and simplified in a way allowing consolidation and comparison across registries (Richesson, 2010).
To manage and own a patient registry requires resources, expertise and tight governance structures. A current trend suggests patients perform this through patient advocacy organizations, yet given the confidentiality of the data recorded, the need for solid data infrastructure, and the value of using a standard medical language, leveraging physicians and large institutions seems to be more conducive.

3.3.9 Uses of RWE

Compared to RCTs which demonstrate efficacy, RWE enables the learning about treatment effectiveness in terms of both clinical and non-clinical impacts. The use of electronic health records and the other data sets mentioned above to evaluate different treatments has dramatically increased over the past decade. The real-world data extracted from patient

experiences is key to decide on how and where best to use new treatments (Malone, 2017). RWE measures patient-reported outcomes including health care-related quality of life and symptoms, which are normally not collected in RCTs. RWE allows for the comparisons of multiple and combined alternative interventions and can include also the economic impact on the patient (and his family) resulting from different coverage and payment policies or other health management programs. It helps to quantify the risk/benefit profile of a new treatment, both on long-term benefits and harms, signal detection and monitoring for prevention or proactive action. With the large numbers of patients producing RWE data, it is possible to segment patient populations for optimal therapeutic response and safety, which enables to assess category dynamics to support different pricing, market access and promotion approaches. RWE may provide insights that allow for better target and patient cohort identification which enhances RCT productivity. HCPs, institutions and payers can analyze and compare the effectiveness of different healthcare solutions to determine optimal treatment algorithms, which need to also incorporate patient adherence (the lack of which indicates both lower costs but also lower efficacy). The pharmaceutical manufacturers of drugs may be interested in learning about RWE as it would help them to better understand how their medicines work in the real world, how they work in patients with co-morbid conditions and concomitant medications, which are normally excluded from the pivotal RCTs used for regulatory registration.

All combined, RWE may enable the optimization of the therapeutic value, the evaluation and strategy development for pricing and market access, the overall assessment of a therapeutic area, the comparison of treatment effectiveness, the segmentation of the population by for safety and pharmacovigilance purposes, the design and optimization of RCTs, the generation/validation of biomarker hypotheses and in summary to optimize the resources dedicated to health care services. To gain market access for new drugs, it is now key to prove the value by demonstrating real-world effectiveness (Davis, 2017).

3.3.10 Barriers to RWE

Generating RWE goes well beyond observing and interpreting reality. Non-traditional sources are used to collect data which is normally not collected for research purposes. This real-world data needs to be scrubbed to be widely accepted for statistical validity. Cost and process of sourcing data from these sources such as health care providers, patient groups, and societies seem not to be fully established and certain. Privacy and security of patient data is a sensitive topic in a world of data breaches also in the health industry. Some institutions appear to be less willing to invest in RWE applications or even to share data, and patients may be less willing to consent to the use of their data. The true value of RWE could come also from offering a complete picture of the patient by linking various sources such as medical records, claims and patient-reported data. However, health care systems are fragmented organizationally, and, in the way, they collect, store, manage and share their data, which in many cases is not even in an electronic format. Overcoming these barriers would require not only investments, but also improved IT security, standardization, updated legal frameworks, and cultural shifts.

3.4 Quality of Life (QoL)

3.4.1 History of QoL

QoL has changed the medical paradigm from a disease-centered approach to a patient-centered approach (Osoba, 1999). In their treatments of patients, physicians should focus on QoL because it helps them understand the patient's point of view about diseases and the prescribed treatments, differentiating what is "normal" and what is "abnormal requiring an intervention". A key goal of health care professionals is to improve patients' QoL, which may be as important as alleviating symptoms and pain, preventing disease, effecting a cure, averting complications, providing humane care or prolonging life. Lastly, for both therapeutic decision-makers and payers, QoL could be an important factor when comparing and choosing from the different treatment methods available (Sajid, 2008). While doctors may hold more information about the patients' health status and the available treatments, patients on the other side can have a better understanding, beliefs and expectations about their lifestyle, the disease and how the treatment should work. Ideally, patients should communicate these preferences to their doctors, who then would act as agents for the patients, maximizing their utility as if it were their own.

3.4.2 QoL terminology

Treatment-induced health outcomes can be divided into five levels: biological and physiological factors, symptoms, functioning, general health perceptions, and overall QoL. The concept of QoL is related to the strict concept of health, albeit distinct. In some literature, the term HRQoL (Health-Related Quality of Life) is used to differentiate to indicate that non-health related aspects of life, such as income, housing, employment, freedom and quality of the environment, are excluded (Guyatt, 1993). In this thesis we chose to use the broader QoL terminology as patients affected by genetic rare disease find other not-directly health-related aspects such as income and employment impacted by the condition, and therefore they should be considered due to their correlation and causality. When a disease is experienced by a patient, almost all aspects of life can become health-related, especially for rare and genetic conditions, as the data illustrates.

3.4.3 Factors influencing QoL

QoL can significantly be affected by cultural, spiritual, economic or political factors, which generally do not fall under the purview of treating physicians and the health care systems (Wilson, 1995). Soon after the introduction of the concept and with increasing experience, it became clear that QoL is influenced more by emotional well-being than by physical functioning (Fitzpatrick, 1998). The concept of QoL goes beyond a general health perception and includes physical functioning, role functioning, social functioning and mental health which affects psychological functioning. When a physician diagnoses and treats patients, not only visible and measurable symptoms are analyzed. Emotional and psychological symptoms, such as the patient's perception, feeling or even belief about the state of the body, such as an abnormal physical, cognitive or emotional state, would also need to be considered. While it is the symptoms, as perceived and reported by the patient or

his caregiver, that cause the patients to enter the journey into the healthcare system, empirical analyses have shown that between 30% and 80% of patients who see a physician may have conditions for which no physiological or organic cause is found after routine investigation (Wilson, 1995).

3.4.4 QoL aspects of rare diseases

There are thousands of rare diseases that have no treatment and cannot be diagnosed by the vast majority of physicians, which may help explain why there are many undiagnosed or misdiagnosed conditions. Such healthcare gaps may have a profound QoL impact as many rare conditions are debilitating and life-shortening if untreated. Additional complications could be added: while functioning is correlated with symptoms and biological and physiological variables, variations in functioning cannot be fully explained by the latter. Functioning and health variables are conceptually distinct aspects of health status (Wilson, 1995). As an example, it is often anticipated that happiness or satisfaction with life is determined by objective life circumstances, including the level of functioning. Reality suggests that measures of life satisfaction tend to be unstable, as people change their perspectives and their expectations, adapting to their (deteriorated) condition caused by disease or age. As such, QoL is a dynamic concept that bridges between past experience, present circumstances, and expectations for the future (Bowling, 2001).

3.4.5 Measures of QoL

There are numerous measures of QoL and little standardization, the reason being that the measures are disease- or population-specific, dimension-specific, and can be both generic or individualized (Garratt, 2002). While RCTs and other evaluative studies of health outcome should incorporate the patient's perspective of outcome, in reality, they neglect them. The attention is on conventional clinical, laboratory, and radiological measures and possibly some limited and inappropriate surrogate indicators of the patient's own experiences, which often cannot be well validated. Different stakeholder also may have different perceptions of QoL and its importance. QoL can have different meanings depending on the severity of the condition: for eye conditions, treatment would provide a health benefit more likely expressed as improved quality of life, whereas for oncologic conditions, treatment aims to extend the patients' life. Comparisons between such and more different benefits are intrinsically difficult and for this reason, NICE and other institutions calculate a figure called a Quality of Adjusted Life Year (QALY) (Goodall).

There are five different types of measures to describe and quantify QoL. The first is specific to particular aspects of health and produce a single score (for example the "Beck depression inventory" measures psychological wellbeing (Garratt, 2002), the EORTC QLQ-C30 is cancer patients participating in international clinical trials, the St George's respiratory disease questionnaire for patients with diseases of airways obstruction). The second type of measure is broader in scope and covers several health domains (for example when the condition has a range of impacts, like for specific genetic diseases like Gaucher). A third type contains generic measures that can be used across different patient cohorts and populations, covering several health domains (for example SF-36 is such a set of generic,

coherent, and easily administered quality-of-life measures, as is the Nottingham Health Profile, also intended as a standardized tool for the survey of health problems in a population (Hunt, 1985)). Generic tools are valid and useful to be used in addition to clinical interviews to evaluate the outcome of medical and/or social interventions. They cover such concepts as health induced limitations in physical activities, social activities and role activities, pain, mental health (psychological distress and well-being), emotional problems, vitality (energy and fatigue), and general perception of health. Individualized measures are the fourth type and they allow respondents to change the weight depending on the importance of certain aspects of their own life. Lastly, to allow for economic evaluation and comparison, there are utility measures which incorporate preferences for health states (for example EuroQol EQ-5D13). Utility measures are derived from economic and decision theory and help represent the preferences of patients for treatment processes and outcomes. The resulting cost-utilities are expressed (e.g. in QUALYs) which can then be compared and help policymakers chose the optimal (or viable) allocation of scarce resources.

3.4.6 Challenges of QoL instruments

The measures defined to determine QoL need to be assessed for reliability (stability and equivalence of repeated measures of the same concept), validity (extent to which a test measures the construct it purports to measure), precision (can they distinguish between health and illness), responsiveness (can they detect clinically important changes), acceptability (are patients willing to complete questionnaires), and feasibility (is the timing and cost to measure commensurate). Methodologically there are different issues when measuring QoL: how to balance or combine objectivity (e.g. mobility) versus subjectivity (e.g. feeling), generic versus specific (to the disease (e.g., cancer or heart disease), to a population of patients (e.g., children or elderly), to a certain function (e.g., sleeping or eating), or to a problem (e.g., pain)), unidimensional versus multidimensional, self-report versus proxy report, reliability, validity, and the selection of measures (Li, 2013). Questionnaires and interview guides designed to measure QoL may often be perceived to be long, complicated, and containing ambiguous statements that leave ample room for subjective interpretation. Especially the scoring and weighting of seriousness can be subjective and influenced by external factors. Some questionnaires focus on a narrow scope or too few dimensions, failing to capture other relevant aspects of QoL. Lastly, to allow for comparability, the answers are consolidated into one score, and index, but there can be many different ways to reach that number, including combining areas that are not logically connected at all.

3.4.7 QoL intersection between clinicians and social scientists

Clinicians and social scientists appear to use two different paradigms or models of health. Clinicians utilize the biomedical model which focuses on etiological agents, pathological processes, and biological, physiological and clinical outcomes. The objective of clinical practice is to diagnose the conditions based on symptoms, determine their causation symptoms and subsequently treat. Discovery and development of drugs are done following controlled experiments where the medical research is directed at fundamental molecular,

genetic, and cellular mechanisms of disease. Biology, biochemistry and physiology are the underlying scientific disciplines (Wilson, 1995). On the other side, QoL is built on a social science paradigm which focuses on overall well-being and functioning, and where research also includes and attempts to measure complex behaviors and feelings. Sociology, psychology and economics are the scientific foundations of these models. A holistic conceptualization of QoL requires the integration of the two paradigms to understand how the QoL outcomes interrelate between them. The difficulty may be compounded by the fact that the concepts and methodologies are different and may be unfamiliar between the researches operating within the two paradigms. At the intersection of the two paradigms, and within the constraints of health economics, physicians can influence the quality of care and QoL by persuading patients to demand reimbursement or funding for more or different diagnostics and care.

3.5 Health Economics (HE)

3.5.1 The need to contain healthcare costs

Already at the beginnings of the diffusion of the EBM concept, some feared that it would be misappropriated by purchasers and managers to cut the costs of health care. Promoters of the concept counter-argued that doctors practicing EBM would identify and apply the most efficacious interventions to maximize the quality and quantity of life for individual patients, with the result of increasing rather than lowering the cost of their care (Sackett, 1996). Experience has shown that costs have increased significantly with the results of inequality, two-class healthcare systems, and virtually every stakeholder in the healthcare space finding itself in an economically not sustainable situation. Healthcare systems around the world have taken three types of pricing policies with the aim to contain costs (Eis, 2012): price controls (price freezes and price cuts), reference pricing and profit controls. These are often combined with other interventions to reduce demand by denying or limiting reimbursement or introducing co-payments. Taken alone, e.g. without including clinical outcomes, these measures cannot optimize the longevity and health of their stakeholders. A comprehensive approach is necessary, and EBM needs to be part of the equation.

3.5.2 History and introduction of HE

Some healthcare systems (e.g. Australian Pharmaceutical Benefits Scheme (PBS) or the National Institute for Health and Clinical Excellence (NICE) in the UK), have been set up to assess the efficacy and comparative cost-effectiveness of medical interventions. They are independent of the government and have a clear mandate to ensure cost-effective access to medicines for the population. This is executed by publishing clinical guidelines, negotiating and publishing prices for reimbursement which can be used as a reference and ultimately can affect prices and sales in other countries as well (Henry, 2005). In most cases of clinical diagnosis and treatment of patients, patient outcomes on an individual basis are the focus of the healthcare professional. EBM seems to have greatly contributed to the alleviation of pain and prolonged life expectancy. On the other hand, cost-effectiveness is still largely ignored: While the individual patient might welcome treatment regardless of cost, any health care system is unlikely to be able to afford or condone such behavior. Society expects doctors, hospitals and payers to allocate resources on the basis of cost-effectiveness. Consequently, in some cases, patients should be denied access to efficacious treatments if such interventions are not cost-effective. The necessity to ration or allocate care on the basis of cost-effectiveness was recognized by Cochrane already in the 1970s (Maynard, 1997).

3.5.3 Changes in the compensation models for healthcare services

Historically physicians have been compensated under a fee for service system that measures the volume of work, but not outcomes. Over the last decade, new models were introduced in an effort to contain expenses and to encourage better use of resource to benefit patient populations. New models have been increasingly introduced to compensate physicians based on patient outcomes and total cost control (Groves, 2013). Payers request access to outcomes information and, if the healthcare providers are not able to demonstrate effective

outcomes, shrinking reimbursement and volume would be the result. This dilemma is especially visible with the treatment of rare diseases, whereas addressing the challenge with a revisit and broadening of the concept of EBM to include costs and socioeconomic factors will help build a stronger basis for decision making while optimizing treatment effectiveness measured in economic terms and ultimately patient outcomes in aggregate (Greenhalgh, 2014).

3.5.4 Two perspectives of health economics

Two perspectives, one being the affected individuals, and the other one being society as a whole, often conflict. At an individual level, the efficacy of treatment being the key factor measured in clinical outcomes (e.g. life expectancy, blood pressure, frequency of attacks, etc.) and quality of life at an affordable price. Key decision-makers are health care professionals, patients, payers, regulatory bodies. At the macro-level instead, the effectiveness of treatment is the key factor, measured in overall clinical outcomes and costs to society benchmarked across therapeutic options, conditions and healthcare systems. Key decision-makers are healthcare authorities, payers, market access and pricing departments in pharmaceutical companies). This thesis incorporates both perspectives, aiming to contribute with a balanced framework which is expected to facilitate the dialogue between the decision-makers and the influencers.

3.5.5 Funding of healthcare – the payers

Initially and still today in the vast majority of the emerging markets, healthcare appears to be funded out of pocket, often in cash by the patients or their direct caregivers. In the more advanced markets, there are private or public health care systems where it might seem the government is paying. However, behind the government is the taxpayer, and that means society as a whole. Even in a private health care system rarely does the patient or his family pay in full for diagnosis and treatment. Some or all of it is covered by the private insurance, which de facto is a distributor of health care across many premium payers who in solidarity cover. For practical purposes, in case of public health plans the government, in case of private health systems the insurers, are called payers. Payers can be public or private insurances and they ultimately fund medical treatment and testing in whole or in part. Payers increasingly encourage physicians to follow treatment guidelines, as customization in general increases costs and on average leads to less effective outcomes (Frank, 2007; McCauley, 2015).

3.5.6 Funding constraints and tradeoffs between therapies

In medical care, there have always been funding constraints where decisions and trade-offs have to be made. To maximize efficiency, payers have to consider if the benefit from reimbursing an orphan drug for a rare disease patient is greater than the foregone benefit from not spending the same resources on other treatments or other conditions. Currently, even well-advanced countries such as the UK need to reconsider the reimbursement of currently funded standard treatments for cancer, well aware that the lives of thousands of patients will be cut short (Donnelly, 2015). Priorities are being set on both who is getting

what type of treatment at whose expense, who will pay the bill. The assessments, decisions and resulting tradeoff are reached by looking at a combination of clinical benefit, survival and quality of life, toxicity and safety of the treatment, level of unmet medical need and the median cost per patient. Independent institutes who decide on new treatments need to evaluate them in a consistent manner that allows for a direct comparison. They review the clinical and economic evidence, compare all treatments in isolation and combination. The thorough evaluation involves gaining information and insights from anyone affected by the decisions: patients, physicians, other healthcare professionals, and the pharmaceutical companies (both of the new treatment and the ones that might be displaced by the proposed new one). An independent academic group reviews the evidence and the public are consulted as well. To compare two treatments, institutes such as NICE calculate the differences in cost (the extra spend), and then divide them by the difference in effect (the extra benefit). The result is known as an incremental cost-effectiveness ratio (ICER). Clinicians, statisticians and health economists integrate all aspects and ultimately the institutes recommend the most cost-effective one (Goodall, N/A). Example of such tradeoffs can be the novel CAR-T treatment for B-cell acute lymphoblastic leukemia which is expected to add decades of life for one child at a cost of fewer than ten years of productive life, or at a cost for a full childhood immunization schedule for hundreds of children.

3.5.7 HE and agency theory

Agency theory has modelled how different patient segments, based on their know-how, confidence and communication skills can influence their relationship with the physician, the chosen treatment and ultimately the clinical outcomes. Even before the application of agency theory, price-discriminating behavior by physicians has been long-observed, representing another form of customized treatment (Kessel, 1958). To address the inefficiencies caused by the three-way double agent relationship described above, reducing and withholding care may not be an answer and would be ethically questionable. This thesis set out to explore the opportunity to increase the quantity and quality of care at existing or reduced costs.

3.5.8 Role of HE in therapeutic decision-making

EBM has been showing how to best apply the proceeds in the form of new diagnostic and therapeutic interventions. The past few decades have seen dramatically rising health care costs driven by ageing populations, increase in lifestyle-driven and chronic diseases coupled with the required care given to terminally ill patients (Lopez-Bastida, 2010). As a result, concerns among governments and health authorities have escalated in raising new questions on both the overall amount that can be funded, and on how resources can optimally and fairly be allocated within the health care sector and across all sectors of public expenditure. The economic evaluation of drugs and health care services, called health economics (HE), is examined from two angles. The first one is the cost of the illness to society, and the second one is the cost-effectiveness which compares both costs and results of treatments in economic terms (Lopez-Bastida, 2010). Payers have in their scope of their analysis and decision making only economic factors, they do not have to conduct clinical trials. Their decisions are for the long term and measured in annualized economic costs (Looney, 2016).

Enforcement of these decisions, which are expressed in policies, takes place through extensive administrative requirements and contracts which include incentives and sanctions for both patients and physicians to select and follow the approved therapies. Prescription budgets for physicians are capped and they cannot give to the patient and bill the treatment they would following the traditional physicians' ethics. Diagnostic and therapeutic activities may be restricted, the best or most comprehensive medical treatment is no longer universally possible. The other instrument available to payers to influence prescribing physicians is through incentives which induce reducing the use of health care resources, improving compliance with guidelines and achieving health targets. Such incentives may negatively impact the doctor-patient relationship, as financial rewards increase the conflict of interests between the two stakeholders, putting their relationship in danger (Chaix-Couturier, 2000). Despite this perspective, the patients still have to be regarded as customers of the payers: high deductibles and co-pays influence how patients, caregivers and physicians decide on treatments to be pursued, and therefore on the clinical outcomes themselves. Patients may hold the power to select the treating physicians for diagnosis and treatment, which has consequences on competition, health assets utilization and costs (Kaba, 2007). To optimize the outcome, payers may have to factor in all consequences, and as such act in different ways as the agent for the patients.

3.5.9 Definition and role of market access

Market access is the key step between a developed, authorized drug or service and it's prescription by doctors and use by patients. Since the early 2000s, reimbursement for new medicines has been secured by submitting formal dossiers to national insurance agencies and managed care organizations for reimbursement approval using cost-benefit models that utilized health economics analysis. This partially shifted the primary driving of treatment decision from physicians to payers. The key importance of market access is also determined by the active role it plays throughout the product life cycle, from clinical development all the way through after the patent on the drug is expired. The value created goes beyond the primary objective of reimbursement at an acceptable price within guidelines. The market access function within companies contributes to the success by developing solutions that shorten the time to approval (allowing to generate revenues earlier), by ensuring formulary listings in cooperation with account management, by developing price defense strategies, by influencing and expanding guidelines, by contributing to patient awareness of disease and treatment, and by driving patient support programs and other initiatives.

3.5.10 Dimensions of market access and impact on decision-making

Market access has three dimensions (Evans, 2013): The drug or service needs to be physically accessible, within reasonable reach of those who need it. Such accessibility requires a distribution system with either opening hours or appointments to allow the patient to obtain what needed when needed. Second, the drug or service needs to be acceptable, patients need to be willing to seek it, which presumes it is effective and not discouraged by social or cultural factors (such as age, sex, ethnicity or religion). Lastly, the healthcare offering has to be financially affordable. Patients need to be able to pay for it without

incurring financial hardship, payers need to be willing to pay for it without incurring ethical tradeoffs. In addition to raw affordability, indirect and opportunity costs need also to be factored in. The National Institute for Health and Care Excellence (NICE), for example, is the independent body in the UK which decides and recommends treatments. When NICE recommends a new expensive treatment for one group of patients, because of limited funding, something else has to give. The criteria to navigate through these difficult decisions is the improvement of the health of the whole population (Goodall).

3.5.11 Information requirements for market access considerations

One can see that the market access parameters cannot be captured by RCTs, but with RWE. To ensure market access, pharmaceutical companies integrate clinical data and RWE and health economic considerations into a "value dossier", which is submitted to payors to negotiate the price and obtain reimbursement. Clinical and real-world data accumulated over the years can be redeployed into disease management solutions, which become relevant post-patent expiry to differentiate established originator products from generic competitors and thus protect the revenue stream built up. From a company stakeholder perspective, a successful market access approach is comprehensive and requires inputs and seamless cooperation from different functions such as government affairs, regulatory affairs, health economics and outcomes research (HEOR), pricing, tender management, medical affairs and marketing and sales.

3.5.12 Shift from volume- to value-based payment models

As part of innovative outcome-based contracts between pharma companies and payers, the former need to provide supporting evidence based on real-life data to document drug treatment efficiency and cost-effectiveness (Saha, 2015). This is part of the industry-wide shift from volume- to value-based payment models which utilize RWE to understand and demonstrate the value diagnostic and healthcare treatment innovations. These payment schemes are health-outcomes-based and are also referred to as "performance-based reimbursement", "pay for performance", "risk-sharing", or "coverage with evidence development" (Carlson, 2010). For example, in 2016, 21st Century Cures Act, charged the Food and Drug Administration (FDA) with evaluating the expanded use of RWE, to include this perspective to support the approval of new indications for previously approved drugs (Davis, 2017). The focus on value-based models is further accentuated by the uncertainties surrounding novel treatments, of which there are two kinds. The first mentioned above is the uncertainty on how the novel treatment will deliver health outcomes within an adequate resource utilization in a real-world setting. The second uncertainty is around if and which cohort of patients should effectively be treated, vs. the population as a whole.

Payers and pharmaceutical companies agree on reimbursement schemes which are based on the performance measured as health outcomes: price, level, or nature of reimbursement are calculated based on future measures of clinical or intermediate endpoints which are clinical and relate to patient quality or quantity of life. These reimbursement schemes enable providing to the patients' access to innovative and potentially beneficial drugs and services under both uncertainty of outcome and pressure on costs. It has to be noted that there are

different approaches than the standard reimbursement schemes which contemplate discounts, rebates, price/volume agreements, market share agreements, or utilization caps, all of which not linking the ultimate price and payment of the drug or service to measurable health outcomes.

3.5.13 Types of value-based schemes

Value-based schemes need to be analyzed further as they contribute to better understand the different stakeholders and their role in the treatment decision-making process. There are mainly two types: the first are schemes where the coverage of the treatment is provided under the condition that data on the treatment will be collected. These schemes create a compromise solution when treatments look promising but the clinical and real-world evidence is not sufficient to warrant full coverage. A side-effect is that the use of the treatment will be limited in cohorts where benefits and cost-effectiveness are most uncertain. A variant can be that only the patients participating in a clinical study are covered, or that a study is conducted exclusively in the population covered by the payer and the payer would receive the details of the outcomes. The second group are schemes where the reimbursement is dependent and calculated based on real-world outcomes. When pharmaceutical companies have more confidence in their drugs than the payers, they might be willing to take the risk of a lower reimbursement level in case the treatment underperforms. To initiate the discussion with the payers, pharmaceutical companies prepare a value dossier for their products where they include a comprehensive overview of clinical benefits, safety, convenience, adherence and implications on quality of life. In this second group either the pharmaceutical companies adjust prices, provide rebates, refunds or substitute therapies if their product does not meet the outcome targets, or reimbursement will be provided at a level calculated based on the clinical outcome of the therapy using the drug in question. Overall both payers and indirectly patients benefit from these schemes as novel therapies are provided at an acceptable value, while the pharmaceutical company bears the risk of overutilization, a key driver of cost-effectiveness (Carlson, 2010; Carlson, 2014; Damberg, 2015).

3.5.14 Price/reimbursement discussions

Drugs are global like electronics or other movable goods. In theory arbitrage in the form of parallel imports and exports should be possible, but in reality, there are still significant pricing differences, which are driven by the differing systems. These can be explained by the varying degrees of monopoly power on the sell-side and by the and varying degrees of monopsony power on the buy side (Anderson, 2003). The US health system operates through a vast network of health care providers which are relatively uncoordinated and funded by households through money flows of different sizes. Different players which need to make a profit which is based on volume, drive prices up. Other geographies such as Europe, Japan and Canada have government-controlled health systems with considerably more market power on the buy side, thus able to command lower prices for the same drugs. Monopsony would reduce total welfare, as it reduces the quantity or quality of the offering. However, in health care systems, if not pushed too far, its primary effect is to control medical spending

by controlling providers' incomes and redistribute the income (Anderson, 2003). When the payers are national, they have a mandate to ultimately decide on coverage for medical treatments for the whole country, they hold strong negotiating power with the pharmaceutical companies. Holding marketing approval to sell the drug or service is not sufficient to generate the bulk of the revenues, as a product that is not reimbursed, i.e. "self-pay", is not competitive in a market where every other one is. QoL plays a key role when assessing the value of a drug and NICE issued guidance indicating to measure a drug's clinical effectiveness, not all additional months of life are equal. Higher value is given to improvements experienced by patients who have worse lifetime health prospects, especially if pediatric patients are affected (Simoens, 2011). When the data needed to justify a high price or reimbursement is incomplete or inconclusive, innovative reimbursement mechanisms have been explored and implemented for orphan drugs. Risk-sharing arrangements enable or force the manufacturer to share with the payer the risk that the product may not be effective. Under such a scheme it is the pharmaceutical company that may lose revenues and profits if the drug does not deliver the expected health benefit. Increasingly when deciding on the coverage of a new drug, payers make reference to the list price in other healthcare systems in other countries. Performance-linked reimbursements or confidential discounts and rebates can be attractive solutions for both pharmaceutical companies and payers, as they do not change the reported list price.

3.5.15 Additional hurdles

Even when healthcare treatments are available, reimbursed or affordable, patients might still not make use of them. The major hurdle, especially in emerging markets, is the lack of awareness. Patients are not aware of having a condition that requires treatment (e.g. hypertension) and therefore they do not seek a doctor. With rare diseases additionally comes the lack of awareness of the doctor. With over 7,000 rare conditions and the high likelihood that the particular physician will never see a patient with that particular condition in his or whole professional life. The physician will not be able to diagnose the patient, or even worse, make a misdiagnosis, followed by a prescription of a wrong therapy or even surgery (Kole, 2010).

3.5.16 Managed care combining of EBM and HE

Managed care described the group of activities, controlled by a Health Maintenance Organization (HMO), aimed to improve the health of the covered patients while at ostensibly reducing costs. This is achieved by so-called "managed care techniques" which include being an essentially exclusive system of delivering and receiving health care, reducing unnecessary health care costs through a variety of mechanisms, including economic incentives for physicians and patients to select less costly forms of care, programs for reviewing the medical necessity of specific services and the inpatient admissions and lengths of stay. Cost-control mechanisms may include guidelines, formularies, financial incentives and gag clauses, which would force physicians to consider other aspects but the individual well-being of the patients, including the managed care organization and their own self-interest. Cost-sharing and selective contracting for better pricing with larger volumes, and

the increased use of home care could contribute to further reduce costs, thus improving healthcare effectiveness. This approach to healthcare has shifted some decision-making power away from physicians and reinforced the concept of the double-agent model to be applied.

3.5.17 Managed care impact on patient relationships and trust

When treating physicians are a priori incentivized to look at cost, the previous patient trust and assumption on the doctor being exclusively focused on the well-being of the patient, can be further eroded. Trust affects the physician-patient relationship and impacts patients' perceptions about the quality of the care received, followed by an impact on adherence to the treatment prescribed, ultimately leading to an impact on health and QoL outcomes. Studies have shown that patients that are part of a managed care organization have significantly lower trust in their primary care physicians than those with more traditional coverage (Dwyer, 2012). The difference in trust may be further accentuated as patients in non-HMO settings are freer to make choices, therefore incentivized to seek information, and influence therapeutic decision making, which can lead to different health outcomes and costs. All factors aggregated need to be considered when deciding on health policy within the health system. Health economists and policymakers have explored the importance of the relationship between patients and physicians on health systems and continuously review the underlying mechanisms to optimize the systems as a whole (Stavropoulou, 2012).

3.5.18 Price differences across healthcare systems, reference pricing

Significant price differences for same or similar treatments exist between healthcare systems around the world. Healthcare spending in the United States is much higher than in other countries. As the use of health services is below the OECD median, the difference in spending is caused mostly by higher prices for treatments, services and drugs. For example, the average U.S. expenditure per hospital day is threefold the OECD median and health care workers' salaries are higher than in other countries (Anderson, 2003). The factors driving the high U.S. health spending can be grouped as follows (Reinhardt, 2004): First the ability to pay, expressed as GDP per capita. Second, as health care is labor-intensive, comparatively costly labor drives the prices up. Third, the highly complex and fragmented payment system weakens the demand side, allocating greater market power to the supply side also driving prices up. Fourth, the approach to financing health care is extremely complex and entails high administrative overhead costs. Fifth, the unwillingness to ration health care and to address two moral dilemmas: How much QALYs should the health system maximally procure and fund, and should the maximum price to be paid for added QALYs be uniformly applied to all members of society or be allowed to vary based on the individual patient's ability to pay, social status or other factors? In the UK on the other side, the National Institute for Clinical Effectiveness (NICE) has been using an apparent cutoff of around USD 53,000 per QALY beyond which treatments should not be publicly funded (Reinhardt, 2004). The figure has become a sort of an international benchmark.

3.5.19 Universal health coverage, donations

The World Health Organization (WHO) defines universal health coverage as a state where everybody has access to any health service or product needed in sufficient quality and quantity to be effective, while not being drawn into financial hardship because of it (Brady, 2017). Such a system would generate economic benefits from a healthier and more productive population and political benefits through social harmony and solidarity. In the meanwhile, the WHO has analyzed in depth the situation in different countries, understanding the root cause of the differences. The advice by the organization is to first improve efficiency, before looking for places to cut spending on health care. A recent report estimated that from 20% to 40% of all health spending was being wasted through inefficiency (WHO, 2010).

Pharmaceutical companies have been enabling the access of life-saving medicines with donations or free of charge programs for decades. Different approaches are possible such as direct donations in kind, or donations to independent charities that cover drug co-pays or health insurance premiums. These programs ensure that financially needy patients get access to treatment that maximize their chances of survival (Johnson, 2018).

3.6 Agency theory

3.6.1 Application of agency theory to healthcare

Exercising control over one's life and well-being is the essence of being human. Medicine has soon become a deeper field of knowledge requiring research and study work, forcing health preservation and improvement activities into an agency model of thinking and operating. Whenever one individual depends on the action of another, an agency relationship arises (Pratt, 1985). Agency theory builds on the principle of separation of ownership and control, which generates the need for governance mechanisms that address the conflicts of interest between principals and agents. For both parties, the question becomes how the agent stays faithful, loyal, honest and diligent while fulfilling his fiduciary duty to the principal. The conflict of interest is described as agency loss, which is the reduced return to the principals, compared to what it would be if they exercised direct control. The more divergent the interests of agents and principals are, the more difficult and costlier it becomes for the principal to monitor the agent, the more significant the agency loss affecting the principal becomes. Principal-agent relationships can be observed in all interaction processes where there is a division of work, hierarchies and relationships of dependence, a delegation of tasks or by the allocation of competencies (Langer, 2008). All three criteria are visible in the physician-patient relationship, which has been modelled within the agency theory frame as patients are principals who depend on physicians for medical advice, while the physicians are agents who are responsible for making optimal health-related decisions on behalf of the patients (Tofan, 2012).

3.6.2 Inefficiencies described by the agency theory

The main aspect and potential source of inefficiency is the information asymmetry which favors the healthcare provider (Dwyer, 2012). Another source of misalignment arises when the principal and agent have different attitudes toward risk (Eisenhardt, 1989), which can be eminent in the healthcare sector (for example when decisions have to be made that directly impact the life expectancy of the principal). The principal-agent model has been extensively used in health economics both because of its conceptual simplicity and the lack of any agreed alternative (Stavropoulou, 2012). Using agency theory, it is possible to explain, address and mitigate potential inefficiencies in health-care provision such as when physicians act in their self-interest at the expense of the patients, further exacerbated by the information asymmetries between the two parties, enabling them to behave opportunistically in front of ill-informed patients. Physicians have considerable incentives to manipulate their billing or to 'cream off' their patients (Kretschmer, 2005). Additionally, physicians face other constraints that need to be taken into consideration, such as administrative constraints, time issues and personal costs (Britten, 2000). Key opinion leaders, doctors who participate in research, who partner with the industry, who are investors or leading own companies, or who simply want to improve their income, status or lifestyle, are not driven only by altruistic elements and empathy, but by other non-altruistic factors.

3.6.3 Disconnects between patients and physicians

The first disconnect may arise when patients expect their treating physicians to be transparent and share information on current health status and potential treatment, allowing to decide together, while the doctors have no incentive to do so. Agency theory thus bridges between medical ethics and economic theory, offering a model to address the ethical challenges in the physician-patient relationship (Langer, 2008). Agency theory specifies mechanisms to reduce agency loss, which include incentive schemes that reward the right behavior and actions. It recommends pay-for-performance models, service contracts and monitoring to prevent or solve such inefficiencies, yet it appears the healthcare space limits the applicability thereof. A second disconnect may arise because the outcome of therapy is not entirely under the physician's control: poor service delivery by other health care professionals or the lack of adherence by the patient to the prescribed therapy, could undermine the clinical outcomes significantly. In the case of the patient-physician agency-relationship, the patient is the principal, the subject of the activity (medical treatment) and the observer who attempts to solve the agency problems using certain measures. Such inefficiency may cause further agency costs. Monitoring itself is challenging, as the ability to do so by the patients may be limited because of their lack of knowledge and experience in the field. Unlike other settings, medical practice by tradition lives (or should live) by moral constraint and professional ethics as guidelines for behavior in the interest of the patient. The physician's dedication to serving the needs of the patients is the "immutable bedrock of medical ethics" (Shortell, 1998).

3.6.4 Double agency theory

A view encompassing all stakeholders identifies the treating physicians as double agents: in the exercise of their profession, they are accountable not only to the patients, but also to the payers and to other organizations such as health insurances. The unsustainable health economic situation is the result of inflationary, open-ended funding of increasingly costly innovative therapies required by larger patient populations diagnosed thanks to more advanced knowledge, techniques, and equipment (Angell, 1993). Physicians are facing increasing pressure from having to compromise between increasing demands, resource scarcity, and continuous search for efficiency. The physicians being exposed to such pressures, while at the same time striving to provide the best possible treatment to the patients, sometimes face dual and conflicting obligations (Tofan, 2012). Health insurance regulations on reimbursement or employer restrictions do increasingly not allow physicians to engage all diagnostic and therapeutic methods available (Shortell, 1998).

3.6.5 Historic therapeutic decision-making, patients and doctors

The objective of the doctor-patient relationship is to maximize the utility of the patient. A number of factors contribute to this utility among which communication, the patients' understanding of the doctor's explanations, how much and how well information is transferred to the patient, or how long the patient has to wait before seeing the doctor. Studies have shown that being able to talk to the doctor is the most important attribute and that the quality of the information exchanged is more important than its quantity (Scott, 2003). This

is consistent with the fact that EBM, RWE, HE, QoL are complex concepts with significant information asymmetry. Utilizing the double-agent agency model, decisions on treatment to pursue have to be taken and during the evolutionary course of healthcare practice, three types of decision-making can be observed. Traditionally doctors were undisputed experts who diagnose and alone decide on the treatment to pursue. The paternalistic model describes the patient seeking help, the doctor using his skills to diagnose and choose a treatment, for the patient to silently comply with. If there is information to be shared, it is selected to encourage the patient to consent to the doctor's decisions (Kaba, 2007). Patients are reduced to a passive role during the decision-making process and to simple executioners of the treatment, taking the medication prescribed as indicated. Increasingly this model is seen as outdated.

3.6.6 Modern therapeutic decision-making

Subsequently, a shared decision-making model (Charles, 1997) became prevalent where both physician and patient are involved in the treatment decision-making process, they share information, they express their preferences and agreement is attained on the decision on how to pursue. At the next level the physician supplies or complements the information already known by the patient, and the latter may decide. On the other side, the sharing of information between physicians and patients may be paved with hurdles. Research has identified fourteen categories of misunderstandings including patient information unknown to the doctor, doctor information unknown to the patient, conflicting information, disagreement about the cause of side effects, or failure of communication about the physician's decision (Britten, 2000). Two main causes are triggering these misunderstandings: patients not participating during the consultation, not voicing their expectations and preferences, or not responding, questioning the doctors' decisions and actions. Such disconnects between patients and physicians lead to adverse clinical outcomes when patients do not obtain, or do not follow the schedule of their prescribed medication. While economic theory has shown utility gains for consumers when they are informed and are free to make their own decisions about the goods and services they purchase, some research seems to suggest that consumers may experience disutility from being involved in decision making about the treatment of their health problems (Shackley, 1994). This can happen when the information or the explanations are too difficult, inconsistent with other sources (such as second opinions or online sources, or simply describing negative long-term outlooks or risks.

3.6.7 Misunderstandings between physicians and patients

It established that to achieve maximum benefit from the patient-physician interaction a simple, clear, transparent and seamless exchange of information and expectations needs to take place. In reality, different reasons for misunderstandings have been observed and they can be categorized (Britten, 2000). Patient information that is relevant to treating physicians, but not always communicated, received or understood in full or in part, includes relevant facts about the medical history, the patients' views or anxieties on treatments, the patients' other comorbidities, or their use of other drugs, over-the-counter or on prescription. Sometimes the information is not shared because of lack of time, because it's thought not to

be relevant, and sometimes it is actively concealed. On the other side there is information known by doctors that is not properly received, understood or accepted by the patients, such as the diagnosis itself, the treatment decision, what the drug does, how it has to be dosed or administered (especially if injectable), what potential downsides or side effects could be. This information can be simply not understood, but also not conveyed in the first place, as some physicians believe the patients do not want to know, do not need to know, or will not understand. Other reasons explaining the disconnects or the lack of shared understanding arise when patients are facing conflicting information from different doctors, from their online search, from family members or their network. Data suggests that doctors make many assumptions that are not correct in particular situations and with specific patients (Britten, 2000). Effort needs to be made in every single consultation, by both physicians and patients, to validate or confute the perceptions, be open, transparent and active, with the objective to close the information gap.

3.6.8 Patients' adherence to decided treatment

Once patients are diagnosed and treatments have been prescribed utilizing EBM, RWE and QoL, and once they have been funded using RWE and HE considerations, there is still one step that needs to be taken to attain a clinical outcome and an improved QoL: follow the treatment. Adherence has been defined as following the recommendation (Stavropoulou, 2012) and studies have shown that confidence in the physicians and the health care system as a whole led to better adherence and thus better outcomes (Kjellgren, 1998). Empirically observed, a follow-up communication style by physicians or clinics, client satisfaction, and mutual understanding between physicians and patients are predictors of better adherence (Berman, 2009).

3.6.9 Guidelines vs. agency theory

Agency theory is well recognized to describe physicians as agents for patients (Arrow, 1963) and implies that physicians attend to each patient's situation acting in their best interests. When this is the case physicians sometimes come into conflict with guidelines or with health economic driven decision-making criteria (Frank, 2007). Vice versa physicians face additional decision complexity when abstaining from prescribing treatments not contemplated by the guidelines, but which would still be covered by the generous insurance coverage of certain patients. The dilemma may exacerbate when the physicians themselves are financially incentivized by a treatment or a test that is not recommended by the guideline, especially when they are disagreeing with administrators, practice policies, or even exposing themselves to potential legal liabilities.

3.6.10 Role of compensation of physicians

Agency theory suggests that agents are more likely to behave in the interests of the principals when they share their goals or when the contract between them is outcome-based (Eisenhardt, 1989). Agency theory was mainly built on economic principles where compensation is performance-based to address the impossibility of factoring in measurements of activities in the context of imperfect information, different attitudes to risk,

multiple interrelated tasks, unexpected events, or team production efficiencies. Clinical practice, the relationship between physicians and patients displays some key features that characterize economic incentives (Robinson, 2003). The main component of the relationship is the physicians spending one-on-one time with the patients, therefore the incentive should be designed towards promoting working long hours, performing many procedures, and being attentive, listening and incorporating the needs and preferences of each patient into the therapeutic decision and the treatment. Physicians should treat also, or especially the sickest patients, the ones with the highest risk. The incentive should, therefore, reward taking risks, respectively disincentivize focusing on the healthy and avoiding the ill. Care should be adequate in quality and quantity, hence the incentive should steer physicians to stay well between over- and undertreating. EBM and guidelines provide a strong validated basis on which to treat the majority of patients, the incentive should lead physicians to follow them.

3.6.11 Forms of compensation for physicians

Whenever decision and behaviors are to be researched, it is key to understand how compensations and incentives drive the different stakeholders. Physicians as agents for patients merit particular attention as these stakeholders ultimately decide and attempt to follow through the therapies prescribed to the patients. The question becomes which form of compensation is most suitable to induce physicians to perform in the interest of the principals, the patients. Intrinsic rewards are what agents receive from the job, like the motivation of contributing to the well-being of patients, alleviating their pain, or even keeping them alive. Extrinsic rewards, such as money, have been shown to lower motivation as they reduce the impact of intrinsic rewards. Financial incentives lead to a degradation in the quality of the output, as the agents then tend to give a narrow focus to the task, try to complete it as rapidly as possible, and take few or no risks. Ultimately agents can feel controlled by the reward system, which would undermine the tenet of healthcare which is precisely to “care” for the person with a medical need (Baker, 1988). A principle of compensation system is that the result of the work or the indicator being measured can clearly be attributed and is under control of the agent. Especially in medical care, objective measures of activity and success of therapy cannot be readily measured, given the complexity and interplay of the different activities and treatment aspects, as well as the large variability across patients. Complex systems and not well-designed compensation schemes can facilitate the achievement of suboptimal results by gaming the system. For example, agents measured and compensated based on linear deliverables (such as the number of patients treated, capitation), are induced to game the system by sacrificing quality for quantity. The next level of fixed-budgets for interventions, and therefore capped compensation, do encourage physicians to behave and treat more efficiently, but they also compromise the nature of the relationship between physicians and patients, exemplifying the effect on of the health-care professional being a “double-agent” for the patients and for the payer (Vick, 1998).

3.6.12 Incentive options

Most compensation systems are designed to be simple, easy to understand, easy to implement and aimed to leave little room for different interpretations or dispute. Simplicity also reduces costs of designing, negotiating, and managing the compensation systems, while facilitating transparency in an otherwise complex environment such as the healthcare system with multiple physicians, procedures, hospitals, labs, and more. Traditionally in health care, one could find fee-for-service, expressed as a linear function of relative value units. Capitation is based on patient enrollment and salary on time worked (Baker, 1988). These cause fee-for-service, salary or capitation, to be suboptimal compensation methods to motivate, physicians as they are not controllable or could be gamed.

3.6.13 Advantages and disadvantages of different compensation types

Fee-for-service could drive physicians towards unneeded or inappropriate services, testing of equipment owned by the practices, fraudulent upcoding of visits and procedures, more frequent calls for visits, referral to radiology centers and clinical laboratories in which the physicians have an ownership stake, and the churning of back and forth referrals among specialists, all serving the objective to maximize reimbursement. From agency theory application in business, it is known that piece-rate, cost-plus-markup, and other retrospective forms of payment drive the agent to provide unnecessary, input-intensive, gold-plated services which do not add incremental value (Rodwin, 1993). This can be mitigated by prospective forms of payment such as pre-assigned or pre-negotiated rates for services (e.g. for surgical procedures, called episode-of-illness payment methodology, where the surgeon is paid a set fee for the whole episode from preoperative workup, through the procedure to postoperative monitoring until dismissal of the patient) including capitation for services or treatments. Capitation can also be misguided if it drives physicians to deny appropriate services, to refuse to treat the chronically ill, and to discriminate or refer out time-consuming patients. Studies have shown that the introduction of capitation reduced the total volume of prescriptions by up to 24% and hospital days by up to 80% compared with fee-for-service. Annual caps on doctors' incomes resulted in referrals to colleagues when target income is reached (Chaix-Couturier, 2000). While fee-for-service encourages, and capitation discourages resource consumption, a result-based pay encourages, and salary reduces productivity and fosters a bureaucratic mentality where "time passed" is more important than "results achieved". Non-monetary compensation follows similar mechanisms, such as promotions, practice ownership, invitations to speak and similar.

3.6.14 Conclusion on compensation types for physicians

Overall financial incentives are effective instruments to increase or reduce the use and the quality of health care resources, improve compliance with guidelines and subsequently achieve health targets. The downside is that these incentives can easily be not aligned with the original motivation of health-care professionals and therefore create a conflict of interest, possibly an ethical dilemma, between the income of the physician and the quantity and quality of care given to the patients. It becomes a task for the payer and society, in general, to ensure that all incentives incorporate EBM, QoL, HE, and the ethical standards of the

population, adjusting for adequate quality and quantity of healthcare, stratified for different levels of severity. Transparency and disclosure of incentives may be key to ensure trust in the healthcare system, all the way to the individual physicians.

3.6.15 Risk considerations

Risk may need to be factored in, as prospective compensation exposes agents to new financial risks for which they might demand extra compensation, which contributes to agency loss. Risk that is linked to an overall probability of success that is independent of the physicians, for example by strictly following guidelines and drug labels, should be spread widely across the population, that is ideally held by a public or private insurance company. The technical risk that is linked to the individual decision or execution by the physician or the institution, should be carried by the provider who has accepted the clinical responsibility (Robinson, 2003). Physicians compensated with a fee-for-service are insulated from both types of risk. The capitation compensation exposes physicians to both types, while case rates, allocate probability risk to the insurers (physician are sufficiently paid to provide the adequate care the patients need) and allocate technical risk to the physicians (i.e. when the cause requires more than the capitation foresaw).

3.6.16 Governance mechanisms in the physician-patient relationship

Other governance mechanisms have to be used. A factor driving positive outcomes is for principals to have access and being able to interpret information to verify the agents' behavior. The interaction between patients and physicians have one objective: diagnosing and treating the medical condition that the patient has. This objective requires a decision on which therapy to follow and there are fundamentally two decision-making models (Gafni, 1998): In the first, patients delegate authority to the physicians to make medical decisions, who then act as the perfect agents for the patients. Physicians are expected to uncover the patients' needs and preferences so they can decide in their best interest, i.e. to produce the best possible outcomes. In the second model, the role of the physicians is limited to provide patients with the necessary information, so that patients can make the right medical decisions. The physicians are expected to transfer their knowledge in a clear and nonbiased way. However, within the patient-physician relationship both models can be difficult, and trust plays a dominant role.

3.6.17 Trust-based governance

Patients seek the physicians' advice and implicitly relinquish direct control on how to treat their condition, assume their physicians will follow best practice and act in the best interest of the patients. Doing so, patients take a risk. The relationship between patients and treating physicians is personal, close and bound by confidentiality. Patients are vulnerable, subject to information asymmetry, uncertain about the outcome measures in life expectancy, symptoms, QoL. Trust is vital for building an effective relationship, for enhancing cooperative behavior and thus a prerequisite for successful healing. There are different reasons for patients to trust their physicians and high moral standards and ethical credo of the profession are a strong starting point. Through the internet and easy sharing of any type

of information, the asymmetrical distribution of the latter can be reduced. Patients nowadays can be empowered which contributes to distrust, or, if the physician is in line with the information found by the patient, strengthening of trust. Increased healthcare costs with resulting tradeoffs that are not always in the best clinical interest of the individual patients, combined with the spreading of managed care systems and the evolution of physicians towards tighter work schedules and efficiency orientation, have eroded the trust relationship. Fewer and fewer physicians exposed to these regulatory, health economics and political pressure may be able and willing to suppress their self-interest. The resulting level of distrust depends on patients' education, confidence, communication style, age, gender, culture and more. More qualified and younger patients ask more questions, tend to receive better information, can exert more influence on their treatment, and likely achieve better outcomes, illustrating distrust-based governance (Tofan, 2012). Such governance itself does not come without side-effects: Medical acting may be affected, as physicians will be driven into investing more time in discussions on treatments and negotiations with patients, which cannot all be billed.

3.7 Rare diseases

3.7.1 Overview

Rare diseases are defined as life-threatening or chronically debilitating diseases which affect five out of 10,000 individuals or less (Hughes, 2005). In the US rare diseases have originally been defined as the ones that afflict fewer than 200,000 individuals (LaMattina, 2018). Although these diseases are individually rare, there are about 7,000 rare diseases and, in aggregation, they affect approximately between 6% and 10% of the population, which is similar to the prevalence of diabetes. In the US estimates indicate more than 25 million people, in the EU about 30 million people, and in Australia, about 1.2 million people suffer from a rare disease (Knight, 2006). Rare diseases are a major cause of morbidity and mortality in western countries. They have major repercussions on individuals, their families and health care systems (Lopez-Bastida, 2010). Some are quite well known such as muscular dystrophy, cystic fibrosis or multiple sclerosis, but the majority are exceedingly rare, and rare are also the physicians that ever see a patient with the specific disease. Approximately 50% of the people affected by rare diseases are children, of which 30% will not live to see their 5th birthday. Rare diseases are responsible for 35% of deaths in the first year of life. 80% of rare diseases are genetic in origin, and thus are present throughout a person's life, even if symptoms do not immediately appear.

3.7.2 Challenges of rare diseases

Rare diseases are also complex since often the causes, the link to the genes and their mechanisms are not well understood. Reliable epidemiological data on prevalence and incidence is often missing, and while the majority is genetic and inherited, a significant number is initiated through mutations and/or acquired through processes triggered by environmental factors. Such variability causes complexity and requires approaches, viewpoint, and collaborations across different specialized areas (Posada de la Paz, 2010).
Only about 5% of the known rare diseases have corresponding treatment plans. There is a huge unmet medical need which requires important scientific discoveries, the exploration of the underlying science and the development of therapies (Shen, 2017). The first step towards rare disease research and diagnosis is to identify and document patients with similar phenotypes, the clinical observable sign or symptoms. The Human Phenotype Ontology (HPO) has been created with the objective to catalog human phenotype information and currently covers most of the 7,000 rare diseases (Shen, 2017). To ensure global use, such ontology and instruments ideally use standardized medical language to described phenotypes, and the natural language processing to assist physicians with the diagnosis. The second step is then to provide ready access to such catalogs, registries and treatment results to all stakeholders. A standard diagnostic coding for a complete and appropriate classification or rare diseases is still a gap that needs to be closed. The presence and the burden of most rare diseases are invisible to the health systems due to misclassification and lack of appropriate coding (Commission of the European Communities, 2008). The generally accepted coding by the International Classification of Diseases (ICD) uses a six-character alphanumeric code to describe diagnoses. Currently the 9th and 10th revisions of

the ICD (ICD-9 and ICD-10) are being simultaneously used in several countries around the world, and within some countries, different versions are used in parallel as well. To further exacerbate the gap, according to the Orphanet database, fewer than 300 specific rare diseases are identified by a single ICD-10 code (Posada de la Paz, 2010). Such coding is also necessary to set up patient registries and to monitor global health trends by the use of reliable statistical data (World Health Organization, 2018). In day-to-day life for patients, physicians and payers, without the code it becomes virtually impossible to trace and recognize the rare disease patient in national healthcare and reimbursement systems, harmonize disease surveillance and promote well-conducted epidemiological studies which ultimately will benefit the whole population. Beyond the coding, information that needs to be collected in a standard way, should cover a number of categories such as general information about the disease, its presumed cause, its prognosis, its inheritance capability, and which approved treatments are available and then outcomes they generate. Also included should be the compounds being researched and developed, the known ongoing and planned studies, and a list of patient associations and advocacy groups which also document real-life experiences with the condition. With above in place, physicians will improve diagnostics and treatments, patient advocacy groups can offer support and contribute to the discourse, research groups gain insights on which assets to pursue, development teams write and follow more impactful and optimized protocols, payers can better assess the economic value and therefore determine the right level of reimbursement of the drugs.

3.7.3 Orphan drugs

Drugs for rare diseases are called orphan drugs in allusion to the lack of support that, in general, would ordinarily take care of their development. Orphan drugs are defined as either a medicinal product intended for a life-threatening or chronically debilitating rare disease or a medicinal product that would not be developed without incentives because its sales are unlikely to generate sufficient return on investment (Gericke, 2005). Additionally, to qualify as an orphan drug, it is required that either there is no satisfactory method to diagnose, prevent or treat the disease or, if such a method exists, that the medicinal product will be of significant benefit to those affected by that disease. Rare diseases not only make up small drug markets that do not justify the investment, but appropriately powered trials are also often impossible with the insufficient patients available, compounded by lack of knowledge, low awareness and lack of critical mass. Due to the few products developed and prescribed, as well as the low number of patients, high-quality evidence about clinical added value outcomes of orphan drugs is rarely available (Simoens, 2011). Such is even more the case at the time the companies are seeking marketing authorization. To overcome such challenges and incentivize innovation, regulators combine push, with development and regulatory incentives, and pull incentives, with market exclusivity and tax incentives (Llinares, 2010). Increasingly pharmaceutical companies are entering this space, possibly as they are tempted to diversify away from the mass market, which is exposed to increased competition, marginal progress, shrinking margins, expensive large-scale trials.

3.7.4 Regulatory aspects of orphan drugs

Orphan drugs appear to offer lower development hurdles, as regulatory bodies such as the FDA can more easily monitor the performance of a rare disease drug once it is approved, while at the same time the risk and benefits are seen differently for a drug that is prescribed to a few patients after launch vs. one that would be prescribed to tens of thousands of patients (LaMattina, 2018). An orphan drug can be qualified as such only if provide a significant benefit (Simoens, 2011) and pharmaceutical companies need to apply for orphan drug designation which, when awarded, provides a few key benefits. The US adopted the first orphan regulation in the world in 1983, using as criteria for ODD (Orphan Drug Designation) a low prevalence and the fact that some drugs would not generate sufficient sales to recoup the necessary investment for their development. Drugs with the ODD designation are incentivized with a 7-year market exclusivity, tax incentives, access to a dedicated development grant programs, access to protocol assistance for the development and fee waivers for regulatory activities. During the first 25 years of the Orphan Drug Act, only 326 new drugs were approved by the FDA and approximately 50% of rare diseases still do not have a disease-specific foundation supporting or researching the condition. In 2010 in the US almost 2,000 products have been designated as orphan medicines and about 340 have received marketing authorization (Llinares, 2010). Regulators globally give more attention to rare diseases and orphan drugs. Since the year 2000, the EU implemented specific policies to stimulate innovation in the field of orphan drugs (Hughes, 2005). Pharmaceutical companies can have their medicinal product awarded orphan status and benefit from protocol assistance (scientific advice during the product development phase), direct access to the European Drugs Agency (EMA) Centralized Procedure with respect to registration, ten-year marketing exclusivity starting from the date of marketing authorization. In some case financial incentives in the form of fee reductions or exemptions, or assistance with research and development, are also possible.

3.7.5 Data paucity on orphan drugs and its consequence

Despite the incentives and support for orphan drugs, there can be situations where the data generated at the time of marketing authorization is still not sufficient. As public interest driven by the unmet medical need is very high which drove regulatory bodies to introduce mechanisms to authorize products under exceptional circumstances and approval conditional to conducting post-marketing studies. For the grant of such conditional marketing authorization, a few conditions need to be met: there has to be a benefit to public health from the immediate availability of the orphan drug, the benefit outweighs the risk from having insufficient data, and there is a clear unmet medical need that would be fulfilled. Until 2010 the EU authorized 40% of the marketed orphan under exceptional circumstances (Llinares, 2010). The combination of the above factors defines a highly dynamic sub-market in the healthcare space where therapeutic, pricing and reimbursement decisions have a high impact, starting with the affected patients. A more rigorous and broader EBM approach is required, which is part of the meta-analysis of this thesis. It is established that using information systems built on electronic medical record platforms are key for decision making: they provide physicians with tools that narrow the gap between knowledge and

practice, improving safety and efficacy (Bates, 2003). Until a few years ago treatment modalities for rare diseases such as HAE had been mostly empiric, and consensus guidelines were primarily based on limited case series, observational studies, and expert opinions, all due to the paucity of controlled studies (Cicardi, 2012). Today in some countries additional criteria are used to decide on reimbursement such as the seriousness of the disease, the availability of other therapies to treat the disease and the cost to the patient if the medicine is not reimbursed (Simoens, 2011). Specifically, the latter drives the need for a broader approach to evidence-based medicine which is the focus of this thesis.

3.7.6 Biopharmaceutical drugs for rare diseases

Some rare diseases can be treated with both chemically-derived drugs and biologics (for example HAE can be treated on-demand with the small molecule icatibant or prophylactically with a plasma-fractionated C1-inhibitor. Prices of biologic drugs tend to additionally be less regulated and higher, due to a few reasons. There are no generics for biologics, but only biosimilars, and demonstrating bio-similarity is more difficult and costlier, hence there is limited competition and less opportunity for price comparison. Biologics are more expensive to develop and manufacture, generating higher cost-effectiveness thresholds, especially if they are intended to treat rare conditions. Lastly, some countries have policies supporting the development or excluding biologic drugs from hospital price regulation.

3.7.7 Awareness and information on rare diseases

Agency theory applied to healthcare has already addressed since its beginnings the information asymmetry between the agent (physician) and the principal (patient), with the resulting inefficiency (Arrow, 1963). With rare diseases, few physicians are aware of the conditions and most physicians never see a patient with a specific rare condition in their whole professional life. Consequences are that a large share of patients has to wait decades from onset of symptoms to a confirmed diagnosis, up to 40% are initially and repeatedly wrongly diagnosed, leading to inappropriate surgery, medication, or psychological care (Knight, 2006). On the other side, thanks to modern and free access to any type of mainstream and scientific media available in the internet, thanks to patient's health literacy skills, and thanks to social media which further accelerate the spread of information between populations and patient segments, it is now easily possible that patients have an information advantage over their doctor. Such new dynamic has to be taken into consideration as it affects the application of the agency model, the decision-making process on which treatment to pursue, and as a consequence the overall costs.

3.7.8 New clinical approaches for rare diseases

Rare diseases force onto most of the physicians a new approach in how to deal with the patients. Both GPs and specialists in every day's life encounter patients sharing in large numbers the same conditions such as hypertension, diabetes, allergy, influenza. For these conditions they have available well-established guidelines, recommending "gold standard" therapies that have "ready-to-wear" characteristics, as they apply to broad classes of

patients. While there might be guidelines for rare conditions, the variability of symptoms and QoL implications are large, requiring a tailored approach to optimize treatment on a patient-by-patient basis, which in itself forces a mindset shift. To foster awareness and the sharing of information and experience, the European Union-funded Orphanet through a consortium of now 40 countries, a web-based database of rare diseases, centers of excellence, patient-support groups and major innovation. It is a unique resource with the objective of gathering, improving and sharing knowledge on rare diseases in order to offer support on diagnosis, care, and treatment of patients affected by rare conditions (Orphanet, 2018). In the US the National Organization of Rare Diseases (NORD) is similarly focused on making information more accessible and on coordinating research efforts into rare conditions. Looking beyond, it can be argued that every country should catalog and detail the epidemiology of rare diseases and then support the setup and coordination of centers of excellence and patient-support groups at a national level. The establishment of umbrella organizations such as NORD with connections and sharing of information and best practices with databases and experts across the world would both improve access to information and strengthen the quality of the content. However, when a rare disease awareness is just at its beginning, when very little is known, when virtually no treatment with strong efficacy exists, there is not yet sufficient information to build databases, patient registries, or organizations. The first step, which treating physicians have been encouraging through the history of medicine and genetic diseases, would be to establish and maintain family histories of the health and illnesses of family members through multiple generations, documenting the occurrence of different inherited conditions.

3.7.9 Diagnoses and misdiagnoses of patients with rare conditions

Unless a newly born of a parent with a genetic disease is tested at birth through a blood sample from the umbilical cord or in the first months through standard tests, normally people seek medical help once symptoms manifest. Some of the rare conditions begin with a genetic mutation and symptoms manifest only much later in life. The journey of a patient with a rare condition is much different compared to the one of a patient with a more common condition like hypertension or diabetes. The first dramatic hurdle for a person living with a rare condition appears to be the difficulty in obtaining the correct diagnosis which may take years or even decades to overcome Most care providers have likely never seen a patient with a specific rare condition before, they are not aware of the condition and lack the necessary knowledge and experience, which frequently results in a misdiagnosis (Shen, 2017). A recent survey has shown 41% of the rare disease suffering participants having initially received at least one misdiagnosis before obtaining the correct one (Kole, 2010). Misdiagnosis may result in erroneous treatments by medication but can also lead to surgery, psychological and psychiatric treatments including psychological therapy, psychiatric hospitalizations, and psychiatric medications, under the assumption that the symptoms are due to mental causes. Other deleterious consequences may include psychological and cognitive consequences, death, the birth of another affected child, strains to the cohesion of the family and loss of confidence in medicine. Misdiagnosis may have a double negative effect: in addition to leading to inappropriate treatments, it is often followed by the cessation

of the search for another, the right diagnosis, thus an additional barrier to correct diagnosis and treatment comes into the way. Therefore, for many people living with a rare condition, it can take years or decades to obtain a diagnosis. Every year close to eight million infants are born severe congenital defects, of which more than three million do not survive beyond five years (Zarocostas, 2006). For a quarter of the sufferers of a rare disease, between five and 30 years elapsed between the appearances of the first symptom and the correct diagnosis (Posada de la Paz, 2010). A late diagnosis delays the beginning of the correct treatments and can have severe, irreversible, debilitating and life-threatening consequences (Kole, 2010). Misdiagnosis can result in the worsening of the clinical status (Bennett, 1991), psychological damage (Merelle, 2003) and in some cases death (Kharrazi, 2005).

3.7.10 Decisions and challenges post diagnoses of rare diseases

Even if correctly diagnosed, for the vast majority of rare conditions there is no guideline, no treatment, and no drug. When they do exist, practice, availability and price can vary enormously across healthcare systems, countries and location (e.g. urban vs. rural). Despite all hurdles, having a diagnosis is an accomplishment that provides relief as it gives a name to the combination of symptoms. A diagnosis would allow patients and physicians to look forward and to focus on identifying and following the right therapies, which not only have the advantage of bringing forward the benefits of the correct treatment, but also prevent undesired consequences of inadequate treatments resulting from a misdiagnosis. Correct diagnoses may also enable possible predictions of prognoses and allow patients and their families to continue to search for specific information about the conditions, their causes, expected outcomes, hereditability, possible future manifestations, the availability of treatments, approved ones or under study. With the correct diagnoses of genetic conditions, patients and their physicians may test within their families for possibly other relatives being carriers of the genes causing the diseases. Assisted conceptions with gamete donation could thereby offer an alternative, preventing the disease from being passed on to successive generations (Bermejo, 2010).

Patients reach out to other patients and associations to exchange experiences and to learn how to cope and manage their conditions. This sharing provides comfort, reduces anxiety and depression, which can be triggers themselves for attacks, such as in the case of HAE. More in general, having a diagnosis is pre-condition for the foreseeing of possible complications and for taking the best possible preventive measures which lead to better clinical outcomes and improved QoL. The ideal approach for physicians who consult patients with a rare condition would follow and include a number of adjusted or additional steps (Knight, 2006). Diagnosis poses the first challenge as it requires physicians to frequently ask themselves if the symptoms observed could be the result of a rare condition. In most cases, definitive answers require the service of a specialist (for example a patient might seek the help of gastroenterologist for abdominal pain, but the diagnosis needs help from an immunologist). Genetic diseases come with a number of co-morbidities and burdens that extend beyond the primary symptoms. The patients need to be attended as a whole with high-quality care that needs to include other issues (e.g. beyond the HAE swellings, patients can also face pain, anxiety, depression, hypertension and more). Once the rare diseases are

diagnosed and treated, the physicians should become knowledgeable about their natural history, the evidence-based treatment options, the systematic long-term care, the associated problems, and genetics. For some rare conditions, there is rapid progress on diagnostics and therapies, to stay abreast it is of great support to seek out and link with the centers of excellence, appropriate specialist services, and local organizations. When available, electronic medical records (EMR) are a good source that can be leveraged to accelerate disease diagnosis. They require providers to document and make available associated phenotypic information to support diagnosis decisions.

3.7.11 Role of genetic testing

Most of the rare diseases are genetic in nature, i.e. they are caused by mutations in a few genes. Globally more than eight million children are affected by congenital and inherited disorders which can cause long-term disability and have a lifelong debilitating impact on health (Jackson, 2010). Birth defects are the leading cause of infant mortality. About 3% of birth in the US are affected by structural defects and chromosomal abnormalities (Mathews, 2008). The number of diseases for which genetic tests are available is growing rapidly and can be divided as chromosomal, molecular, or biochemical. In theory, genetic testing could be the key approach to determine if there are abnormalities or mutations with the genetic code and thus confirm not only the conditions, but also their most likely impact on health. Genetic tests have to be validated: their analytical validity confirms the test is able to accurately and reliably measure the genotype of interest. Clinical validity confirms the test's ability to detect or predict the clinical disorder or phenotype associated with the genotype. Lastly, clinical utility measures how useful it is in the clinic (Grosse, 2010). Genetic testing has also its challenges. The patient with inexplicable yet life-altering symptoms is expected to achieve great personal utility from having a diagnosis. Such personal utility manifests through multiple dimensions, such as reduced anxiety, reassurance, help with family planning, career planning, housing, and lifestyle modification. People with a family history of the disease, yet test negative, that is confirming they are not carrying and not at risk for the condition, feel strong reassurance. On the other side, an asymptomatic person who has been tested positive, might be subject to potentially unnecessary treatments, discrimination (job market, insurance) and thus to a negative personal utility impact (Grosse, 2010). Along the same line, professional organizations do not endorse testing asymptomatic children for mutations associated with untreatable diseases (Trott, 2009). Testing even earlier such as newborn screening, prenatal or pre-implantation diagnosis or screening raises another set of ethical questions depending on what is then done with the acquired information (Barrera, 2010).

3.7.12 Role of the family

Families of patients are also an integral part of the journey, as they are affected in many domains of their lives. Either or both patient and caregivers often have to stop working or take lower paying part-time or flexible jobs, creating further financial burdens (Kole, 2010). Families should be encouraged to ask questions, to join (or even build) patient organization and patient advocacy group that collectively can share information, lobby for treatment and

reimbursement, or just help navigate through the humanistic burden of the condition. Patient advocacy groups play also a role in educating health care providers about optimal care or in identifying for their members the most skillful and knowledgeable clinicians who are able to provide the best services (Posada de la Paz, 2010). Treating physicians should also support the families of patients, contributing to the physical, emotional, psychological, spiritual, and social needs of the patient's support network. At the minimum for some conditions, support would be in the form of training on how to administer the drugs when they intravenous or subcutaneous. Treating physicians may also be advocates assisting the patient's journey through the medical bureaucracies or social service.

3.7.13 Data and evidence challenges with rare diseases

Clinical evidence from orphan drug trials may be limited on purpose when the trials are halted early on ethical grounds when an interim analysis demonstrates clinical superiority of the orphan drug in terms of an intermediate outcome measure. To overcome the lack of data, this approach requires the commitment to continue collecting long term data to assess uncertainties and effectiveness (including cost-effectiveness) of the studied compound. Ongoing data collection can happen through patient registries, even though they may be biased if the patient etiology and disease severity change over time. The above considerations can pose a new and unique challenge to the regulator, the payer and ultimately the treating physicians: how can weak clinical data, small health benefit, high cost and absence of an alternative therapy for orphan drugs be aggregated and taken into account for evidence-based decision making? In 2009 NICE issued methodological guidance stating the use of the value that patients place on additional months of life to counterweigh the uncertainty around the evidence of the drug's clinical effectiveness. Such an approach is based on the fact that society attaches a higher value to health improvements experienced by patients who have worse lifetime health prospects.

3.7.14 Innovative mechanisms to decide on reimbursement despite lack of data

Another approach to address the lack of data and uncertainty on effectiveness builds on innovative reimbursement mechanisms for orphan drugs. Orphan drug companies and health care payers close risk-sharing agreements in which companies share the risk that the products may not be effective for particular patients. The arrangements provide that the companies may lose some or all product revenues (or needs to provide replacement products) if the drugs do not have the expected effects. Such solutions are fairly recent, rare and need to be analyzed and negotiated on a case by case basis, which also requires resources and time (which could have been used to treat patients with the often severe, unmet medical need). Orphan drugs have to be assessed on an individual basis to determine whether their specific features warrant the high prices demanded by the manufacturers. Current and planned indications, the existence of alternative health technologies, the total number of patients across registered and off-label indications, and R&D costs should all be incorporated (Simoens, 2011). Such assessments require and then build the fundament of a broader EBM approach to be used in the clinical practice, once the drug is approved, the prices are determined, reimbursement is set up and standard of care is defined. Already now

some European countries appear to tend to demand data on the effectiveness of orphan drugs in a real-world setting rather than on their efficacy in a structured setting to gain reimbursement. The formal economic evaluation requires the calculation of the cost-effectiveness of an orphan drug relative to a relevant comparator, reinforcing the need for comparative data and for a transparent and evidence-based approach towards pricing and reimbursement of orphan drugs (Simoens, 2011).

3.7.15 Importance of RCTs (Randomized Clinical Trials)

Clinical trials are the bedrock for a number of decisions, from the approval to make new compounds available for treatment for medical conditions, to the price at which they are sold, to additional information that has to be shared such as safety, side-effects, eligibility criteria, and more. Normally RCTs need to satisfy three basic requirements. They should examine and validate valuable and important biomedical research questions, they must utilize a rigorous methodology, and they must follow ethical considerations, minimizing the risks to participating subjects (Evans, 2001). Standard methodological approaches for design, execution, and analysis should be applied, and are required by regulatory bodies to ensure the quality and applicability of the results. These determine for example the number of subjects necessary to achieve statistical significance when producing therapeutic claims from the results.

3.7.16 Challenges for RCTs for rare diseases

With rare diseases comes the challenge that the number of experimental subjects who can be recruited into a trial can be very small. In such circumstances, alternative approaches to standard statistical methodology should be considered as the way out from the dilemma of having no RCT at all, or one that can still provide some evidence for potential use. Different several specific methodological approaches have been explored, that either improve the efficiency of standard statistical procedures, or that innovate design and analysis away from the classic paradigms (Gerss, 2010). Caution is exercised to ensure that the limits of scientific quality are not under-run, in which case alternatives to an RCT can be pursued as for example the set-up of an observational registry for the rare disease under study. These should include as many patients as possible and can be either complementary to RCT, or contribute to providing the bases for setting up a future RCT. Within the scope of RCTs, several methodological approaches can be pursued. Some enhance existing statistical methods, providing better leverage of the limited sample sizes available, others abandon the classical paradigms. None are universally applicable, they need to be reviewed case by case for usefulness and viability. As rare diseases pose additional hurdles and challenges compounded by smaller patient populations that ultimately help the Pharma companies to generate a return on investment, different healthcare systems create more favorable conditions. Some regulatory bodies and health authorities offer incentives for development (through scientific advice and research grants) and marketing (through market exclusivity, regulatory fee reductions) (Llinares, 2010). Rare disease by definition have fewer patients, yet this is compounded by the fact that due to low awareness and diagnostic capabilities and experience by the general physician community, even less are diagnosed and identified, and

subsequently treated. The unmet medical need can be enormous, and compassion could dictate exploring potential drug candidates and small clinical trials can be the only option. On the other side, small clinical trials may pose a few issues: the validity of results may be questionable or might miss some effects (positive or negative) due to low statistical power and bias, and they are more prone to variability, resulting in lower precision when quantifying the intervention impact (Gerss, 2010). Very small clinical trials might also raise new questions on privacy and data protection. Clinical trials on patients with rare diseases also raise additional ethical questions. For example, with HAE, patients can suffer life-threatening laryngeal attacks, and when this is the case, eligible subjects with these attacks were not randomized, but treated with open-label icatibant, as it was expected to be the most effective treatment (Lumry, 2011). It would be unethical to give a placebo to a patient suffering potentially fatal events. However, on the positive side, working with smaller sample populations might have them more likely to share specific characteristics which subsequently yield more homogeneous results with less variability, which then reduces the generalizability, though. Small clinical trials tend to bring investigators and patients closer together. Combined with the fact that for many rare diseases the studied new drug is the first or last hope of therapy, participants are more involved, willing to participate and comply with the protocol.

3.7.17 Other RCT approaches for rare diseases

When recruitment of sufficient study subjects is difficult, or when ethical considerations, for example, because of a significant unmet clinical need that asks for minimizing the size of the placebo control group, alternative randomization approaches can be used. Response-adaptive randomization, also called “play by the winner”, is such an approach, where the probabilities of allocation change through the course of the study based on the cumulative and accrued efficacy response data (Gerss, 2010). If one of the one intervention is beginning to emerge as superior, new patients will more likely be allocated to that arm, with the benefit more patients can benefit from a possibly superior treatment. Another approach that is even more flexible, does not predetermine the sample sizes a priori. The RCT is divided into stages with initially fixed sample sizes. At every stage, interim analyses would be performed, and the sizes for the next stage re-determined. As soon as the trial results are strong enough to prove the hypothesis, the trial would be stopped. When several existing trials measure the same outcome, a meta-analysis may become possible, an approach also used as part of this thesis. Meta-analysis describes a set of statistical procedures which enable the combination of two or more independent studies to produce an overall answer to the research question (Schulze, 2004). Combining different studies provides results with more power compared to each study on its own, and the studies don’t necessarily need to follow the same design, protocol (Gerss, 2010). The effects and the differences in precision are weighted by sample size, before being pooled into an overall effect estimate, where the power is automatically increased. The effect estimate is, therefore, more precise than when it was concluded with the single and separate studies.

3.7.18 From RCT to RWE for rare diseases

Some orphan drugs are fast-tracked into approval for ethical reasons: the condition is life-threatening, there is no alternative treatment, and due to the difficulty in recruiting patients for an RCT, market authorization is given faster. For many rare conditions there is yet no other treatment option which poses a compelling and compassionate argument to provide patients, that is study subjects, a hope that there is or there will be a cure, which will extend or improve their life, relieve them of symptoms, or possibly even enables a normal life (Day, 2010). In some other cases, RCTs are initiated but may be halted early for ethical reasons, once the first results demonstrate clinical superiority. Either path still requires a commitment to ongoing evaluations which can be in form of post-marketing surveillance studies to produce efficacy and safety data, or in form of patient registries which collect the necessary data to evaluate uncertainties surrounding the longer-term effectiveness and cost-effectiveness of the orphan drug. Patient registries represent the first step in systematically cataloging available information that can be used to estimating prevalence or incidence of rare diseases. Combined with the data around patient profiles and treatment outcomes, the registries build the base for research, for recruiting patients into trials, and for the exchange of information between physicians, including the building of consensus for the writing of treatment guidelines. Patient advocacy groups demand and fund registries as it is established that they are a strong contributor to improve health and QoL of the affected patients. All combined, RWE can enable an expedited assessment of the treatment, for when there is no time or opportunity to conduct an RCT.

3.7.19 QoL with rare diseases

Not all rare diseases affect life expectancy, but they lead to physical, emotional and psychosocial limitations with a wide range of disabilities (Rajmil, 2010). QoL is one of the patient-reported outcomes and evolved from simple measures such as pain intensity, to more complex constructs such as patient satisfaction, further refined and broadened to multidimensional concepts covering the physical, psychological, and social domains. Many rare diseases can combine multi-morbidities and may be substantially debilitating, causing significant burden not only for the patients, but also for the families, the caregivers, and the system. At prima facie “rare disease” and “serious disease” seem not to have a reason to correlate, but in reality, and in many cases, they go hand in hand. Particularly when infants are born with a hereditary and congenital disease, the severity of it often results in a limited life span (Day, 2010). Also, in case of survival into adolescence and adulthood, genetic rare diseases often have a debilitating impact that affects virtually all aspects of life. These need also to be included in all aspects of therapy, costs and funding. People living with a rare condition face a number of obstacles that each have a strong impact on QoL. For most rare conditions there is a lack of scientific knowledge and lack of awareness of the disease, which undermines any effort for a positive outlook. Most patients don’t have access to the right physicians which results in incorrect or delayed diagnosis. When diagnosed, there is still limited or low-quality information or support. Rare diseases often come with multi-morbidities which require multidisciplinary healthcare that is not available or not coordinated. Irrespective of diagnosis, patients with rare conditions face social

consequences that include isolation, stigma (in some cultures patient seen as cursed), impaired education, career and income progression. Patients can be exposed to inequities and difficulties in accessing treatment, rehabilitation and care, especially in multi-tier healthcare systems. Overall patient studies documented dissatisfaction and loss of confidence in medical and social services (Kole, 2010).

3.7.20 Rare disease costs

Rare diseases generate a range of negative effects on the QoL of the patients, their caregivers and on society. The effects also include the use of health care and other resources. The primary disease impact is often further exacerbated by co-morbidities such as anxiety, pain, depression, or premature death, which all have an effect on productivity (Lopez-Bastida, 2010). When looking at costs, different types have to be distinguished. The first type of costs are the direct treatment costs that result from the use of resources, outpatient (such as physicians, specialists) and inpatient (such as hospital care, emergency rooms), the use of diagnostic and other equipment, and the drugs themselves. The second type of costs are the non-healthcare costs resulting from the need for additional help at home, special housing and transportation requirements. The third type of costs results from the loss of productivity caused by sick leave, disability, or early demise.

3.7.21 The link between QoL and costs of the conditions

A link is made between QoL and costs by assigning a value to the QALYs, the quality-adjusted life years, which are calculated by multiplying life years with their quality weight. Cost of illness estimated and expressed this way allows to define each condition in monetary terms and be compared and allows a direct assessment and justification of an intervention or a therapy, therefore an optimized allocation of limited resources through objective tradeoffs. The QALY approach can provide an economic framework for evaluation of healthcare services which would enable the determination of the most efficient service, technology or therapy (Lopez-Bastida, 2010). Combining units that measure both quantity and quality of life gained through medical intervention, the QALY, allows more advanced analysis of effects compared to mere cost-effectiveness studies. QALY as an index takes into account also patient-subjective aspects, which can vary significantly between treatments even for the same precise indication (for example a hospital administered infusion every two days vs. an oral capsule that can be taken at home once a week). The QALY approach may also have disadvantages that need to be weighted in: It can be difficult to measure health in monetary terms (how much are ten hours of pain worth?) and how to deal with ethical dilemmas (how much more is the life of a child worth compared to a middle-aged adult?).

3.7.22 Pricing of orphan drugs

Same as with all pharmaceuticals, the price of an orphan drug is set by a manufacturer in an effort to recoup all its costs, especially in research and development, and to return a healthy profit in line with market expectations and the investment risk is taken. However, the market for orphan drugs has inherent market failures resulting in high prices due to a number of reasons (Simoens, 2011). Orphan drugs command a high price for a number of reasons. Even at a high price these drugs can save the healthcare system significant amounts of money, as these conditions, when left untreated, cost the healthcare system much more mainly through their significantly debilitating impact and their comorbidities. Drug pricing, in general, follows the same economic logic as for most goods and services, yet orphan drugs also show higher prices than drugs in general for a few reasons that can be explained as monopolistic power, or market inherent market failure. High-quality evidence about the clinical added value of orphan drugs is rarely available because to the challenge in recruiting a large number of patients for the studies but orphan drugs serve a small number of patients from which they need to recoup the significant R&D costs. They benefit from a period of marketing exclusivity in a narrow market where few alternative health technologies are available.

3.7.23 Orphan drugs price finding dynamics

For the reason explained in section 3.7.22, payers and patients have few, if any, alternative options and thus limited negotiating power, compounded by lack of information on the real cost structure of orphan drugs. Payers also need to take into account not only the current, but also any future planned or possible indications, including possible off-label indications. Patient advocacy groups and media may exert additional social pressure, and, in such settings, pharmaceutical companies have more leverage when attempting to maximize orphan drug prices (Simoens, 2011). Each state governs its own pricing and reimbursement of orphan drugs, the stakes and the incentives can further induce the companies to artificially create monopolistic market conditions. This can be achieved by splitting up a disease into several sub-diseases, which would qualify as a separate rare disease each, in order to attain the benefits above. Health care payers on the other side may have limited negotiating power and often lack information about the cost structure of orphan drugs. In addition, both regulatory bodies and payers can be exposed to pressure from patient advocacy groups and media to accommodate new orphan drugs. Under these border conditions, the laws of competition don’t necessarily work. Interestingly countries with free-market pharmaceutical pricing (e.g. Germany) generally seem to have higher orphan drug prices than countries that regulate prices (e.g. Portugal, Spain). Not for all orphan drugs, the need to recoup substantial R&D costs from a small number of patients applies: some orphan drugs were approved for other indications or on the basis of historical use, when there was no requirement to produce new evidence on efficacy to gain marketing authorization.

3.7.24 Specific aspects of biological and biopharmaceutical drugs

Many orphan drugs are biologic and biopharmaceutical prices may be less regulated and higher than those of chemically-derived drugs, as in some countries they are excluded from price regulation when used in hospitals. Price comparisons with other products are often not possible, as there are only very few and highly differentiated products. Competition from biosimilars can also be hindered by the difficulties to develop, to demonstrate bio-similarity and the additional studies (e.g. immunogenicity) that need to be performed. When an unmet clinical need or the first treatment for a rare disease is being offered, the cost-effectiveness thresholds are also lower. For all these reasons over the recent years, an increasing number of Pharmaceutical and Biotech companies seem to have increasingly focused on rare diseases, attracted by the opportunities of better differentiation and higher profitability compared to mass market Pharma which has come under intense political scrutiny. In all markets, manufacturers have an incentive to game the system by artificially creating monopolistic market conditions, hence it is no surprise that the same dynamic is observable in rare diseases. This and the growth have now made pricing and reimbursement of orphan drugs an issue of high priority for policymakers, legislators, health care professionals, industry leaders, academics and patients as well.

3.7.25 Reimbursement of treatments for rare diseases

Price is the single greatest barrier to patient access to orphan drugs, forcing health care systems to developed special systems to ensure patient access whilst managing overall budgets (McCabe, 2010). The costs of treating rare diseases have averaged USD 140,000 per year in 2016 in the US, according to analyst firm Evaluate Pharma (Johnson, 2018). There are about 6,500 US citizens suffering from HAE and the annual average cost of medications per patient was more than USD 2 million in 2017, according to report by Express Scripts Holding (Johnson, 2018). Public health systems and private insurers have been set up and are designed for the mass market health challenges that affect large segments of the population. Such systems are structured for overall performance and not for unusual and unfavorable circumstances (Pratt, 1985), like rare conditions. Policy makers, legislators, health care professionals, industry leaders, and patients are driving and witnessing a surge in the diagnosis and treatment of rare diseases with orphan drugs. Pricing and reimbursement are an issue of high priority. While in some healthcare systems reimbursement of treatment is virtually unlimited, in many there are limitations based on such criteria as the seriousness of the disease, the availability of alternative therapies, the financial impact to the patient if the treatment is not reimbursed (Simoens, 2011). On the other side, while disease severity justifies a premium price for drugs, disease rarity does not. For this reason, authorities and payers tend to review the effectiveness of orphan drugs in a real-world setting, rather than assessing their clinical efficacy in structured and controlled RCT settings. Prices and reimbursement are calculated compared to relevant comparators; therefore, comparative data should ideally be developed and provided. Many of the new orphan drugs are biologic and are priced highly. The US FDA has initially set up a separate category for biologicals for the first five cell and gene therapies, which has contributed to a dramatic shift in drug prices. Between 2010 and 2014 median annual drug costs per patient rose more than

sevenfold from USD 1,258 to USD 9,396. The number of the top 100 drugs costing more than USD 10,000 per year increased from 26 in 2010 to 47 in 2014 (Campaign for sustainable drug pricing, 2016).

3.7.26 Efficacy and efficiency of healthcare treatments

With classical medicine and EBM, the focus on the evaluation of treatments is measured in efficacy. Drugs are not only a medical good but also an economic good that needs to be paid for, and as such standard economic theory applies. When having to choose between goods or services or how much to pay for them, efficiency is the variable to be considered. Positive efficiency is obtained when the surplus, the excess value to the consumer over the price paid is positive (consumer surplus) and/or the excess in price received is above the costs for the seller (producer surplus). The sum has to be positive for a product or service to be viable, and free markets evolve to maximize this variable. The challenge with rare diseases is that under normal conditions the surplus of orphan drugs would be negative, they would be inefficient and pharmaceutical companies should not develop them and patients would not receive them. To achieve efficiency – and enable treatments to be developed for patients with rare conditions - pharmaceutical companies need to receive sufficient return to invest and supply, and payers can justify covering such treatments, as with overall budgetary constraints, tradeoffs have to be made (McCabe, 2010). Hence, the health economy of rare diseases has to be viewed from two perspectives. First, the condition itself causes an economic impact from impaired education, professional success, reduced income, additional expensed for housing and more. Second, diagnosis and treatment result in additional costs that need to be evaluated and weighted against to assess their cost-effectiveness (Lopez-Bastida, 2010).

3.7.27 HE challenges of rare diseases

Each rare disease has by definition few cases and within the large scheme, initially orphan drugs were and often still are exempted from the same rigorous value for money consideration. This paradigm might have to be revisited as the number of authorized and reimbursed orphan drugs is growing rapidly and having a significant impact on healthcare budgets (McCabe, 2010). Major regulatory bodies and healthcare systems have introduced highly effective measures to incentivize the development of rare diseases, like the Orphan Drugs Regulation in Europe. In the meanwhile, the premium prices requested and paid for these products added up to such measure as to challenge the notion that the treatments can be made available to all patients who may benefit from them (Miles, 2007). Some payers still offer unrestricted access, others have introduced regulation ranging from requiring individual patient approvals to blanket bans for certain treatments. It can happen that, despite regulatory action such as resulting from the orphan drug designation, the development and reimbursement of an orphan drug remains inefficient. In such cases, it has been suggested to place higher on treating rare diseases than on treating other diseases (McCabe, 2010). This claim for rarity rests on the assumption that treating patients with rare diseases is more important than treating individuals with common diseases, as the severity, life impairment, is much higher. The approach is questioned by the fact that there are many common severe

conditions which would have an equal claim on resources. In Australia, for example, the reimbursement scheme acknowledges that not all health gains are valued the same. The health gains for patients with severe and rare conditions for which there is no other treatment and who face a significant mortality burden, are valued more than others (Australian Government, 2016).

3.7.28 Use of QoL for rare disease HE considerations

The classic methods to appraise treatments for reimbursement show to be inadequate for rare conditions: RCTs are often not viable and alternative approaches have to be pursued to obtain regulatory approval to market a new orphan drug. Sometimes is it not possible to measure the effectiveness of orphan drugs vs. conventional therapies, the measures themselves are not adequate for rare conditions (McCabe, 2010). The QoL perspective offers an equity-based approach for HE-driven decisions.

When having to decide if to fund or which treatment to fund, institutions such a NICE attach a monetary value to QALY. Empirical evidence suggests that treatments costing between USD 25,000 and USD 35,000 raise questions and the institute reviews carefully at the certainty of the outcomes, if the new treatments deliver substantial benefits and whether the QoL impact has been measured and reflected adequately. Treatments costing over USD 35,000 per QALY need increasingly strong evidence for them to be recommended and ultimately reimbursed (Goodall). Despite the intent and the models aimed to fully quantify QoL, there remains a social value judgement that needs to be considered. For example, people strongly fear losing their eyesight and efforts to save children's lives have strong public support. Appraisers and decision-makers on policy, recommendations and funding appreciate that (Goodall).

3.8 Hereditary Angioedema (HAE)

3.8.1 Description of HAE

The rare condition Hereditary Angioedema (HAE) with a prevalence of 1:40,000 has been selected to study the research questions. It is a rare disease characterized by recurrent swelling of subcutaneous or mucosal tissue primarily caused by a deficient or dysfunctional C1-inhibitor.

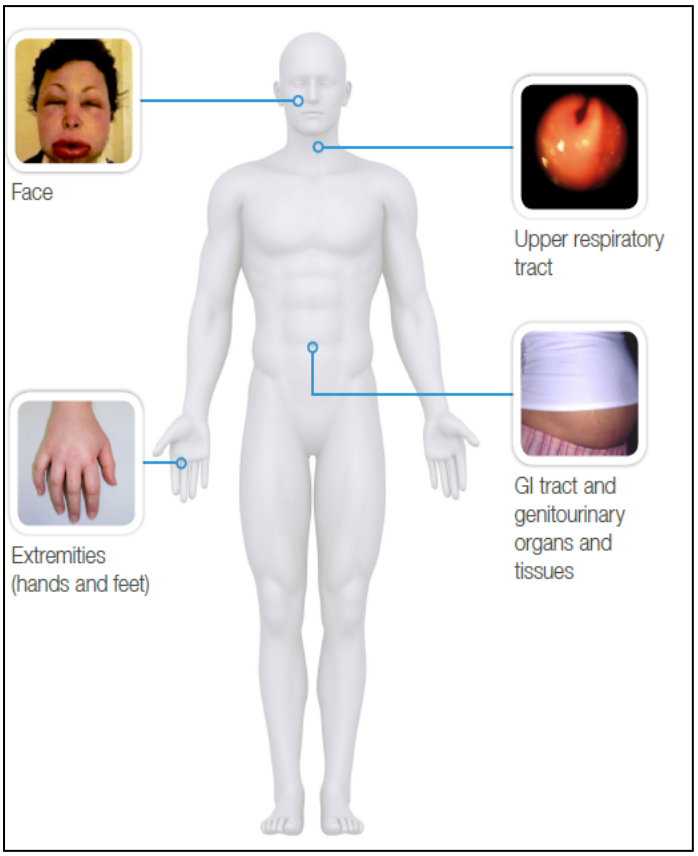

Figure 3.8.1 - Attack sites of HAE

Hereditary Angioedema was first described by JL Milton in 1876 and Sir William Osler in 1888 was the first to note the hereditary component of the condition providing a detailed description of HAE over five generations. It took several decades before Donaldson and Evans discovered the absence of C1-inhibitor as the biochemical basis of the disease in 1963 (Ghazi, 2013). HAE is a condition characterized by transient swelling of cutaneous, subcutaneous, and submucosal tissues resulting from leakage of fluid. Divided into histamine-mediated and bradykinin-mediated, HAE is the latter form and hereditary. A child of a sufferer has a 50% chance of inheriting HAE. 75% of cases are inherited, 25% spontaneous mutation. The condition manifests through swelling attacks which can be isolated or recurrent, unpredictable in frequency, severity and site as illustrated in Figure 3.8.1.1. The attacks can be disfiguring as illustrated in Figure 3.8.1.2, life-threatening if the larynx and airway are affected due to the risk of asphyxiation (Lumry, 2018).

HAE causes a significant burden of disease with absenteeism from work or school increasing with attack severity and frequency. Between attacks, the burden of disease is reported through reduced productivity, emotional impairment and reduced Quality of Life (QoL).

3.8.2 Treatment of HAE

Figure 3.8.2 - HAE during attack and between attacks

(Source: (https://nuwaupianism.com/360-questions/malachi-york/397-ask-the-nuwaupians-what-about-malachi-york-s-acute-case-of-angioedema

Studies have shown QoL to be the single most meaningful way to measure how well treatment works (Lumry, 2018). The treatment goal is to prevent or attenuate angioedema attack recurrence, and to reduce the symptoms of angioedema attacks as soon as possible. Treating physicians are specialists, often Immunologists or Allergists, but in some countries Dermatologists, ENT clinicians, Internal Medicine Specialists or others. There are two treatment approaches: (1) Treatment of attacks - Acute or on-demand treatment, and (2) Prevention of attacks - Both long term and pre-procedure. The WAO (World Allergy Organization) guideline says that every patient on prophylaxis should also hold on-demand treatment at hand in case of breakthrough attacks. Based on published data it is estimated that of the global around 190,000 people living with HAE, about one quarter is diagnosed, of which about half is treated, of which about one fifth has access and is treated with modern therapies. There is a strong unmet medical need. Most patients are not diagnosed, not treated and have limited or no treatment options which leave them completely exposed to the attacks which can be fatal.

3.9 The three perspectives EBM, QoL and HE in the literature search

A literature review spanning the healthcare industry from a general to a specific rare disease focus has been performed and a number of challenges faced by the different stakeholders have been identified. Generally speaking, the review has identified many issues centered around decision-making processes, incentives and the subsequent impact on patients. EBM, the first perspective, was reviewed as described in section 3.1. It is an approach which is generally accepted and used across all steps from diagnosis, prognosis, treatment, quality of care, and health economics. This review raised the challenge that data pools and insights currently remain still fragmented and dispersed, opening the opportunity for this thesis to attempt to combine some with the expectation to strengthen content and depth. QoL, the second perspective was reviewed in section 3.4, which describes all aspects of life experienced by a patient that is impacted when he or she suffers under a disease. The third perspective on HE was researched in section 3.5, highlighting the increased need to balance between universal access to modern therapies and the limited funds available. The three perspectives, affecting the individual, his immediate surroundings and society as a whole, are often in conflict. This thesis aimed to incorporate all perspectives, in order to contribute with a balanced framework which was expected to facilitate the dialogue necessary between the decision-makers and the influencers. Rare diseases and HAE with their specific attributes and challenges have been researched in the literature in sections 3.7 and 3.8. Rare diseases pose additional challenges such as low awareness of the conditions, how to diagnose them and treat them.

3.10 Emerging themes from the literature search

The literature search identified recurring themes which could be connected to the problem statements and RQs proposed in section 2 and which are illustrated in Table 3.10.1

RQ 1.1: How do different stakeholders and decision-makers have an impact on patients with rare diseases?

RQ 1.2 Are diagnosis and treatment decisions made with EBM, QoL, HE and RWE considerations in mind?

RQ 2: How can the decision-making process and the available and potentially available data be combined to allow the stakeholders to make economically more efficient therapeutic decisions with better health and QoL outcomes?

A thematic analysis was conducted while performing the literature search where the different themes, key words and concepts were extracted from the sources and clustered. Their importance in the literature was established by the frequency of occurrence, the quantity of their citations, and the importance of the role they played in reaching conclusions or interpreting observations. Table 3.10.1 crystallizes the themes by cluster indicating the sections from which they were extracted and indicating in which RQ they become relevant.

Theme	Sections	Related RQ
Physicians treat patients based on a combination of scientific evidence and personal experience.	3.1.1	RQ 1.1
Healthcare is mostly funded by payers who face tradeoffs and constraints.	3.5.5, 3.5.6	RQ 1.1
Pharmaceutical companies pursue market access activities to enable and influence the prescription of drugs and treatments by the physicians for the patients.	3.5.9, 3.5.10, 3.5.11	RQ 1.1
Agency theory describes the dynamics between the stakeholders, the resulting potential challenges and approaches to overcome them.	3.5.7, 3.6.1, 3.6.2, 3.6.3, 3.6.4	RQ 1.1
Established instruments to support Evidence-Based Medicine (EBM) such as Randomized Clinical Trials (RCT) are available, have been introduced and studied.	3.1.2, 3.1.3, 3.1.4, 3.1.5, 3.1.6, 3.1.7, 3.1.8, 3.1.9	RQ 1.1, RQ 1.2
RCTs have limitations especially for rare conditions. Other innovative approaches are being used-	3.2.1, 3.2.2, 3.7.13, 3.7.15, 3.7.16, 3.7.17	RQ 1.2
Clinical guidelines support the execution of EBM by ensuring high quality medical practice from a clinical perspective.	3.1.10, 3.1.11, 3.1.12	RQ 1.2
Treatment guidelines have limitations due to information gaps, their strict focus on medical parameters (vs. incorporating also QoL and HE considerations) and the incomplete involvement of all stakeholders.	3.1.13, 3.1.14, 3.1.15, 3.1.16	RQ 1.2, RQ 2
QoL is a key factor which describes the patient's point of view. For rare conditions the families of the patients also play a prominent role and QoL acquires more importance due to the severely debilitating manifestations of the conditions.	3.4.1, 3.4.2, 3.4.3, 3.4.5, 3.4.6, 3.7.12, 3.7.19l	RQ 1.1, RQ 1.2
Health Economics (HE) and the need to contain healthcare costs influence the decisions on treatments	3.5.1, 3.5.2, 3.5.3, 3.5.4, 3.5.8	RQ 1.1, RQ 1.2
The significant QoL implications of rare conditions generate additional costs.	3.7.20, 3.7.21	RQ 1.2
Rare diseases face additional challenges on clinical evidence, QoL and HE, which pose additional hurdles and complexities for all stakeholders, caused by data paucity, low awareness, high treatment costs, and in most cases no definitive cure.	3.4.4, 3.5, 3.7.1, 3.7.2, 3.7.3, 3.7.4, 3.7.5, 3.7.6, 3.7.7, 3.7.8, 3.7.9, 3.7.10	RQ 1.2
Orphan drugs treating rare conditions are subject to similar costs compared to other drugs, but command significantly higher prices for different reasons, adding pressure on reimbursement decisions for the payers.	3.7.22, 3.7.23, 3.7.24, 3.7.25, 3.7.26, 3.7.27, 3.7.28	RQ 1.2

Theme	Sections	Related RQ
Theme Physicians could face dilemmas between the clinical guidelines and the need to meet the expectations as described by the agency theory. The compensation and the incentives for the physicians effectively drive the decision-making process and are essential to successfully achieve the desired outcomes.	3.6.9, 3.6.10, 3.6.11, 3.6.12, 3.6.13, 3.6.14, 3.6.15	RQ 1.2
Additional considerations (such as risk management) and governance mechanisms (such as trust-based governance) need to be factored into the decision-making process and the integration of the perspectives.	3.6.15, 3.6.16, 3.6.17	RQ 1.2
Real World Evidence (RWE) complements RCTs to enable more comprehensive treatment decisions based on clinical evidence.	3.3.1, **Error! Reference source not found.**, 3.3.2, 3.3.3, 3.3.4, 3.3.6,	RQ 1.2
HE discussions between payers and pharmaceutical companies are shifting from volume- to value-based payment models which build on RWE	3.5.12, 3.5.13, 3.5.14, 3.5.15	RQ 1.2
When deciding on the reimbursement of orphan drugs, payers need to look at innovative approaches	3.7.14	RQ 1.2
RWE is required to understand and include QoL and HE into therapeutic decision making and funding. For rare diseases the importance of RWE is higher to compensate for the limitations of RCT.	3.3.5, 3.3.7, 3.3.8, 3.3.9, 3.7.18	RQ 2
Therapeutic decision making has evolved over time paving the way for a more holistic approach that combines all perspectives and builds on the double-agency model	3.6.5, 3.6.6, 3.6.7, 3.6.8	RQ 2
Price differences for same treatments across healthcare systems and different levels of payment coverage suggest different levels of development and possible inequalities and inefficiencies.	3.5.18	RQ 2
Combining EBM, QoL and HE requires the intersection of different paradigms and managed care models aim to improve the health of the covered patients while reducing costs.	3.4.7, 3.5.16, 3.5.17	RQ 2

Table 3.10.1- Emerging themes from literature search and their connections to the RQs

3.11 Research gaps

The literature search on EBM, rare diseases, HAE, QoL, HE, RWE showed that each discipline or perspective of healthcare management has been subject to detailed inquiry and research. Scientific findings have led to theories, consensus for treatment, but also challenges. From an examination of the literature review, three gaps became clear. First, existing studies and papers are scattered across geographies and specific aspects. A meta-analysis combining them would allow for stronger conclusions to be drawn; second, the three perspectives EBM, QoL and HE inherent to the three groups of stakeholders HCPs, patients and payers are taken individually, sometimes mentioned together in context, but not fully integrated for consideration and decision making. Third, agency theory has been utilized to describe the patient-doctor relationship and partially also the role of the payer. Some real-life complications still need to be researched and agency theory can be used to explore these complications. This thesis aimed to inform these three gaps by leveraging HAE as a representative for all rare diseases, where need and impact are among the largest.

4 CHAPTER FOUR - RESEARCH DESIGN AND METHODOLOGY

4.1 Research design

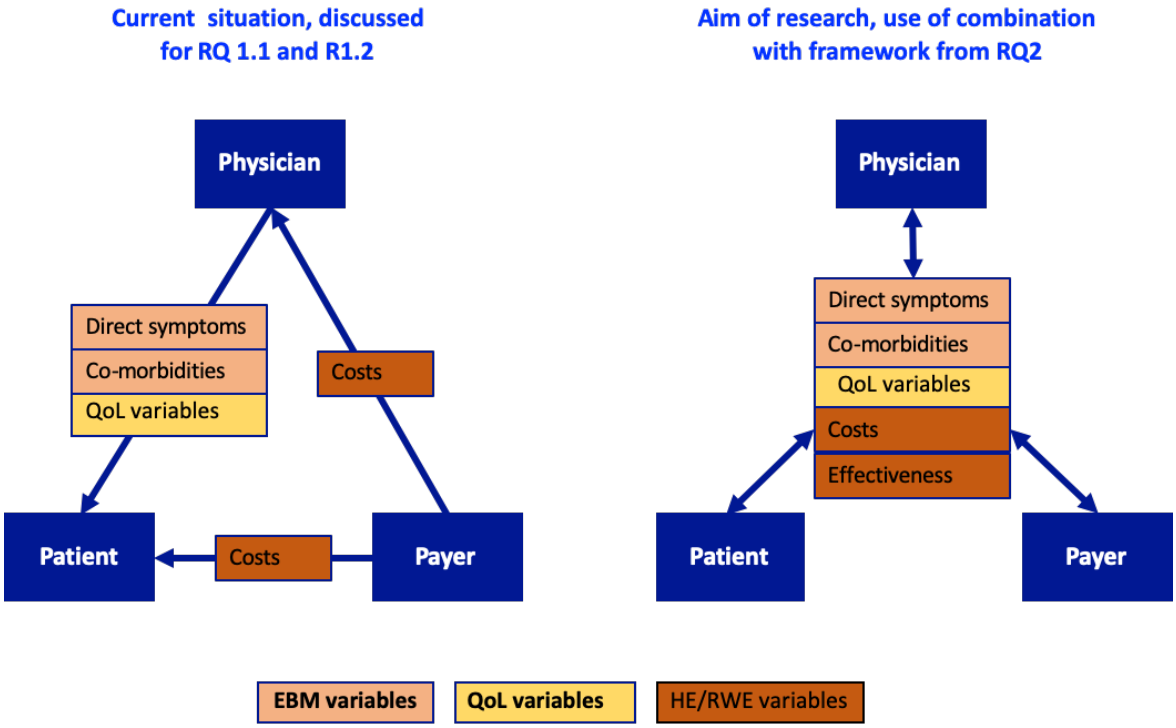

Figure 4.1.1 - Stakeholder mapping with variables

To answer RQ 1.1. and RQ 1.2 a literature review and three studies were conducted with a specific focus on HAE as an example of a rare disease.

4.1.1 Selection of research method

For this thesis, a deductive research method was selected. Within the chosen area of rare diseases and medical treatment, a body of research and concepts were available within the three dimensions EBM (Evidence Based Medicine), HE (Health Economics) and QoL (Quality of Life). With the selected research method and the data collection from different perspectives, this thesis aimed to combine them into one framework. The type of research is explanatory as it aimed to connect different perspectives and data sources, while explaining the interrelations and how these could be used for better clinical, QoL and economical outcomes for the stakeholders involved. Figure 4.1 illustrates the framework of combining the variables to allow for a more comprehensive therapeutic decision-making to allow for improved clinical, HE and QoL outcomes. For the research design, both a qualitative and a quantitative research method were pursued. The qualitative method aimed to obtain answers to RQ 1.1 and RQ 1.2, while the qualitative method aimed to quantify the variables identified and discover how they relate to each other. When devising the sampling strategy, two of the three stakeholders were selected: the patients and the physicians. Physicians could be approached directly (for example through a survey) while ensuring the

privacy of the patients by way of anonymizing the survey. To ensure additional privacy protection for the patients, the participation by the physicians themselves was also anonymized. Data from the patients were collected through a non-interventional search on social media, with special attention not to put at risk the patients' privacy, which is particularly sensitive given the focus of the thesis is on an incurable genetic and rare disease with significant impact on health, QoL and costs.

The RQs formulated in section 2 based on the identified knowledge gaps, determined the variables which were researched in the literature review in section 3. The agency theory selected as the theoretical framework in section 2.3 and explained in section 3.6 provided the backbone of the thesis, establishing the logic, helping to synthesize the findings and providing guidance on when gaps could be clarified or closed.

The survey with physicians was designed to be retrospective, therefore not experimental and ensuring that variables could not be controlled or manipulated. The same can be said of the research on social media, where the data points (postings) were in existence already before the thesis was executed.

The answer to RQ 2 was to be built on a model which incorporates all variables and their values, as verified and measured by the research, into one algorithm that could be used to perform simulations which help ascertain the optimal treatment approach which maximizes clinical outcomes, QoL and economic efficiency. Such a model could be in the form of a formula that utilizes the variables illustrated in Figure 4.1.1. The treating physician, the payer and the patient would enter the values relevant for the specific situation of the patiend and his or her condition, and the algorithm would suggest the optimal therapeutic decision.

4.1.2 The three selected study areas

Consistent with the literature review and personal experience in the field suggested three possible study areas with prospects of generating new data which could be cross-checked for consistency while enabling to answer the RQs.

Study 1: Survey with treating physicians
Study 2: Search on social media
Study 3: Meta-analysis of existing studies

Each of the studies analyzed the stakeholders - patients, physicians and payers, as well as the three perspectives of EBM for diagnosis and treatment, and QoL and HE/RWE for funding. The objective was to understand the gaps of not using all variables for treatment decisions and consequently how this impacted patients and society. The approach of a meta-analysis was selected to achieve more rigorous conclusions due to higher statistical significance and which were subsequently combined into a research framework. It is expected that following the illustrative framework and testing of the data, that the various quantitative conclusions will be derived from the three studies.

Given the rarity of the medical condition and the relatively limited number of both patients suffering and physicians treating the chosen condition, the thesis did not constrain the reach of the sources of data. All available literature, the available treating physicians and the full breadth of social media postings on the condition were included in the thesis. The

expectation was that in this specific scope of the thesis the selected convenience sampling might prove to be sufficiently representative, generalizable and consistent across the studies.

4.2 Variables studied

4.2.1 Stakeholders

Stakeholders are persons and institutions relevant to the treatment of the condition of the patient. These are either decision-makers, payers or influencers. The objective was to provide a qualitative description of stakeholder roles, qualifications, activities and their impact on the patients. This part of the thesis was exploratory/descriptive to scope out and describe all stakeholders involved or influencing, directly and indirectly, awareness, diagnosis, treatment and funding. Data were collected cross-sectionally with primary (survey, interviews, and social media) and secondary analysis (secondary published literature). The literature search suggested that relevant stakeholders are patients, healthcare professionals (physicians, nurses, and pharmacists), payers (for reimbursement), patient advocacy groups, caregivers, regulatory bodies, and pharmaceutical companies, with the first three being the most relevant ones. The thesis focused on patients, physicians, and payers following the double-agency framework described in section 3.6.4.

4.2.2 Criteria for diagnosis, treatment and to assess success

The objective of this section was to provide a qualitative and quantitative description of criteria utilized by treating physicians for diagnosis, treatment decisions and for assessment of outcomes. The literature research appeared to indicate that epidemiology (prevalence in population), frequency of HAE attacks (# per year), location of attacks (extremities, abdomen, face, laryngeal, etc.), severity of attacks (pain index), fatalities (%), co-morbidities (e.g. depression, anxiety, hypertension, obesity, etc.), QoL impact (e.g. absenteeism, lost income) and treatment costs are the relevant variables.

4.2.3 QoL aspects

The objective of this section was to analyze and structure the QoL aspects affecting the patients and their caregivers due to the relevant condition including its main symptoms with the co-morbidities, the burden of disease and treatment, and the costs of having and managing the disease (income and expense).

The literature search suggested that variables that provide definitions, meanings and quantification of QoL (QALY and other parameters) and which cover both qualitative (social impact) and quantitative (income and costs) aspects could be used for therapeutic decision-making. The key was to utilize the variables that provided values for the HAE condition before diagnosis, compared across different treatments and with the healthy population.

4.2.4 HE and RWE considerations

The objective was to analyze the economics of the condition, undiagnosed vs. treated, and to provide a qualitative and quantitative description of HE and RWE variables, their current

use in therapeutic and funding decision making, and their dependency on different types of treatment and QoL considerations.

The variables utilized were expressed as cost to the individual and to society of the undiagnosed patient vs. the diagnosed and treated patient. These variables were supposed to include all financial implications such as the economic burden driven by symptoms, co-morbidities, QoL implications, and cost-effectiveness of the different treatment options.

4.3 Study 1 – Survey with physicians treating HAE

4.3.1 Participants and objective

The community of physicians working on or exposed to HAE is relatively limited as it is a rare condition about which there is only recent awareness, diagnosis, and treatment. Convenience sampling was expected to allow for a sufficiently strong overview and representation of the community of treating clinicians. The survey was designed to collect data related to HAE. Authors of articles, participants at HAE and Immunology conferences and physicians treating HAE were invited to participate in the voluntary survey. The latter were identified through online searches of allergology and immunology clinics or departments at hospitals. These treating physicians are highly trained and educated specialists who on a daily basis see patients with severe genetic conditions that often result in fatalities and a shorter life due to their conditions. The survey was designed to better understand the diagnostic and therapeutic decision-making process.

4.3.2 Survey process

Potential participants were sent an email with an invitation to follow a link if they would like to proceed with the survey. Clicking on the link, the participants were led to the survey participation sheet, following which they could provide their consent implicitly, by continuing to the survey itself and submitting the answers to the questionnaire. In order to obtain more and better-quality data, the survey was conducted anonymously, with no collection of personal or personally identifying data of either physicians or patients. Answers to the questions were entered into an anonymized online questionnaire and analyzed statistically.

4.3.3 Privacy considerations

This study was chosen to be anonymous for two reasons: first, physicians might be more inclined to answer honestly in how they make treatment decisions on their patients, and second, due to privacy laws, no patient data of any kind can be shared with anyone outside the physician's office. As the survey and its responses were anonymous, coercion was practically impossible. Participants were informed that there was no obligation of any kind to complete the survey, and that the data would be utilized purely for research purposes, with no commercial objective, and that results would only be published or shared in an aggregated way, in form of collective statements not referring to any individual. Since the thesis was related to patients with rare conditions, some physicians may have only referred to very few patients. With the double protection of anonymized data from both patients and the treating physicians, the patients were better protected. To preserve the privacy of the participants, all data were checked for any information that might help identify individuals. The researcher was careful to delete any data of this type.

4.3.4 Other aspects of the survey

While the survey was conducted across multiple countries with as many different languages, the language of the survey and all communications were in English. The presumption was that potential participants were fluent in English, as all relevant studies, literature and scientific/medical discussions identified for the condition are in English. This thesis and the survey did not aim to address issues of physician competency and sought to avoid the issue. It would have been difficult to ascertain with 100% confidence if an answer to a question is based on incompetence. Also, it might have been difficult for the researcher to challenge the answers. The participants are trained medical specialists in their field (selection criteria) and known to provide treatments in the therapeutic area studied. As the research is anonymous and there is no direct benefit, the thesis was built on the good faith and ethical standards of the participants including the researcher. Thanks to the high commitment of stakeholders, a participation rate of physicians treating close to 3,000 patients. Taking the prevalence of HAE of 1:40,000 (see section 3.8) from the scientific literature, this represents an overall hypothetical population of 108 million people. Lastly, the data were analyzed to help confirm (or confute) the findings from the other studies.
Ethics approval for the research was obtained under the number H19REA061 on April 18th, 2019.

4.4 Study 2 – Social media research

4.4.1 Sources and process

Due to stringent privacy rules and the confidentiality of the doctor-patient relationship, it is difficult to contact patients directly for surveys or interviews. Stakeholders who have direct access to patients, such as medical insurance groups and patient organizations, do not enable or facilitate direct contacts. This thesis aimed to incorporate the voice of the patients in its data pool to answer the RQs. The instrument of a social media search was deployed to confirm or disprove different perceptions, ranking, and relevance of the variables within the patient community.

Two platforms, Facebook and Twitter, were selected as they have a broad diffusion in the population, are used to share all kind of information, and are easily accessible and searchable through their own or widely available data mining tools. The search for posts and tweets mentioning the combination of keywords was repeated multiple times to obtain sufficient data volume and enable statistical analysis.

4.4.2 Privacy considerations

The collection of social media postings contemplated no intervention and no interaction with the posters. Only existing publicly posted information was collected. Implicit consent of the posters on Facebook and Twitter was presumed, as they agreed to the terms of conditions of the platforms: The Facebook privacy policy stated that “Public information can be seen by anyone, on or off our products, including if they don't have an account. The first statement of the Twitter privacy policy was that "Twitter is public and Tweets are immediately viewable and searchable by anyone around the world.” However, the thesis acknowledges that “just because the data is in the public domain, it does not mean it is automatically open to be used for research purposes”. For this reason, two layers of protection were introduced: (1) identifiers and posts were separated. Only the posts themselves were saved and used for the thesis (Identifiers such as names, nicknames, addresses, locations, were ignored). (2) Only aggregated data, no single posts, was presented in the thesis.

With these steps, the researcher sought to significantly reduce and possibly eliminate any risk to the posters, as only data already accessible to the general public was collected. No participant was engaged in any activity or was influenced in any direct way by the study or the data provided. To be sure, participants were not even actively participating as the data already existed in the public domain.

This part of the thesis on social media could be categorized as a non-interventional observational study, but it differs from other data collection methods used in this thesis in that participants were not selected by any criteria related to a potential vulnerability such as age, religion, or ethnicity. “Participants” on social media are not and cannot be selected, and the presumption is that postings were made only by people exposed to the condition, their caregivers or potentially physicians or any other person.

4.5 Study 3 – Meta-analysis

For the meta-analysis, a structured and systematic review of available sources was performed. Relevant databases for studies and reports such as *Medline*, *Embase*, *Cochrane Central Register of Controlled Trials*, *EconLit* were searched for keywords relevant to the thesis. Other sources such as articles, study reports and publications in general, which were gathered by the research and assessed to be relevant, were included as well. To strengthen the pool of sources, relevant citations and references were additionally followed to the original sources themselves. Preference for inclusion was given to the most recent sources. Few sources had to be filtered out as the vast majority was less than ten years old, and the topic of the thesis was relatively new. Sources included reports on CTs, observational studies, publications on specific cohorts (e.g. pediatric populations), specific settings (e.g. ERs) or aspects such as QoL and HE considerations.

4.6 Ethical Considerations

Ethical considerations came into play in a few areas of this thesis.

4.6.1 Survey with physicians treating HAE

The survey with the physicians was a simple online multiple-choice questionnaire (see section 4.3) which was completely voluntary. The objective was to better understand their interactions with patients including the diagnostic and therapeutic decision-making process. The survey was not expected to generate any form of distress to the participants. If an invited physician at any point decided to stop participation, he/she could simply close the browser with no consequence of any kind. Participants were also invited to contact the researcher and/or his supervisors should they have any question or concern or experience any distress arising from the thesis.

4.6.2 Study 2 – Social media research

To incorporate the voice of the patients in its data pool, this thesis searched for posts on Facebook and tweets on Twitter by HAE stakeholders to analyze the real-life application and the quantification of the variables and concepts inherent to HAE (see sections 4.1 and 4.2). The thesis uses data in the public domain but acknowledges that there could still be risks for the posters, which are mitigated as described above: anything that could potentially identify individuals or compromise their privacy was not collected or deleted, and only aggregated data was reported.

This thesis follows the guidance and recommendations by the Social Media Research Group which was established to ensure ethical social media research (Social Media Research Group, 2016), the British Psychological Society Ethics Guidelines for Internet-Mediated Research (British Psychological Society, 2017), the Australian National Statement on Ethical Conduct in Human Research (Australian Government, National Health and Medical Research Council, Australian Research Council, 2018) and the Swiss Ethics Code on research with human subjects (Swiss Academy of Sciences, 2015). The study on social media was non-interventional, retrospective and all data had been posted for the general public to see. Under this condition, the thesis followed the qualifying or waiving conditions when explicit consent is not appropriate or impracticable to be obtained, as described by the Australian National Statement.

4.6.3 Study 3 – Meta-analysis

For the literature search and especially the meta-analysis this thesis collected and analyzed the practice of EBM, by building on scientific research and clinical practice. Scientific research traditionally was mainly in-vitro and/or already subjected to the ethical guidelines and scrutiny of the institute or organization performing the research. As the focus is on rare diseases and orphan drugs, only fewer institutions conduct such studies given the high degree of specialization and a large amount of funding required (e.g. bio-therapeutics, monoclonal antibodies). Clinical practice, on the other side, is built on clinical trials which are performed for regulatory submission. The first priority for patient applications is to build advanced and high-cost healthcare systems (rare disease treatments require special

diagnostics, specialized physicians and cost in the hundreds of thousands of US dollars per year per patient. These trials conform to US FDA and EMA guidelines, which require the most stringent ethical standards and reviews by independent ethical committees.
No additional independent clinical studies were performed as part of this thesis. The research on real-world evidence and socio-economic considerations is by definition a retrospective study and analysis of patterns and behaviors in real life. As such, this key part of the thesis was not subject to ethical considerations as it studied phenomena that had already taken place independently and without influence by the researcher. Authors of articles, studies, and reports were contacted when clarification was required or when additional information or insight was solicited. The participants were exclusively academic physicians, department heads at hospitals performing research and treating patients or patients undergoing treatment. These contacts were in the form of discussions that were purely voluntary and based on goodwill.

4.6.4 Answering the RQs

The last phase of the thesis was concerned with addressing the RQs and combining the findings into a framework for analysis. The latter was built on information that was either describing real situations or developed as part of ethically conducted experiments (i.e. clinical studies) related to studies 1, 2 and 3 mentioned earlier.
However, it was expected that some of the derived conclusions reflected in the framework could be perceived as "unethical" by some stakeholders. For example, a framework built on current clinical data related to therapeutic decisions while common to socio-economic practices and ethical standards, might be perceived by a patient's caregiver as unfair. It was acknowledged by the researcher that if such perception gaps existed, they could be closed by education and communication. The funding of orphan drug research raises new ethical issues and dilemmas, for example, when questions on justice and the moral obligation of advancing medical science are considered (Gericke, 2005). These are intrinsic to the overall topic but not part of or impacted by this thesis.

5 CHAPTER FIVE - RESULTS

5.1 Study 1 – Results from a survey of physicians

5.1.1 Importance of different stakeholders for HAE treatment decision

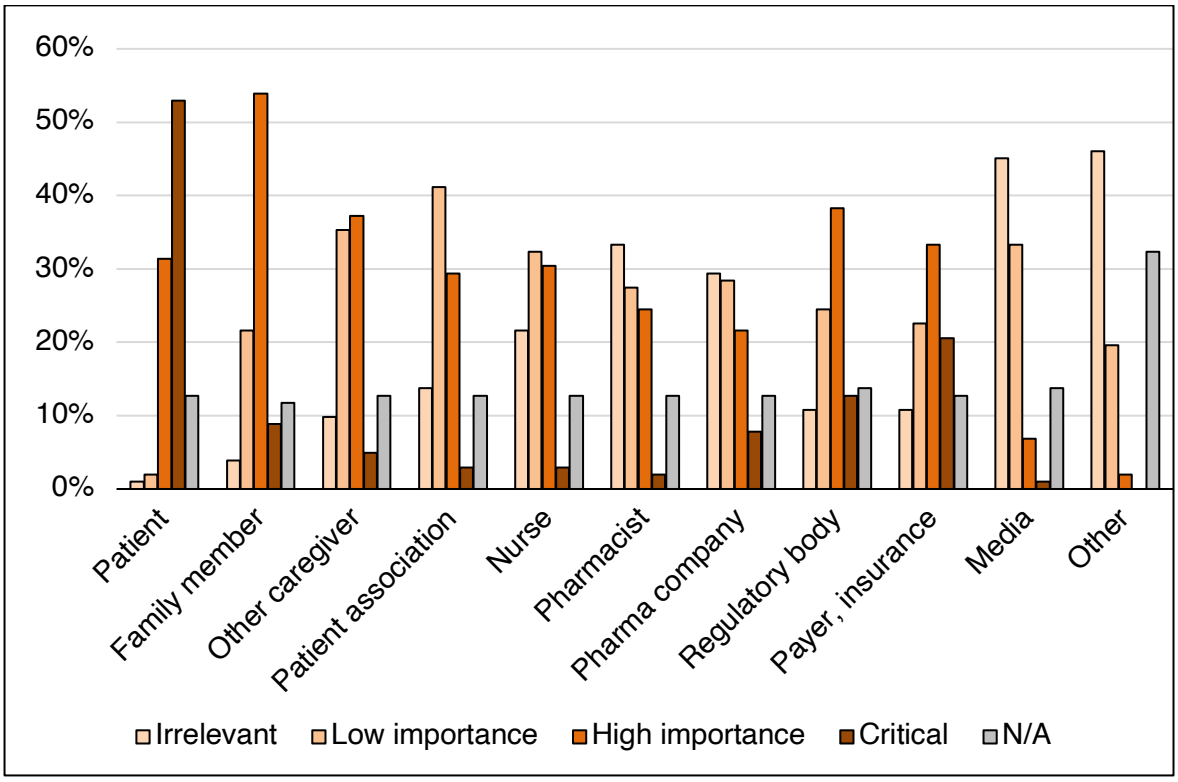

Figure 5.1.1- Percentage of HAE physicians rating the importance of stakeholders for treatment decision

The question highlights from the physicians' perspective that the patients are the most important stakeholders for 84% of doctors when deciding which treatment to pursue for treating the rare HAE condition, as illustrated in Figure 5.1.1. Combining "high importance" and "critical", the second most important stakeholders (64%) are family members according to participating physicians. While not critical, they are very important as family members are also affected as caregivers or indirectly by the condition of the patient. The second most mentioned critical stakeholders are the payers and the insurance companies (54%). About a third (32%) of physicians also estimate patient associations playing an important role, which could be an indicator of the success achieved with their advocacy efforts. Regulatory bodies are perceived as critical or very important by about half the physicians (51%), as they maintain that only drugs which provide value from an efficacy viewpoint - while offering an acceptable safety profile - are approved for commercialization. Pharma companies (29%) are seen as very important and critical for therapeutic decision making for mainly two reasons. At the forefront, they develop and make new drugs available, and provide and sponsor medical education through publications, events (such as congresses, symposia, scientific meetings, advisory boards) and medical calls.

5.1.2 Clinical aspects

5.1.2.1 HAE Patients in treatment

The 87 physicians who have completed the survey are treating in aggregate 2,952 patients which, utilizing a prevalence of 1:40'000 (see section 3.8), would correspond to an overall population of about 108 million people. This is a relatively significant figure when factoring in that diagnosis and treatment with modern therapies are mostly performed in advanced healthcare systems in North America, Europe and parts of Latin America and in countries with an advanced reimbursement system in place. The average number of patients per treating physician is 33 with a variance that spans from one patient to 150 in Germany, probably as that physician is associated with one of the few centers of excellence.

5.1.2.2 Diagnosed and misdiagnosed HAE patients

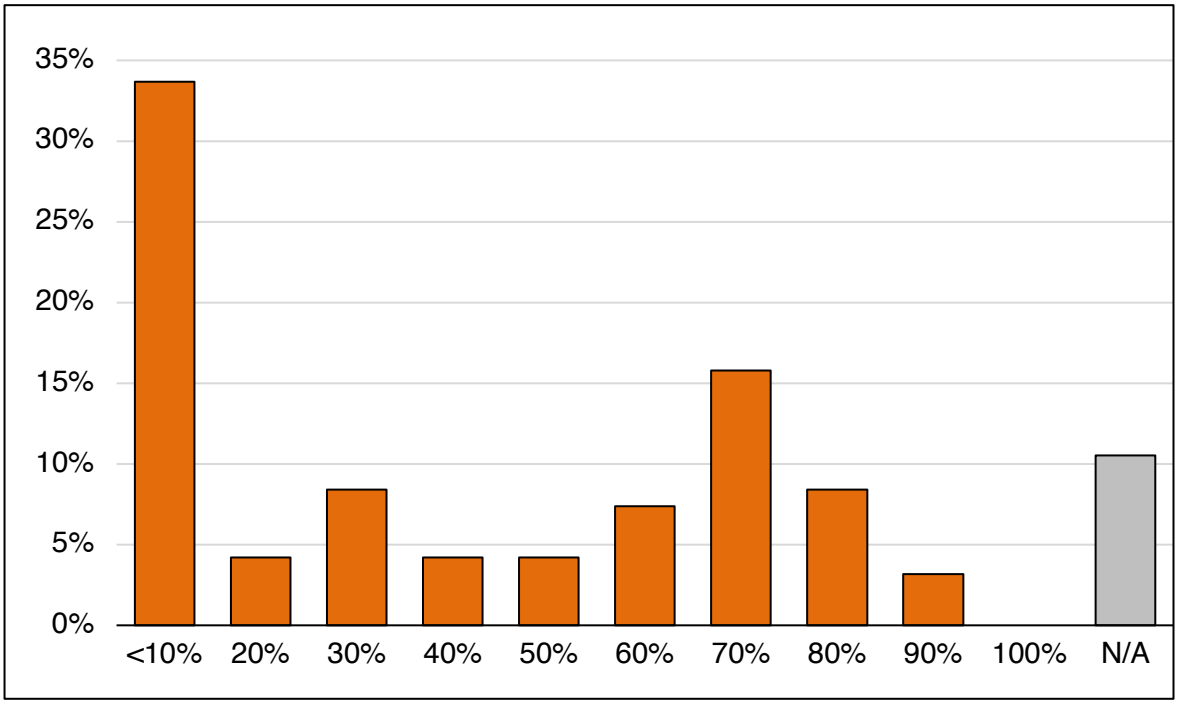

Figure 5.1.2- Percentage of physicians estimating the percentage of patients in their country has been diagnosed with HAE

Figure 5.1.2 illustrates that about a third of physicians estimate that less than 10% of patients have been diagnosed with HAE in their respective countries. A secondary concentration of another third of physicians estimates that between 60% and 80% of patients have been diagnosed with HAE.

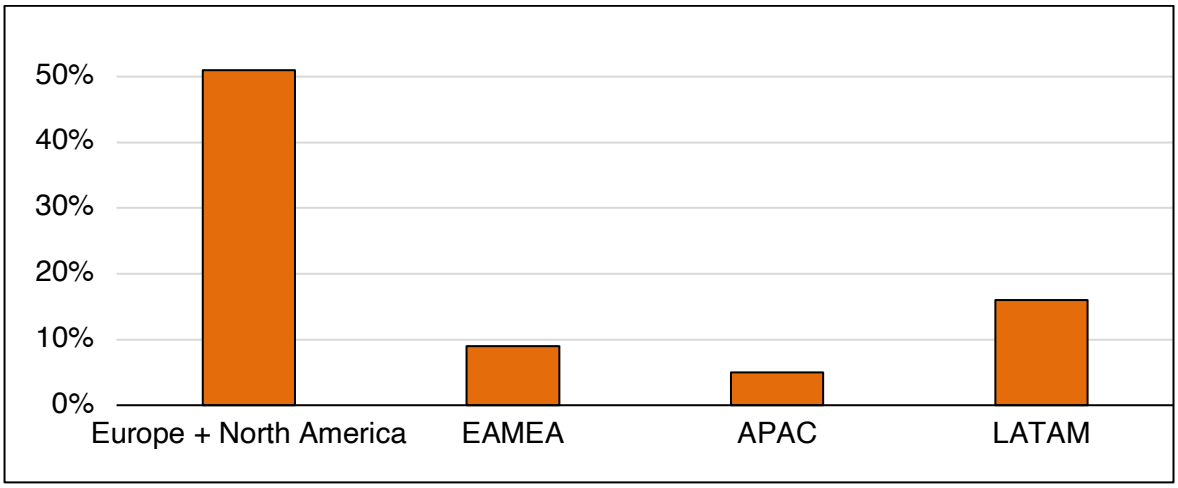

Figure 5.1.3 - Percentage of estimated patients diagnosed by region

Separating the answers to the question by the country of origin of the participating physicians, and grouping them by regions, Figure 5.1.3 illustrates the disparity across the world. More advanced healthcare systems in Europe and North America suggest a higher likelihood for patients born there to be diagnosed. It should be a source of concern that in the highly populous regions of the Asia Pacific and Eurasia, the Middle East and Africa, that only around 10% or fewer people living with a devastating condition such as HAE are diagnosed.

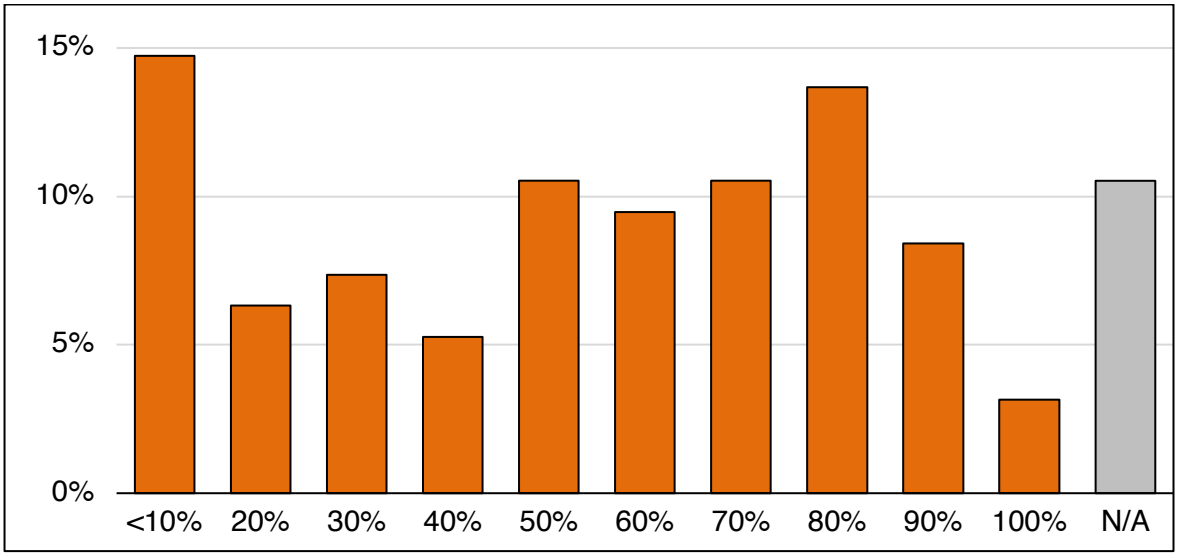

Figure 5.1.4 - Percentage of physicians estimating the percentage of patients in their country who have been misdiagnosed before

Participating physicians treating HAE distribute widely in their estimate of how many patients living with HAE have been misdiagnosed before receiving the correct diagnosis, as illustrated in Figure 5.1.4. The weighted average of 53% suggests about half the number of patients have been misdiagnosed.

5.1.2.3 HAE attacks per year for untreated patients

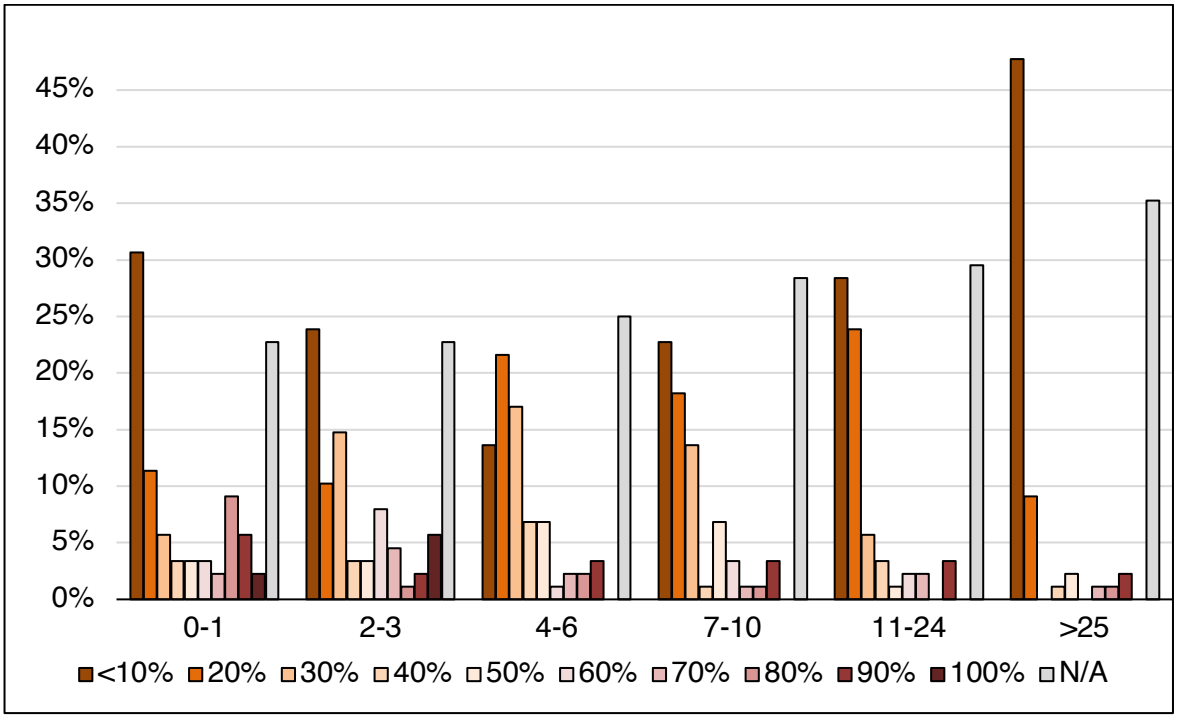

Figure 5.1.5 - Percentage of physicians estimating the percentage of untreated HAE patients who have so many attacks per year

A first observation indicates that about a quarter of physicians are unable to estimate how many HAE attacks for untreated patients occur each year. Figure 5.1.5 illustrates, however, an increasing trend with higher frequency numbers. The number is surprisingly high given that all participants are treating HAE patients.

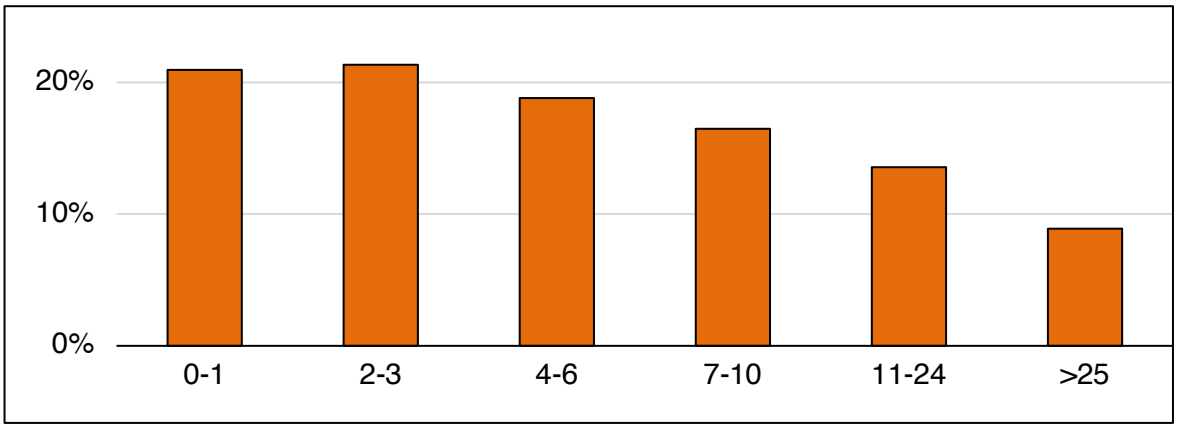

Figure 5.1.6 - Normalized percentage of untreated HAE patients who have so many attacks per year

Some participants provided estimates of patient percentages which do not add up to 100%. The percentages have been normalized and then weighted with the number of patients that each physician is self-reportedly treating, as illustrated in Figure 5.1.6. The increase of the share of patients in the higher intervals can be explained by the ranges being broader.

5.1.2.4 HAE attacks per year for treated patients

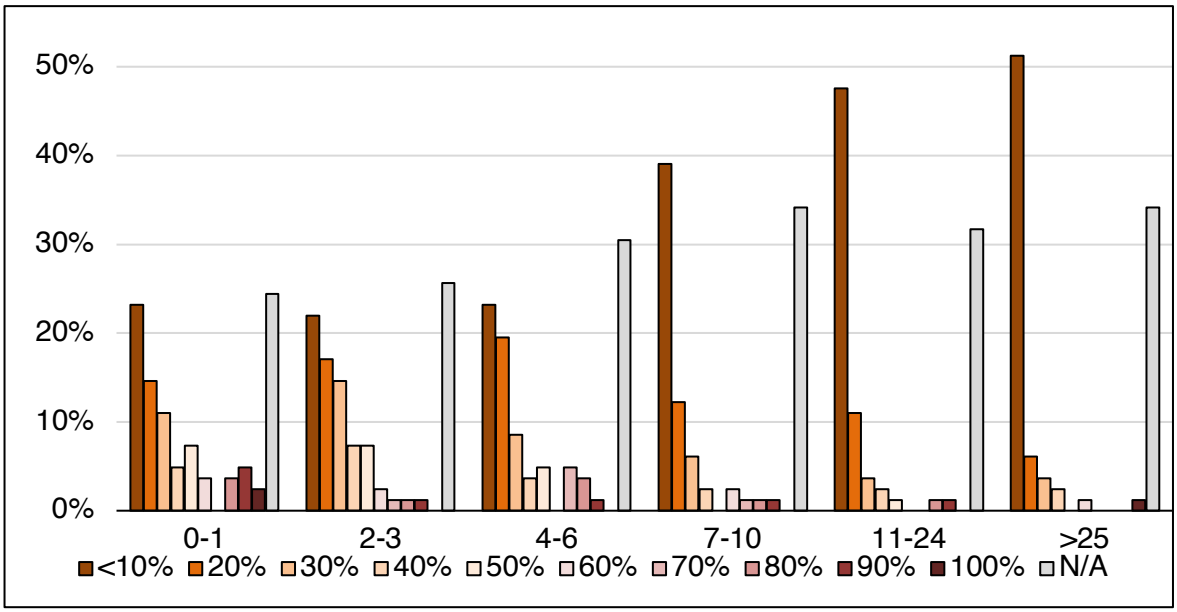

Figure 5.1.7 - Percentage of physicians estimating the percentage of treated HAE patients who have so many attacks per year

Figure 5.1.7. illustrates that for treated patients about a quarter of physicians was not able or willing to provide the number of attacks per year. Quite possibly, although participants agreed to the ethical strategies for this thesis, patient confidentiality may be the key reason for patient non-disclosure. These results, at first sight, appear to show a similar dispersion as in the previous section 5.1.2.3.

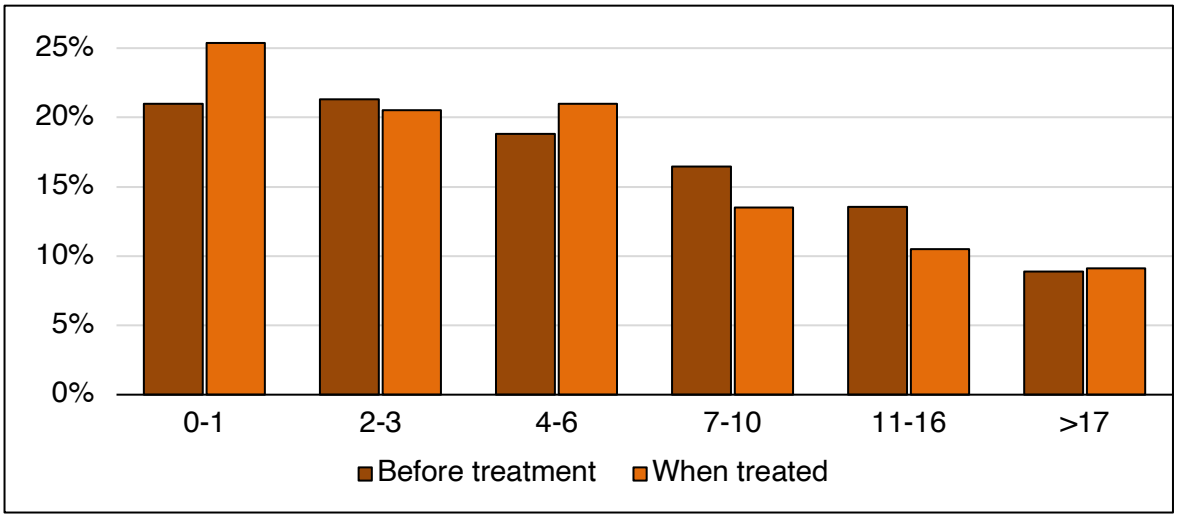

Figure 5.1.8 - Comparison of normalized percentage of HAE patients who have so many attacks per year between untreated and treated patients

Normalizing the data as shown in Figure 5.1.8 seems to suggest that the distribution of attacks among treated patients changes significantly. The share of patients with higher attack rates per year (more than 7) falls significantly, apparently generating a new peak at about 4-6 attacks per year and another new maximum at 0.1 attacks per year.

5.1.2.5 Criteria for selection of HAE treatment

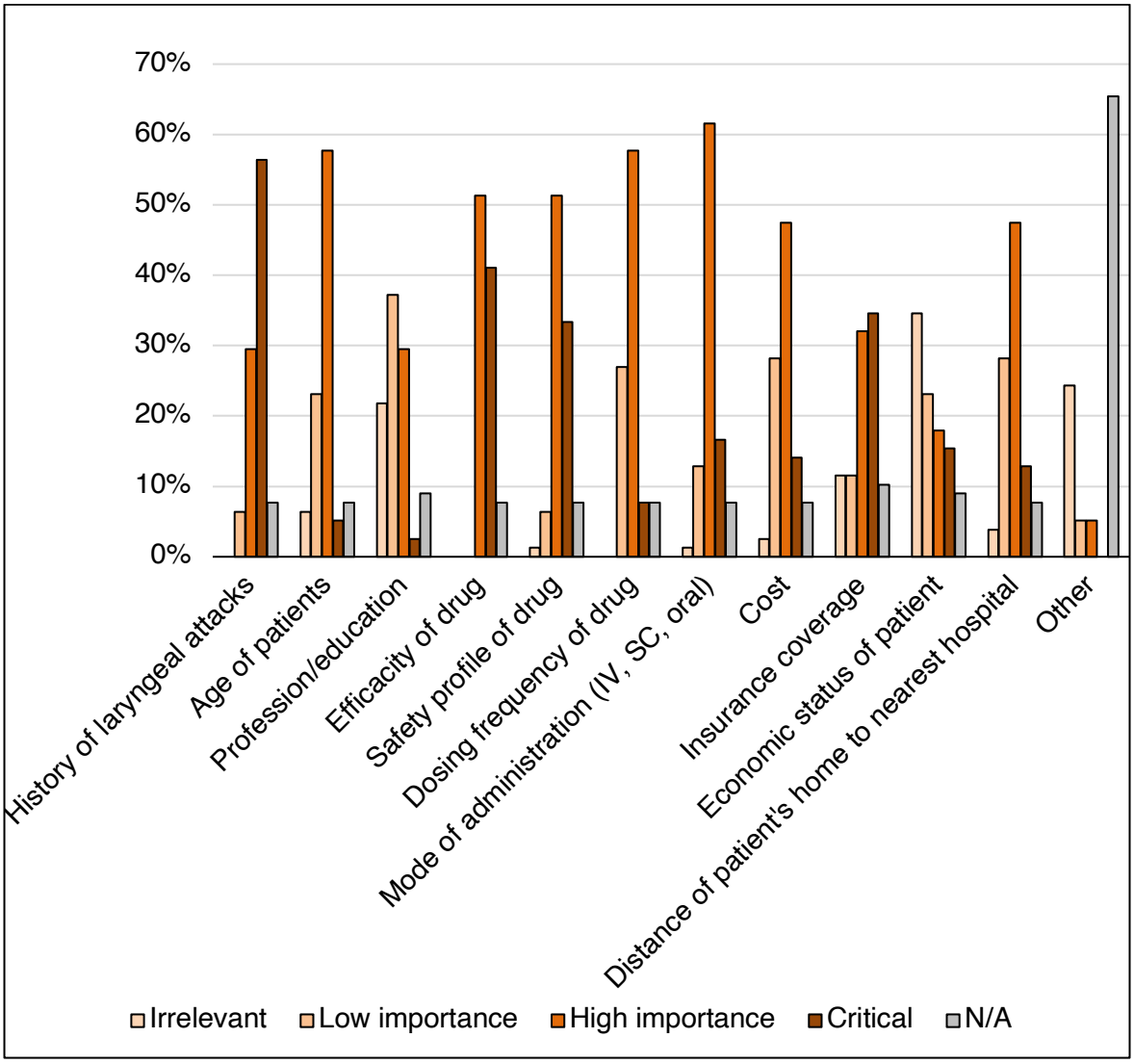

Figure 5.1.9 - Percentage of HAE physicians rating the importance of criteria for selection of the treatment

The most important criteria for physicians selecting a treatment for their HAE patients is the previous history of laryngeal attacks (56%), assessed as critical or highly important by 86% of physicians, as presented in Figure 5.1.9, The following two most important criteria are the efficacy of the drug (41%) and the safety profile of the drug (33%), assessed as critical or highly important by 92% and 84% of physicians respectively. Treatment costs are mentioned to be critical or highly important for the treatment decision by 62% of the physicians, consistent with the level of insurance coverage which is considered critical or highly important by 67% of the physicians. Combined, the treating physicians have to justify the necessity for a patient to be prescribed more expensive modern prophylaxis treatment, confirming the insurance will reimburse it, when possibly on-demand therapy might lead to only marginal inferior clinical outcomes or QoL.

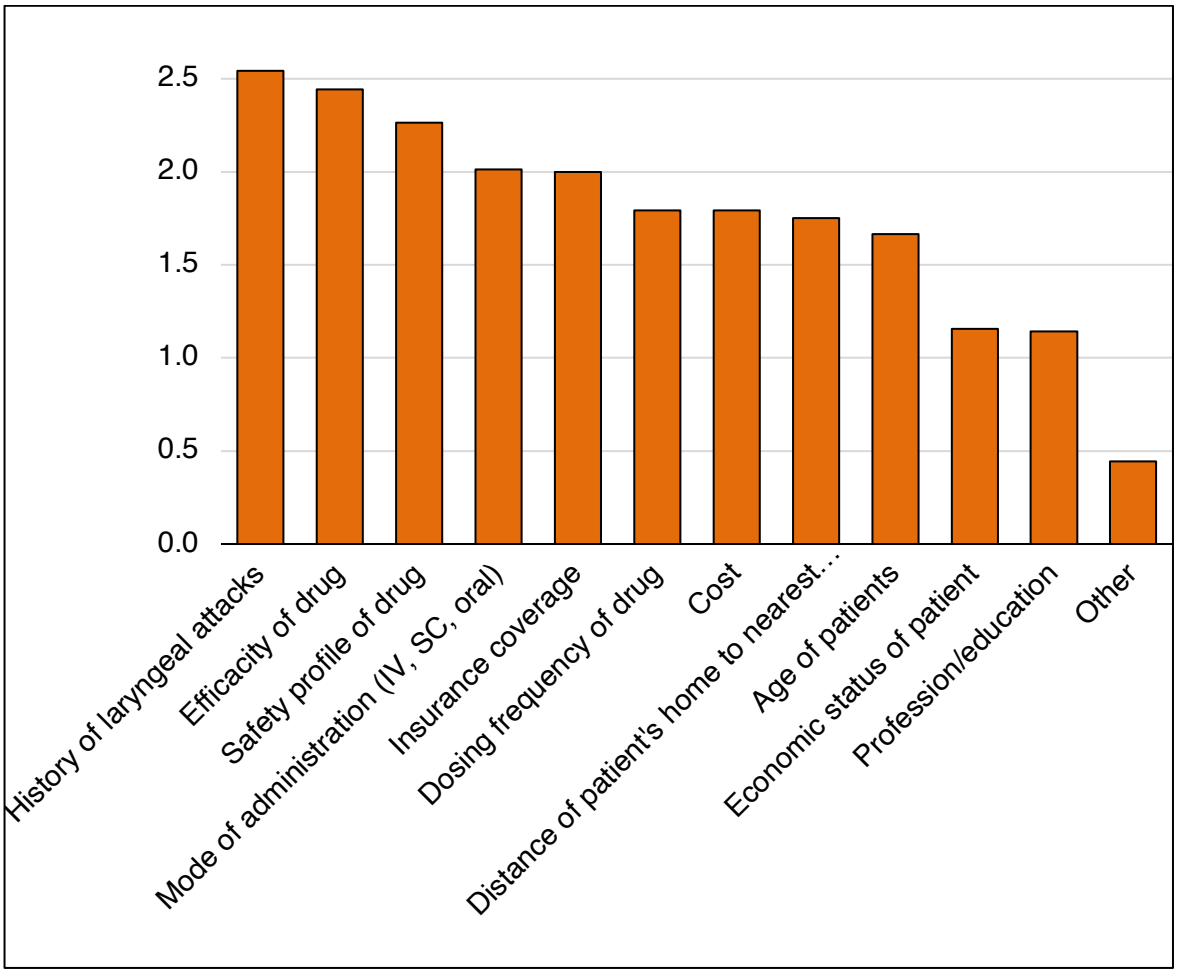

Figure 5.1.10 - Distribution of weighted averages of importance of selection criteria ("irrelevant" = 0, "low importance" = 1, "high importance" = 2, "critical" = 4

The mode of administration and dosing frequency are assessed to be critical or highly important by 73% and 65% of the physicians respectively. The survey shows that one-third of the physicians assess the economic status of the patient to be irrelevant when deciding the treatment, indicating the degree of pervasiveness of universal health coverage (see Section 0) and the functioning of reimbursement systems for patients in need. However, another third of physicians see the economic status of the patients as critical or highly important when selecting the therapy, suggesting that work still needs to be done in those healthcare systems where not everybody qualifies for some form of reimbursement. Figure 5.1.10 illustrates ranking and relative importance of the different selection criteria based on the weighted averages of the variable. In the comment section, some physicians mentioned that in some healthcare systems not having access to some medications forces the patients to follow the treatments that are available, and not the ones they would choose if they had the opportunity to do so. One participant mentioned the approach in his center is to first achieve control with androgens, and then to reduce the dosing of the drug down to a few minor breakthrough attacks (no hospital visits necessary), suggesting a more HE-driven protocol.

5.1.2.6 Medications prescribed for HAE on-demand treatment

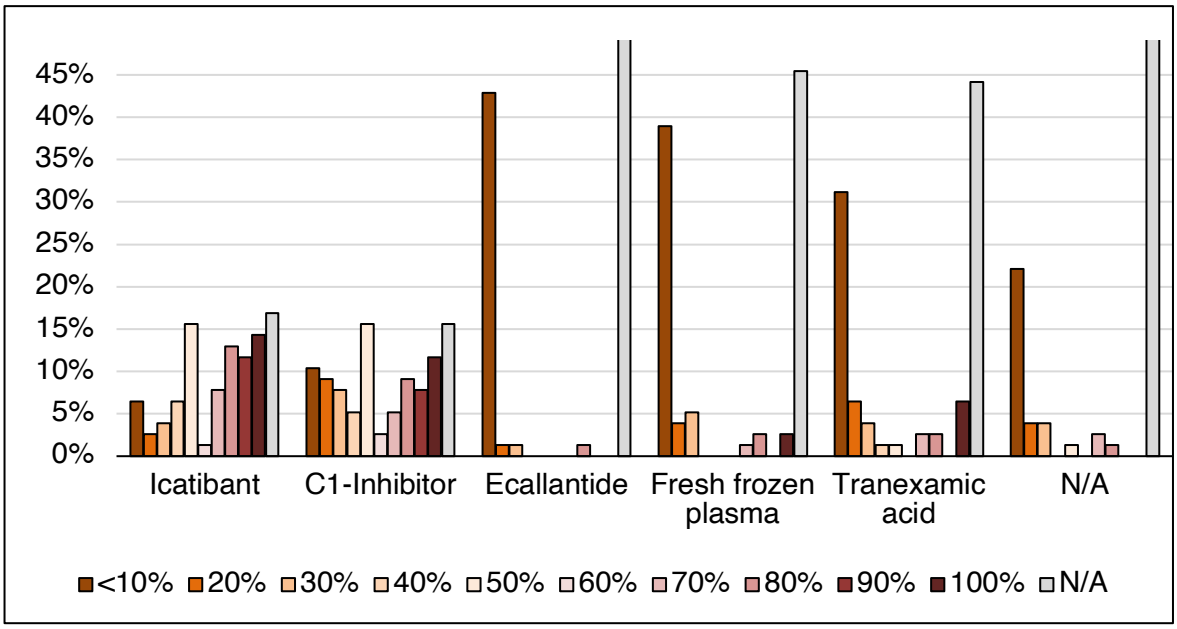

Figure 5.1.11 - Percentage of physicians prescribing HAE drug for on-demand treatment

Figure 5.1.11 suggests that overall there is a wide distribution of percentages in relation to demand treatments, indicating a diversity of physicians' attitudes towards prescribing these types of drugs.

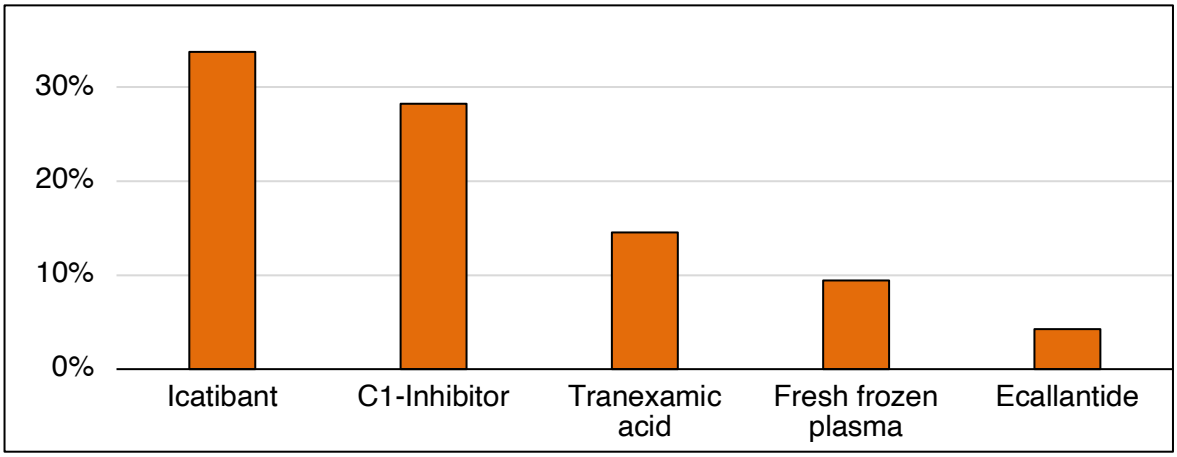

Figure 5.1.12 - Weighted percentage of HAE patients being prescribed different on-demand treatments

Figure 5.1.12 illustrates that Icatibant and C1-inhibitors are the most prescribed on-demand therapies. 40% of physicians prescribe on-demand therapy to less than a third of their patients.

5.1.2.7 Medications prescribed for HAE prophylaxis treatment

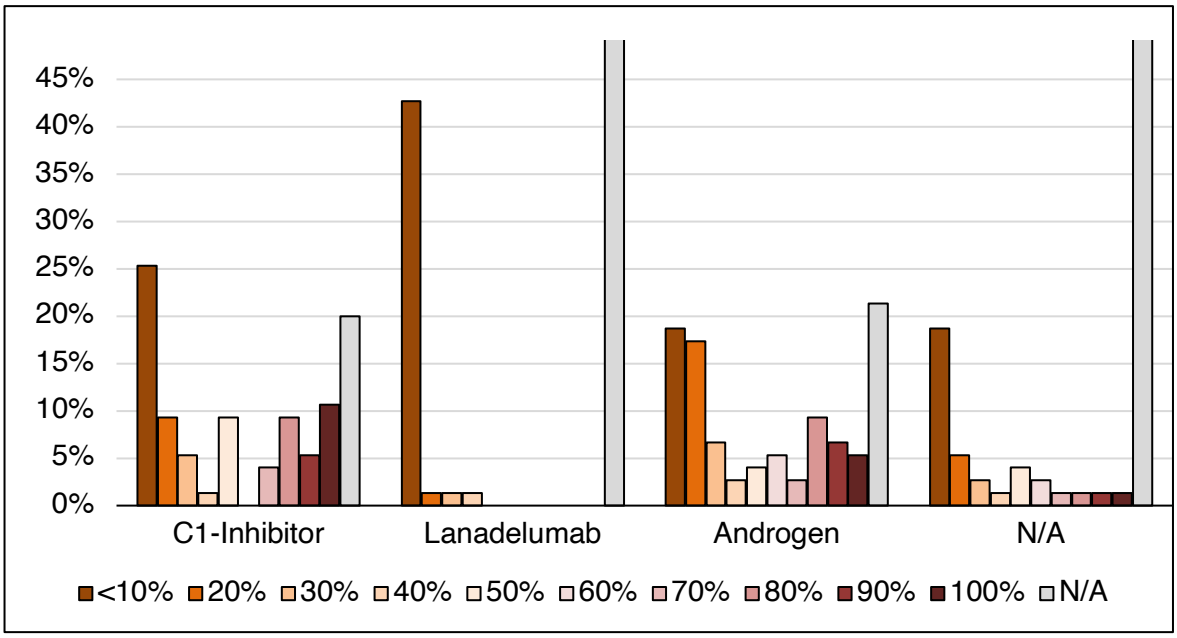

Figure 5.1.13 - Percentage of physicians prescribing HAE drugs for prophylaxis treatment

C1-inhibitors appear to be the most prescribed prophylaxis treatment (36% of patients) followed directly by androgens (35%). Lanadelumab (Takhzyro®) was prescribed to 6% of patients, as illustrated in Figure 5.1.13.

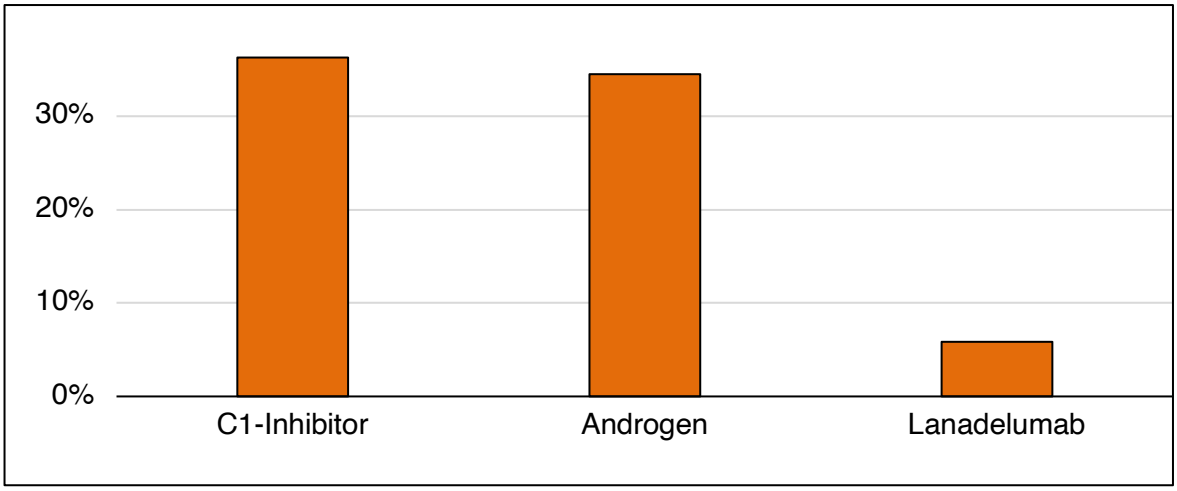

Figure 5.1.14 - Weighted percentage of patients being prescribed different prophylaxis treatments for HAE

The distribution of prescribed treatments illustrated in Figure 5.1.14 is expected to change as the latter has just recently been launched into the markets.

5.1.2.8 HAE Patients switching medication over a lifetime

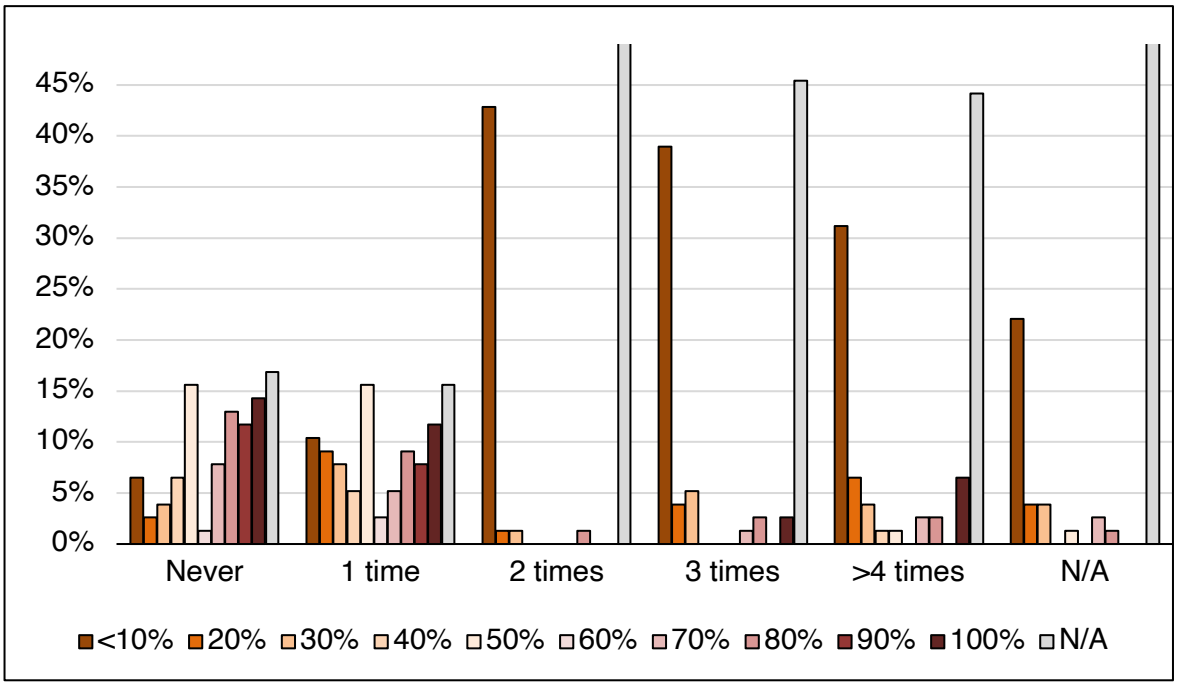

Figure 5.1.15 - Percentage of physicians estimating the number of times HAE patients switch treatment over a lifetime

Two key results become visible from Figure 5.1.15: treating physicians see the vast majority of patients not changing medication more than once during their life, and about half of the patients never changing the treatment (weighted average 54%) with the other half only once.

5.1.2.9 Reasons for HAE patients switching medication

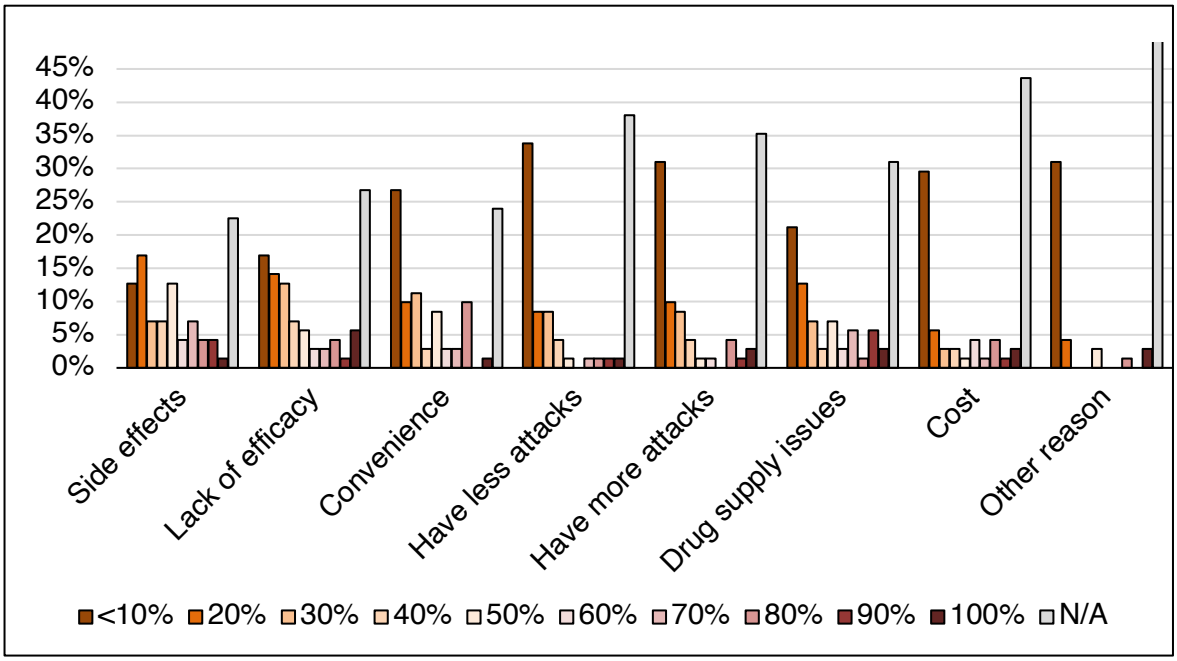

Figure 5.1.16 - Percentage of physicians estimating the percentage of HAE patients switching for a specific reason

Figure 5.1.16 illustrates a wide dispersion of shares of physicians estimating the shares of patients who switch HAE medication for different reasons. When calculating the weighted percentage of patients switching medications as illustrated in Figure 5.1.17, the most frequent reasons relate to the side effects, for about 17% of patients. The second most frequently mentioned reason for a switch is the lack of efficacy (15%) which could also be the rationale for moving from older therapies to modern ones, for both on-demand and prophylaxis treatment. Using costs as a reason to switch medications relates to about 12% of patients according to physicians.

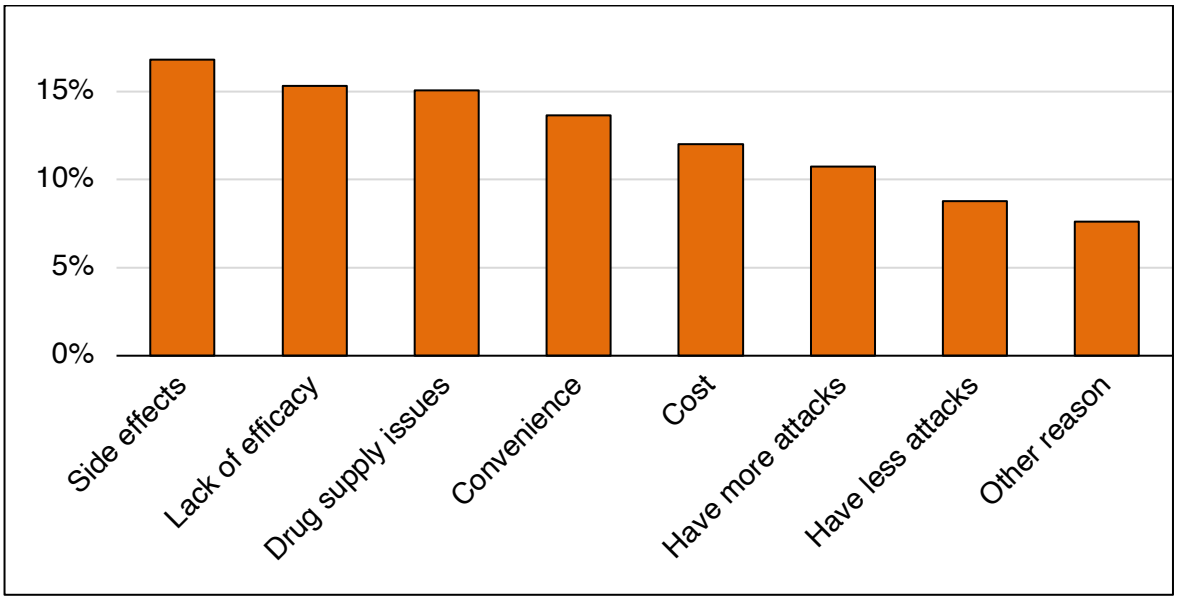

Figure 5.1.17 - Weighted percentage of HAE patients switching treatment for a specific reason

5.1.2.10 Number of HAE attacks considered "acceptable stable condition"

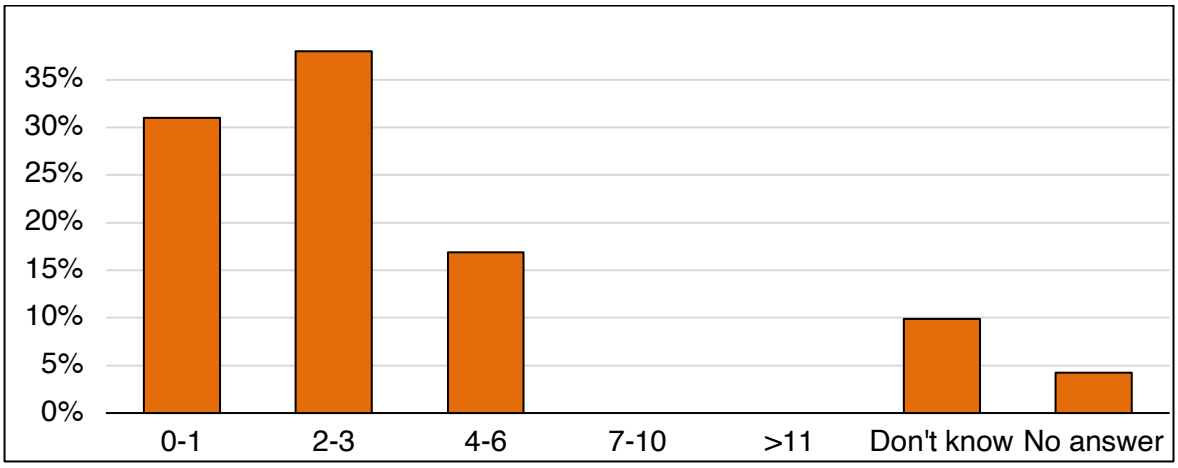

Figure 5.1.18 - Percentage of HAE physicians how many attacks per year is still an "acceptable condition"

Figure 5.1.18 illustrates that the vast majority of physicians (69%) believe an HAE patient needs to have less than three attacks per year to be considered in control, and virtually all physicians believe it should be less than one attack every two months.

5.1.2.11 Observed, treated and referred co-morbidities to HAE

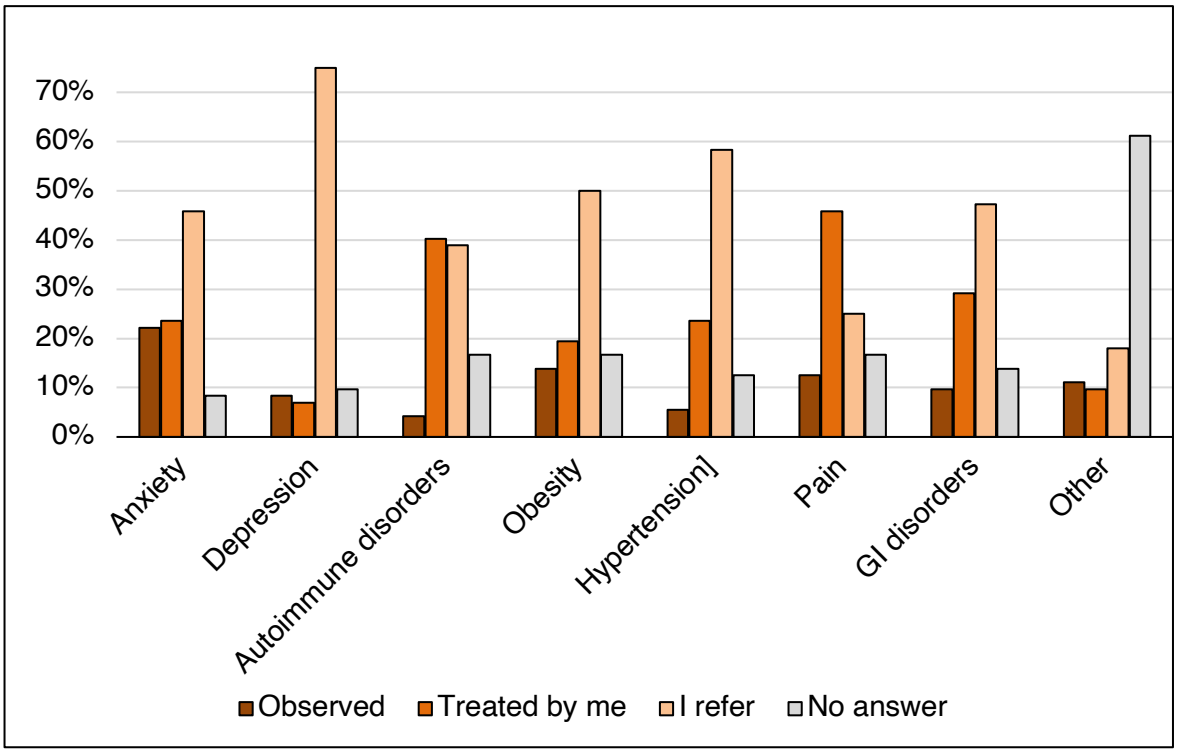

Figure 5.1.19 - Percentage of physicians observing, treating or referring co-morbidities to HAE

The co-morbidity most observed by the participating physicians is anxiety which occurs about 22% of the time, illustrated in Figure 5.1.19. Depression seems to be observed by only 8% of treating physicians, the participating physicians refer the patients to other specialists in 75% of the cases with depression and 46% of the cases with anxiety, indicating that additional specialized medical help is warranted. 40% per cent of physicians treat observed additional autoimmune disorders themselves, in line with the fact that the vast majority of physicians treating HAE are immunologists and allergists. For the pain indication, the share is 46% suggesting that this is standard practice.

5.1.2.12 Patients requiring help during HAE attacks or for treatment

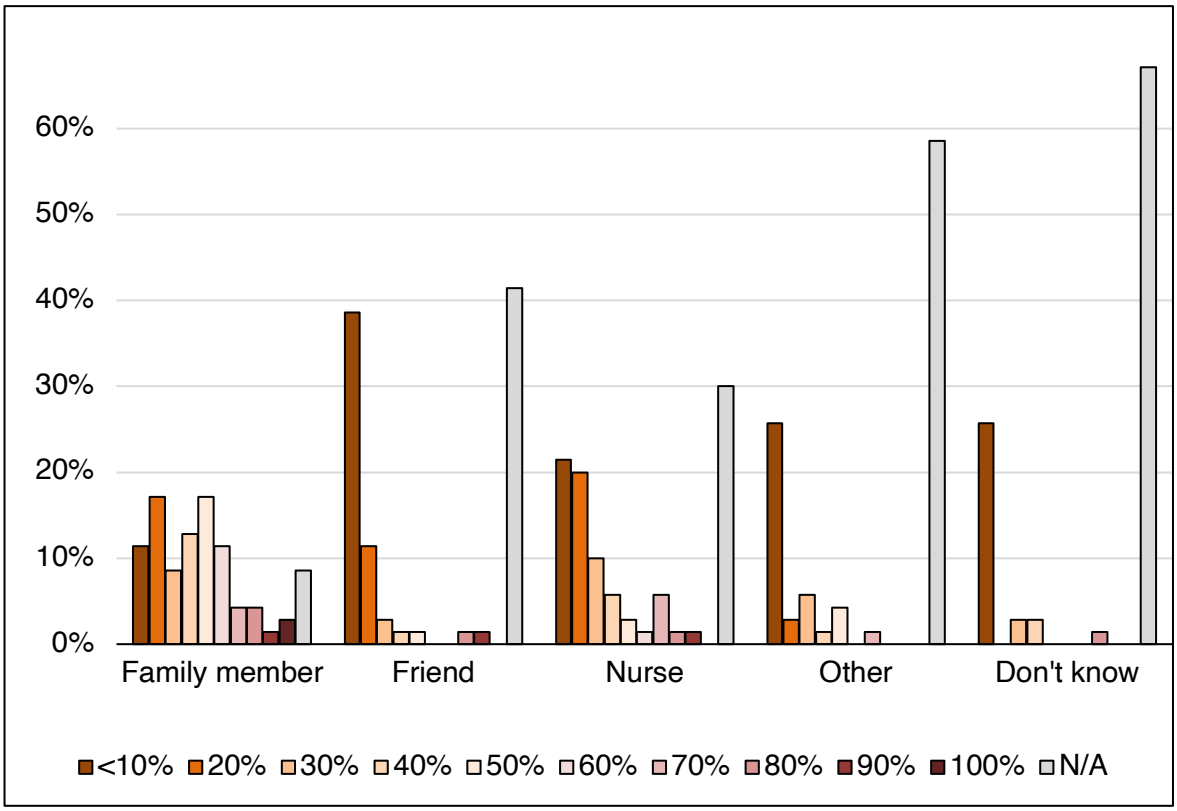

Figure 5.1.20 - Percentage of physicians estimating the percentage of HAE patients requiring help during attacks or for treatment

Figure 5.1.20 illustrates that a weighted average of 38% of patients is observed to require help from family members when having an attack or when administering treatment. Friends or nurses are reportedly providing help for patients in 11% and 20% of the time. The survey also illustrates that on average 41% of treating physicians don't know if their patients are requiring support.

5.1.2.13 Most important desired outcome of HAE treatment

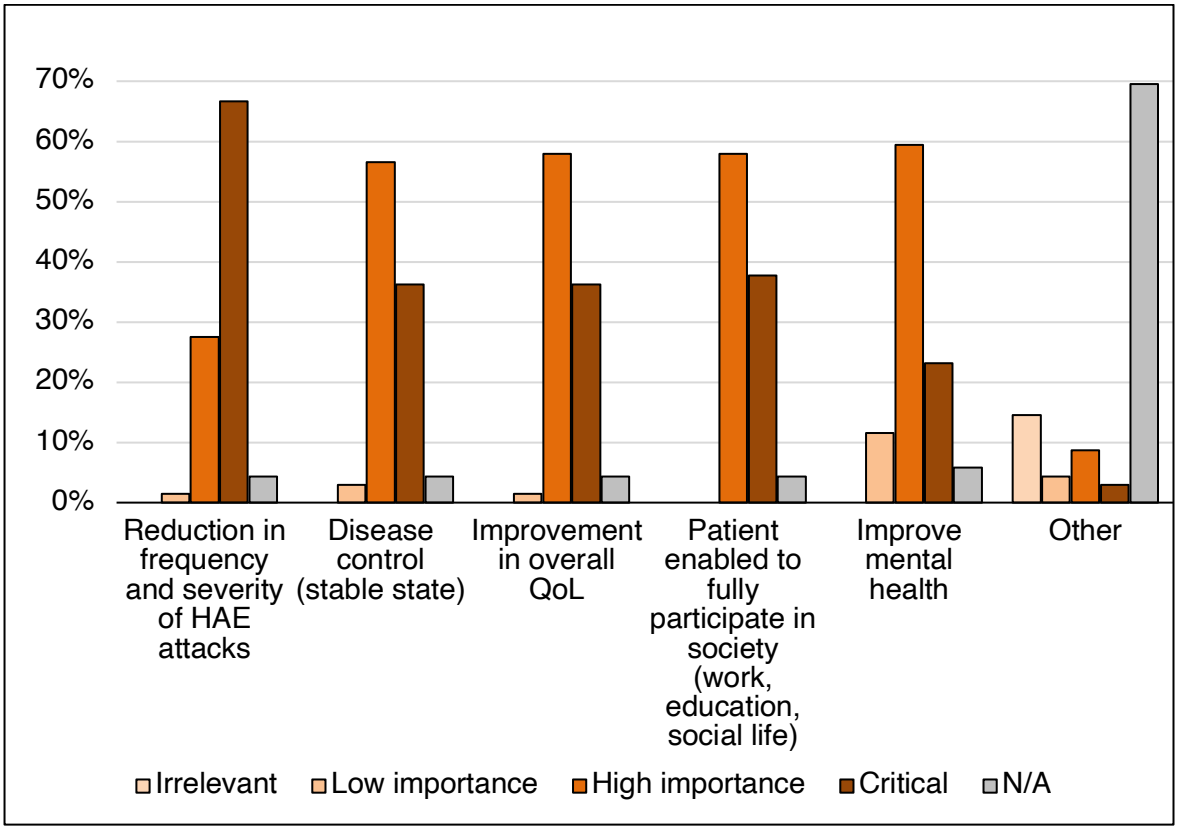

Figure 5.1.21 - Percentage of HAE physicians rating the importance of desired treatment outcomes

Two-thirds of physicians deem a reduction in frequency and severity of HAE attacks as critical, and virtually all of the physicians (94%) see this as a critical or highly important and most desired outcome. The data presented in figure 5.1. 21 also illustrates that achieving control over the condition, improving QoL and enabling patients to conduct a normal life are assessed to be critical for about a third of the physicians in about equal proportion. These are factors that are critical or highly important for over 90% of participants suggesting that modern medicine has moved beyond the narrow scope of clinical outcomes to encompass the holistic view of patients' QoL and roles in society. The low number of "other" desired outcomes indicates that the four main factors provide the key criteria for the importance of desired treatment outcomes. In the comment section a few participating physicians noted the challenge in answering some of the questions due to the high variability and unpredictability of the disease even among members of the same family.

5.1.3 QoL aspects

5.1.3.1 Days of work, school, commitments missed per year by HAE patients before diagnosis

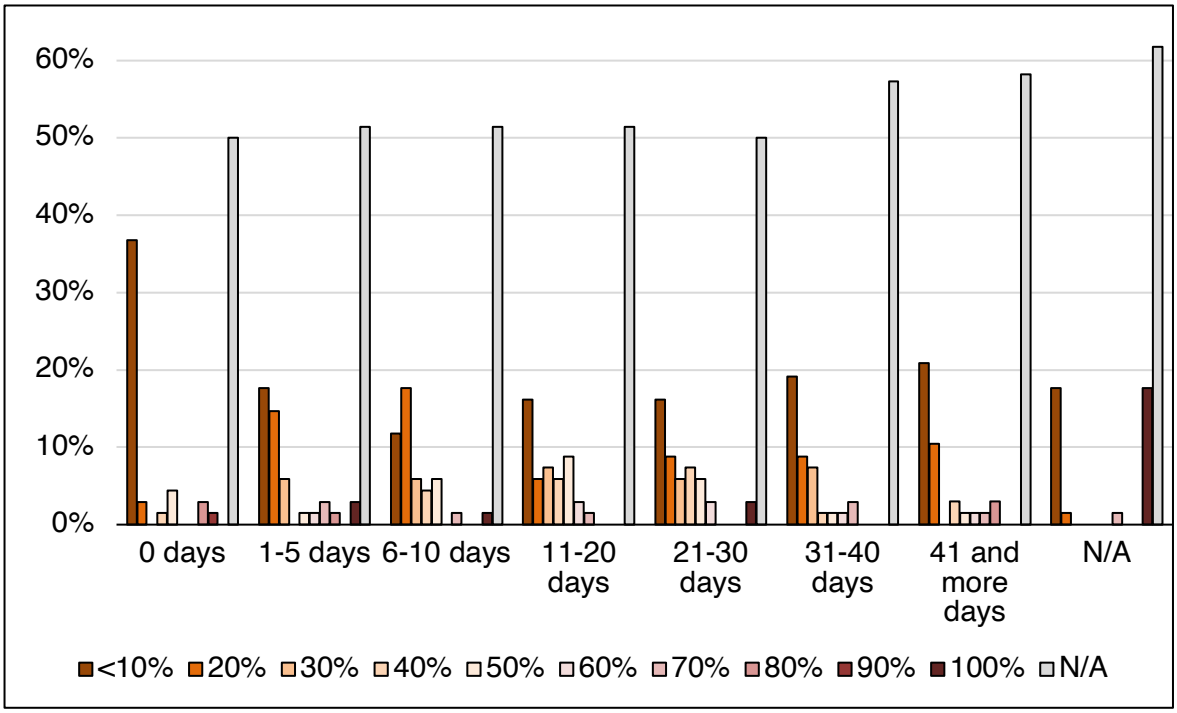

Figure 5.1.22 - Percentage of physicians estimating percentage of HAE patients missing number of days of work, school, commitments per year before diagnosis

The first observation to be made is that for all possible answers illustrated in Figure 5.1.22, half or more of the participating physicians responded that they didn't know how many days their patients were missing from work or school. This would indicate that less than half of the physicians know or can estimate roughly how many times people with HAE were untreated, were missing professionally, educationally and socially. This suggests that the contextual aspect related to patients' economic, social, emotional and other professional needs are simply not known. The strongest statement is that 38% of physicians estimated that only 10% of patients without treatment can survive a whole year without missing treatment days. Figure 5.1.23 illustrates that the estimates for all other number of days missed were spread relatively equally at around 12% of patients. In summary it could be confirmed that the repercussions of HAE are highly variable, while significant QoL aspects of untreated (and likely undiagnosed) patients are still unknown.

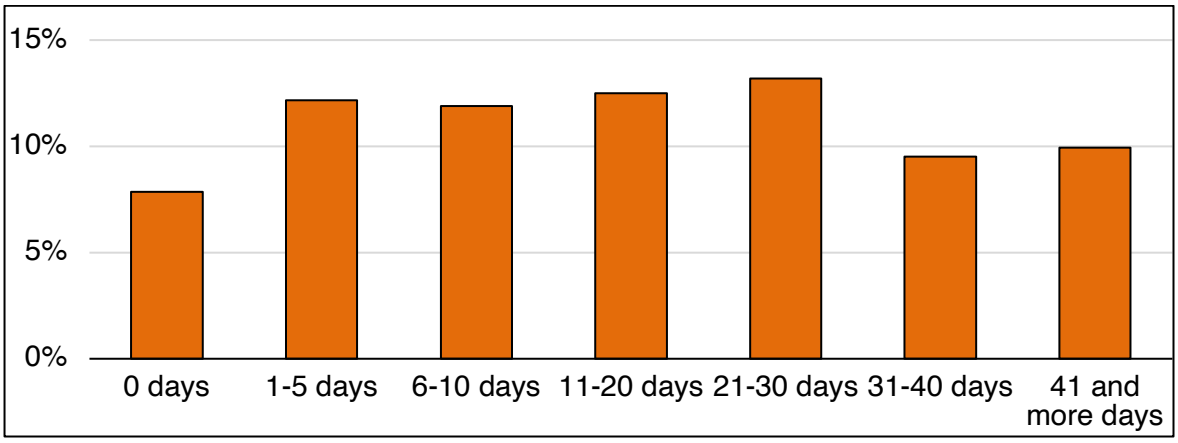

Figure 5.1.23 - Weighted distribution of percentage of HAE patients missing number of days of work, school, commitments per year before diagnosis

5.1.3.2 Days of work, school, commitments missed per year by HAE patients when treated

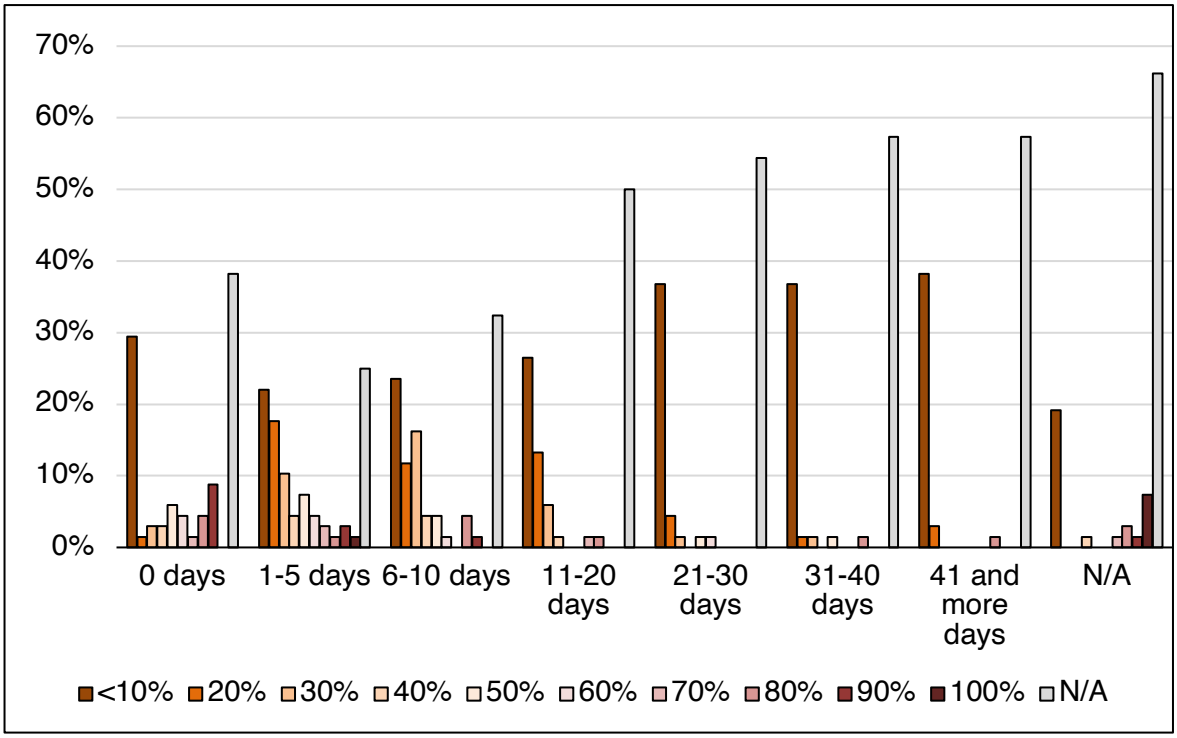

Figure 5.1.24 - Percentage of physicians estimating percentage of HAE patients missing number of days of work, school, commitments per year when treated

Participating physicians have been asked to estimate what percentage of treated HAE patients is missing how many days of work, school or other commitments per year. The purpose was to be able to compare if treated patients are able to conduct a more normal life, missing out less than the ones without treatment studied in section 5.1.3.1). Comparing with Figure 5.1.22, Figure 5.1.24 illustrates that the number of "don't know" (grey bar "N/A") is lower for numbers of days passed less than 21. However, when asked how many patients are missing 21 or more days per year, more than 50% of physicians are unable to answer.

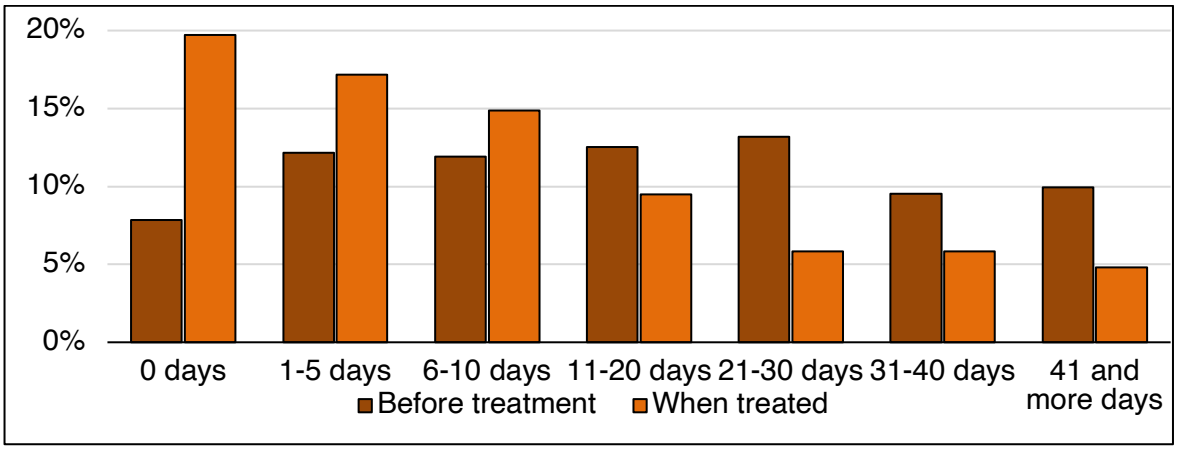

Figure 5.1.25 - Comparison of weighted distribution of percentage of HAE patients missing number of days of work, school, commitments per year before treatment vs. when treated

Comparing directly the numbers before and with treatment, as illustrated in Figure 5.1.25, the share of patients who do not miss any days any more thanks to HAE doubles from about 8% to 20%. Proportionally less but still strong positive impact is observed also for the ranges 1-5 days and 6-10 days.

5.1.3.3 Long term consequences from HAE

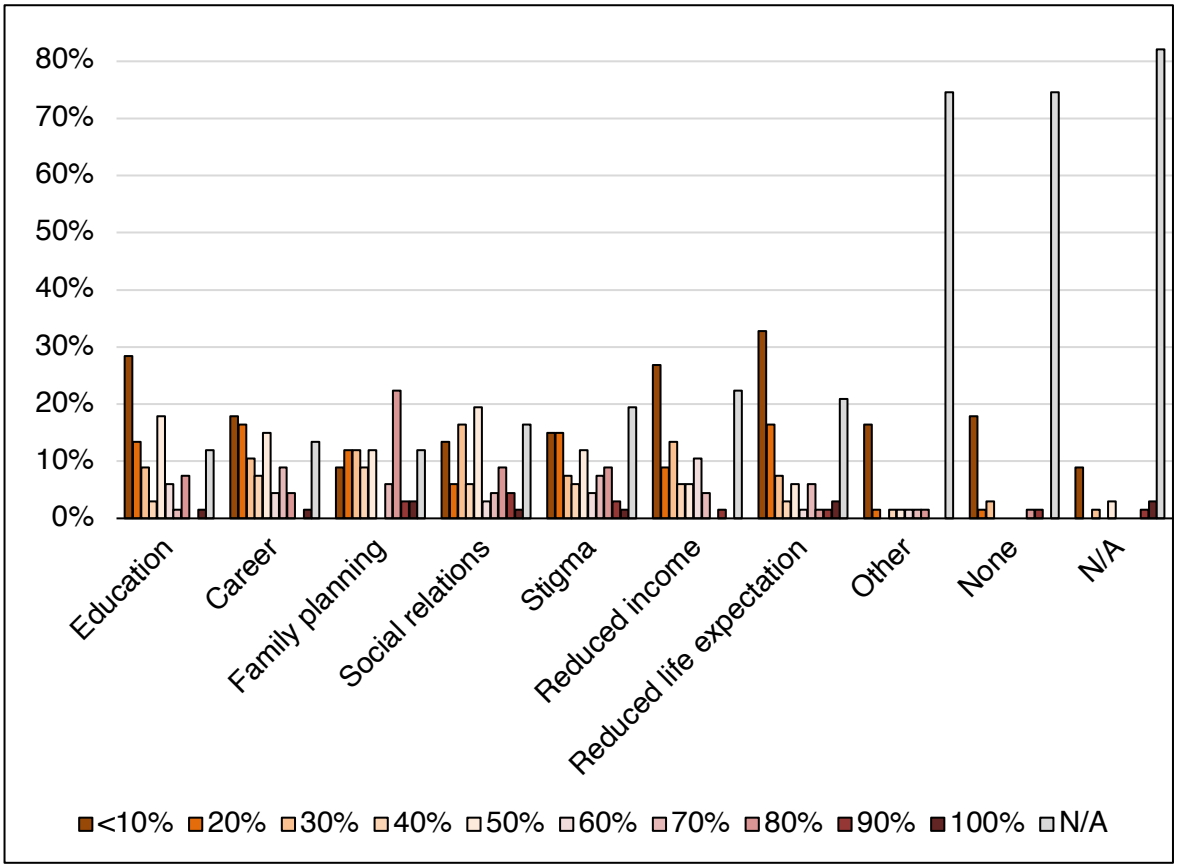

Figure 5.1.26 - Percentage of physicians estimating the percentage of patients suffering from specific long-term consequences due to HAE

The long-term consequences of HAE in Figure 5.1.26 are spread among answers displaying the high variability of the condition, its consequences and possibly the physician's knowledge of the full long-term implications to the patients.

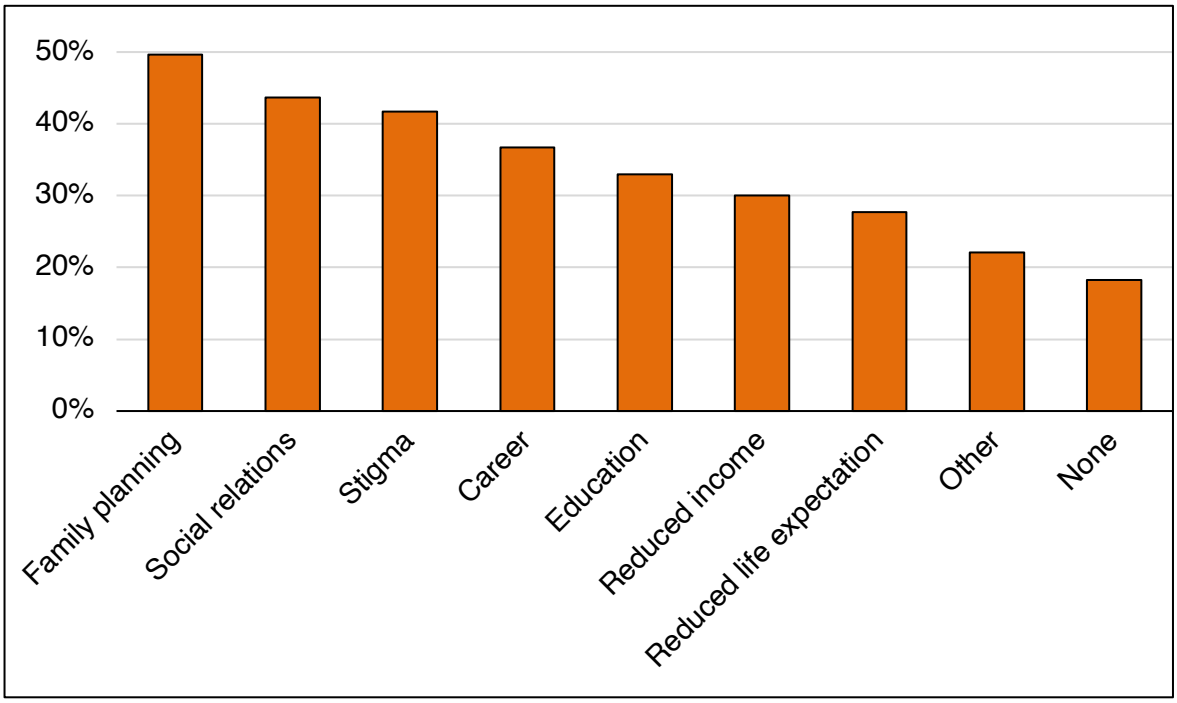

Figure 5.1.27 - Weighted percentage of patients facing long term consequences due to HAE

The impact on family planning is the one with the highest weighted average as illustrated in Figure 5.1.27, impacting 50% of the patients. This could be explained by the hereditary nature of the condition. The next four most frequently estimated long-term impacts are on social relations (44% of patients), stigma (42% weighted average), career repercussion (37%) and education hindrance (33%). Reduced income and reduced life expectancy are estimated to still impact about 30% and 28% of patients respectively.

5.1.3.4 Working status of HAE patients

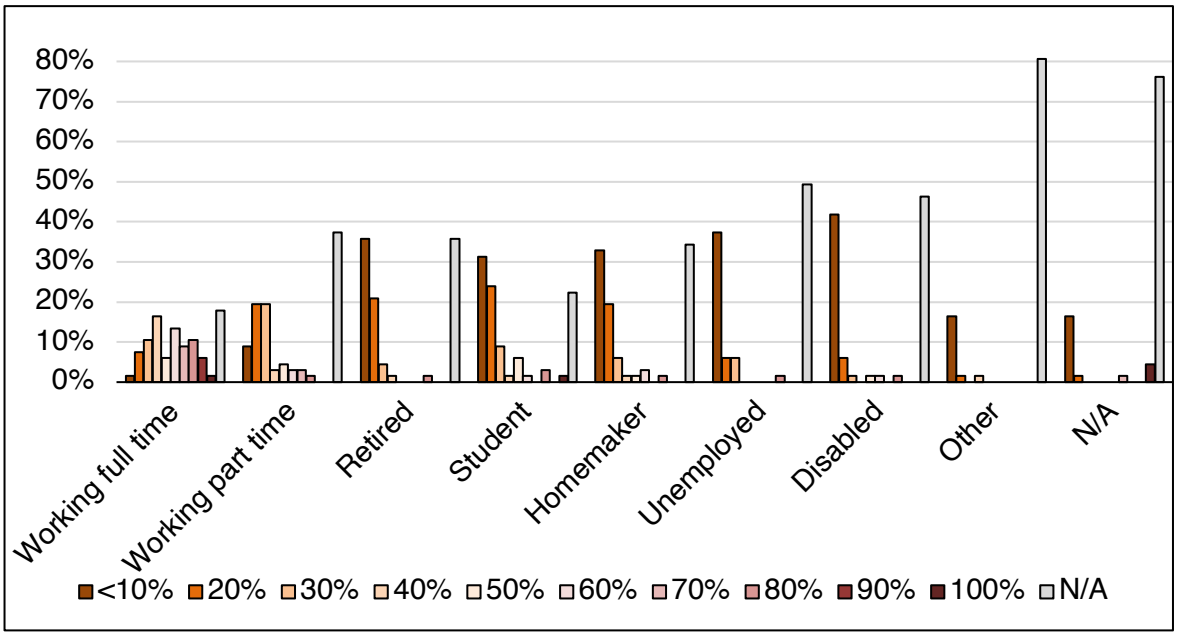

Figure 5.1.28 - Percentage of physicians estimating the percentage of HAE patients in different states of working status

In average across the questions, 40% of physicians answered that they do not know the working status of their patients, as illustrated in Figure 5.1.28. Particularly in the sub-questions on unemployment status or disability, almost half the physicians indicated they didn't know the status of their patients.

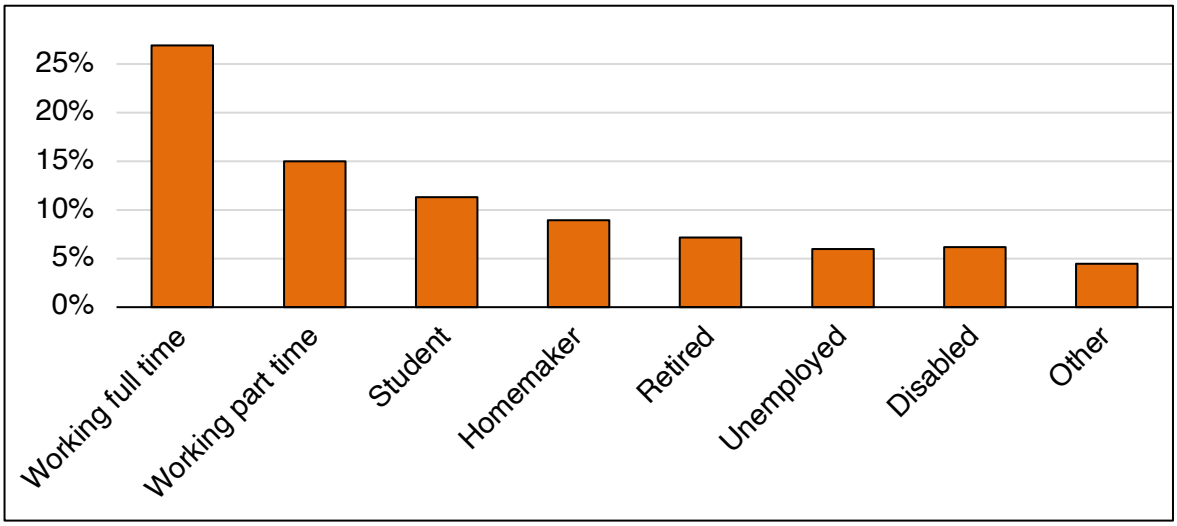

Figure 5.1.29 - Weighted percentage of HAE patients in different states of working status

The most frequent working status of patients is full time working with a weighted average of 27% of patients, illustrated in Figure 5.1.29. They are followed with part-time working patients and students comprising about 15% and 11%. Homemakers are 9% and retired patients about 7%. The share of unemployed and disabled patients is about 6% each of the patients consulting the participating physicians because of HAE:

5.2 Economic aspects

5.2.1.1 Financial impact of HAE on patients

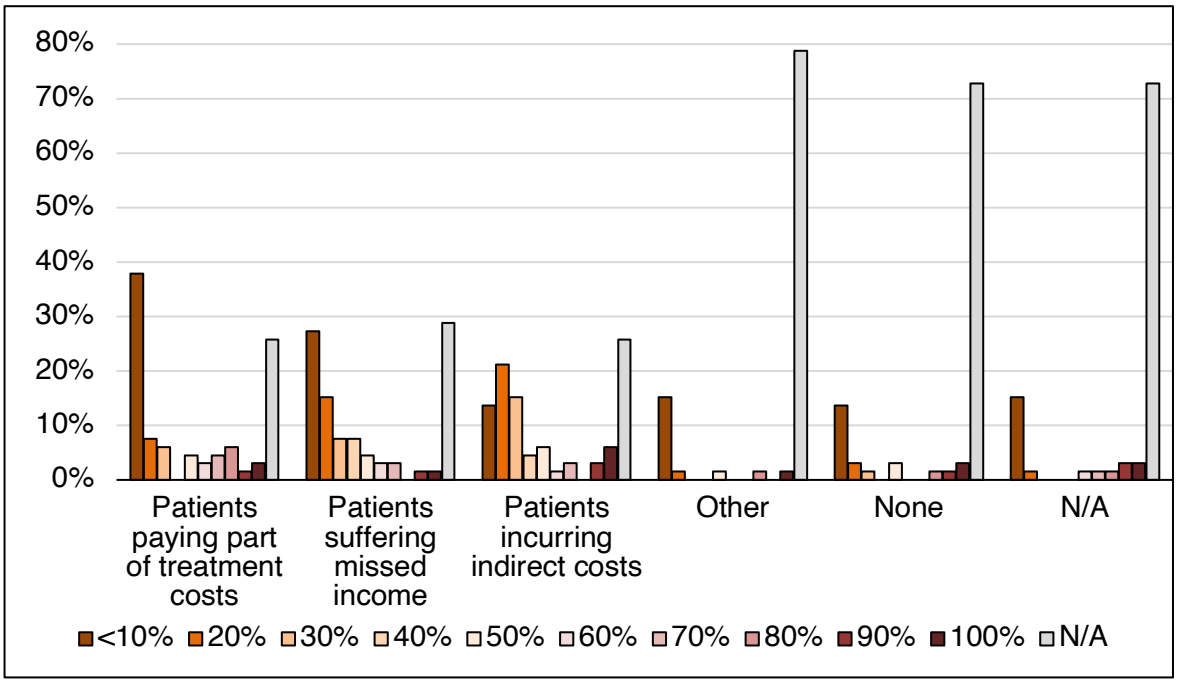

Figure 5.2.1 - Percentage of physicians estimating the percentage of HAE patients exposed to a financial impact due to their condition

Figure 5.1.30 illustrates that one-quarter of physicians treating HAE patients answered that they don't know if their patients carry part of their treatment costs, if they suffer from missed income or if they incur indirect costs. 38% of physicians believe that less than 10% of the patients are paying any part of the treatment costs.

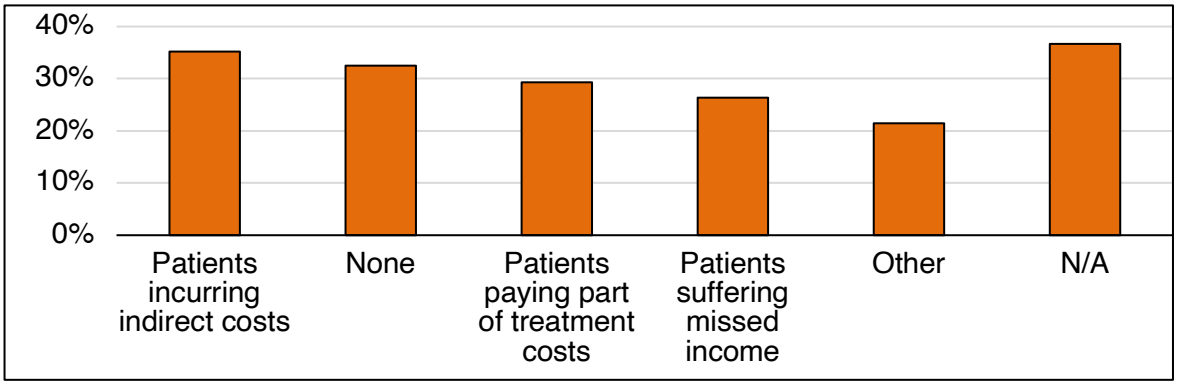

Figure 5.2.2 - Weighted percentage of HAE patients exposed to a financial impact due to their condition

An analysis on weighted averages (see Figure 5.1.31) suggests that only 35% of HAE patients incur indirect costs, that 33% incur no financial impact at all, and that less than 30% of the patients with HAE participate in the funding of their treatments. Lastly, physicians estimate that 26% of patients suffer from an income impact and 21% of some other form of financial impact.

5.2.1.2 Funding for HAE treatment

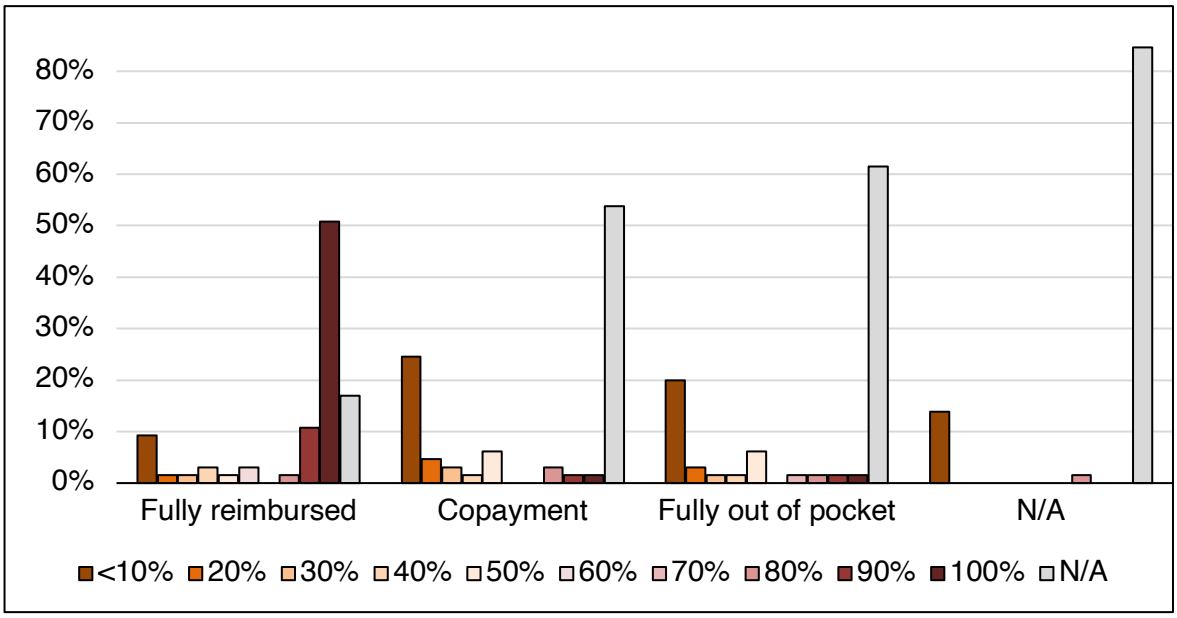

Figure 5.2.3 - Percentage of physicians estimating the percentage of HAE patients subject to full or partial reimbursement vs. fully self-pay

More than 50% of physicians estimate that 100% of their patients are fully reimbursed and do not need to spend or contribute anything to their treatment of each, as illustrated in Figure 5.1.32.

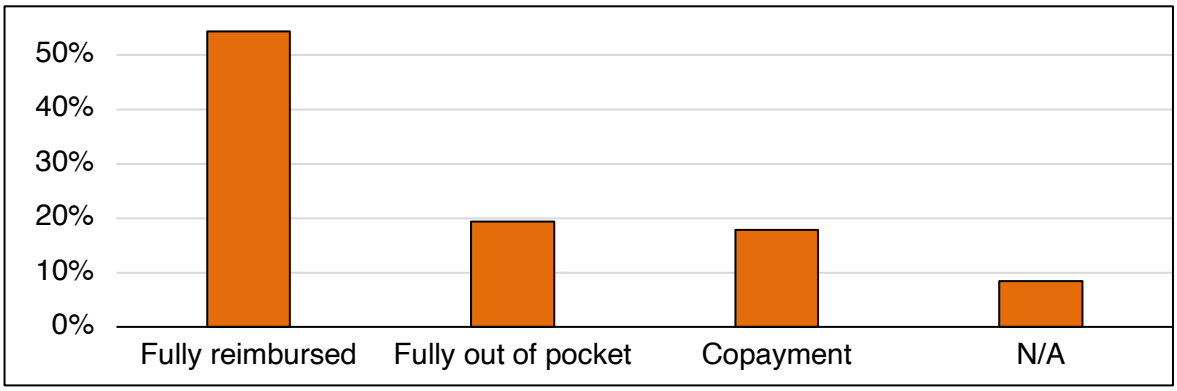

Figure 5.2.4 - Weighted percentage of HAE patients subject to full or partial reimbursement vs. fully self-pay

Figure 5.1.33 illustrates that a weighted average of 54% of patients are fully reimbursed. At first sight, this would represent a maximum scenario where the physician and the patient could completely focus on clinical outcomes and QoL without any economic considerations. Close to 20% are estimated to carry all treatment costs out of pocket.

5.2.1.3 Yearly costs to HAE patients due to condition

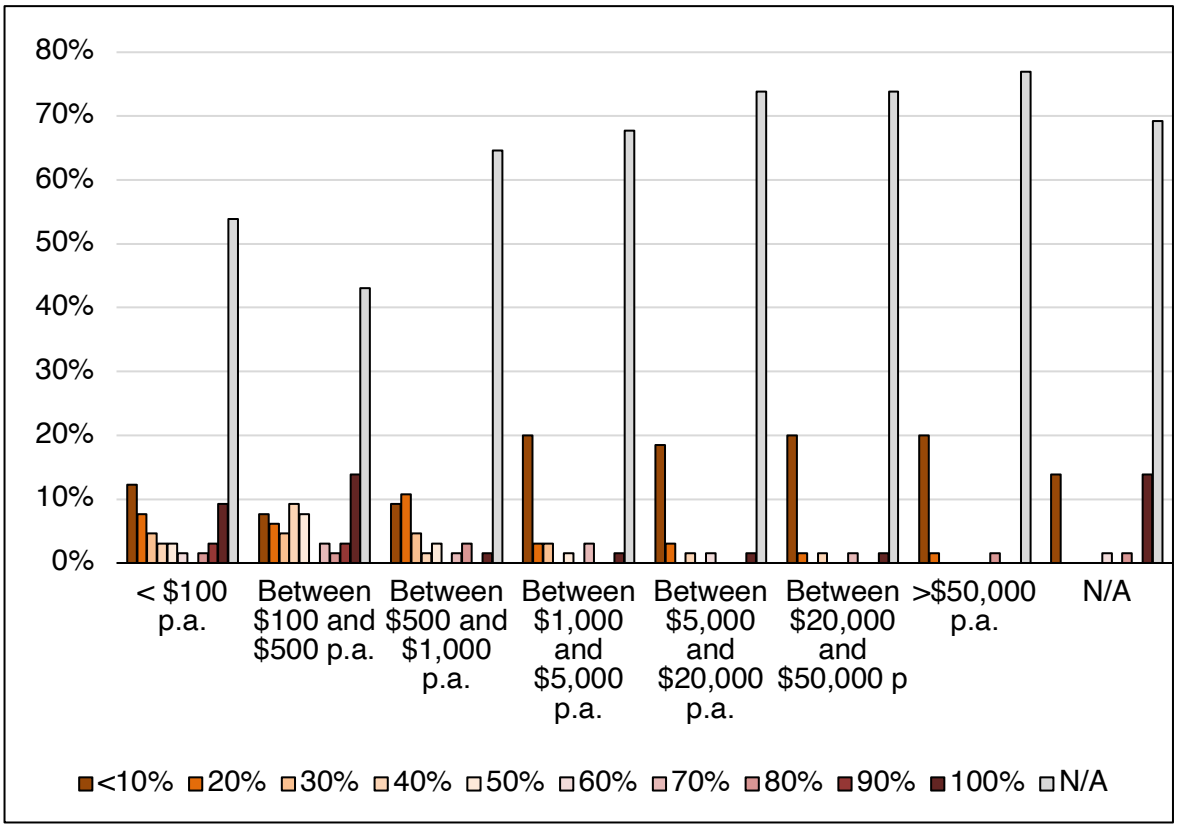

Figure 5.2.5 - Percentage of physicians estimating the percentage of HAE patients bearing different costs per year due to condition

Figure 5.1.34 illustrates that for every question between 43% and 77% of the physicians were not able to estimate the costs that HAE patients have to bear due to their condition. The physicians who answered, estimated in average about 39% of the patients incurred between zero and USD 500 of expenses per year due to HAE - the question specifically asked to consider all costs including treatment, medical help, support, transportation, etc. The remaining patients estimated to incur higher costs with 21% between USD 500 and USD 5'000, the remaining above.

5.2.1.4 Yearly costs to payer per HAE patient due to condition

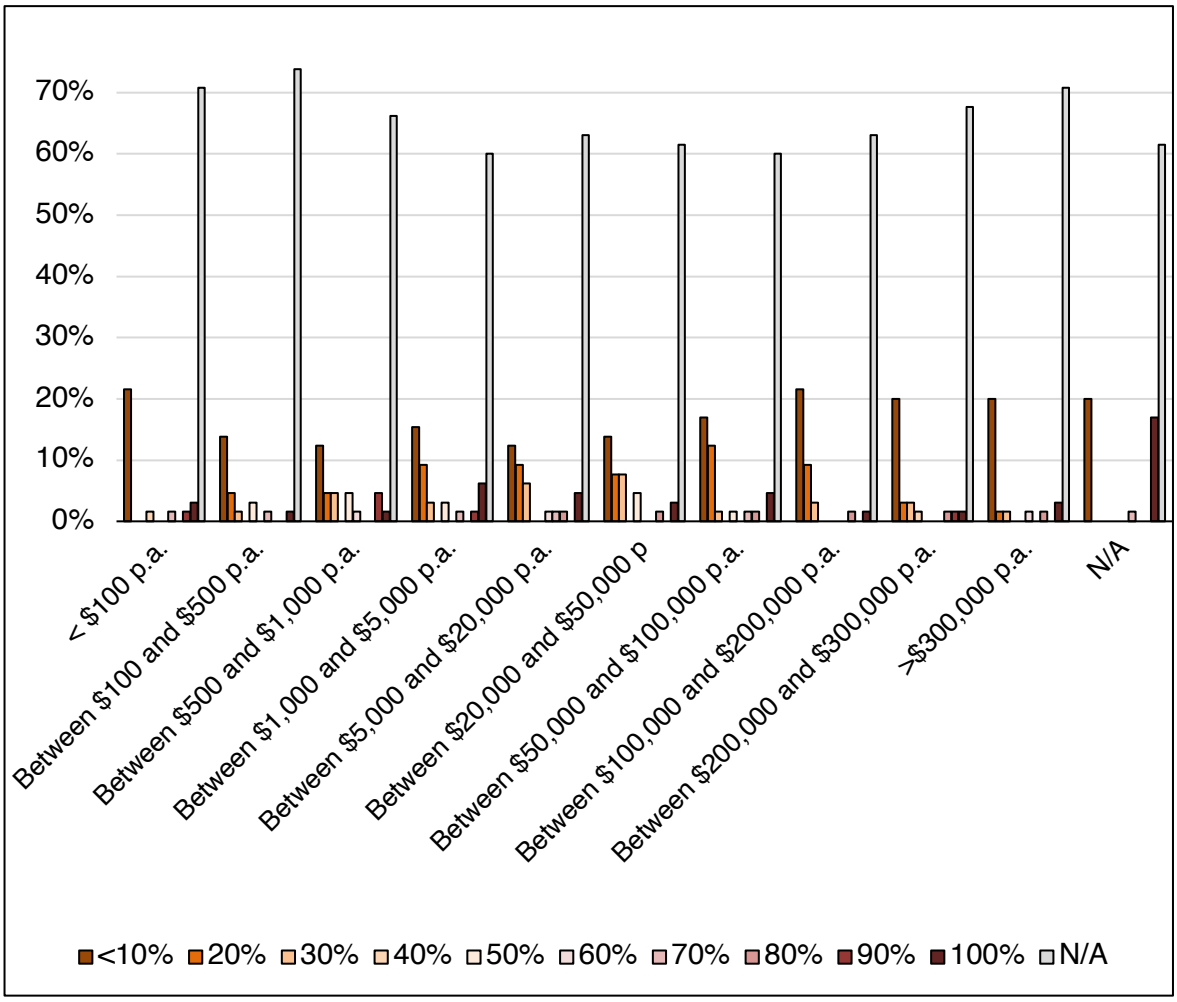

Figure 5.2.6 - Percentage of physicians estimating the percentage of HAE patients' insurances bearing different costs per year due to condition

Estimating the cost that the payers are incurring per HAE patient per year appeared to be even more difficult for treating physicians with between 60% and 70% answering that they didn't know, as shown in Figure 5.1.35. The answers by the physicians who were able to provide an estimate distributed almost equally across all ranges. Due to privacy and system-challenges (see section 3.5.5) it is very difficult to obtain the real data. A significant share of answers suggested that payers are funding well over USD 100,000 per year for some patients.

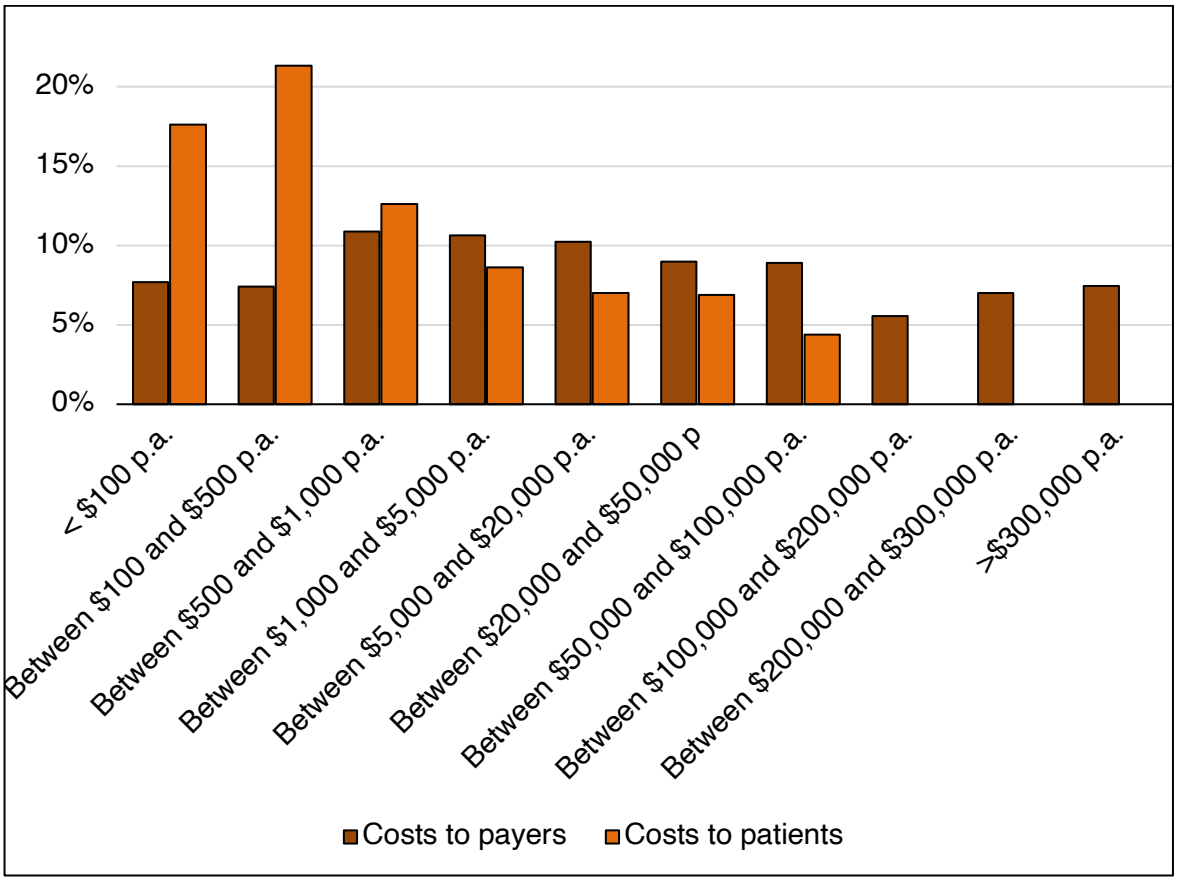

Figure 5.2.7 - Comparison of weighted distribution yearly costs to HAE patients vs to payers

Comparing the two questions on costs in Figure 5.1.36, it appears patients bear a higher share of costs in the lower ranges and the situation becomes inverse for higher ranges. Based on the survey payers are funding more than USD 100,000 per year to about 20% of the HAE patients, while less than 4% of patients incur costs of more than USD 50,000 per year.

5.3 Study 2 – Results from search on social media

Social media are pervasive and part of people's everyday life. Beyond the distribution of mundane updates, social media can be an excellent instrument to build communities, share content and experiences, invite to events or activities. This thesis has analyzed two social media channels, Facebook and Twitter, with the objective to qualify the published HAE content and to quantify the distribution by topics. The privacy policies of the two channels are intrinsically accepted by the users when they post content, and state that the postings have to be presumed accessible and visible by anybody anytime anywhere. Such setup poses limitations which will be discussed later in section 8.10. Postings have been searched over the past two calendar years to ensure a sufficient number of data points and to include events that occur during longer time intervals such as launches of new treatments, publications of new clinical results, or recurring events such as "HAE day" which have been created to generate awareness.

5.3.1 Facebook

The thesis analyzed over a couple of thousand postings relevant to HAE across different geographies and time intervals. Once information and data appeared to be repeated, the analysis reached data saturation. This led to all postings being grouped into nine segments.

5.3.1.1 Invitations to HAE events and activities

People living with HAE and suffering from a rare condition are often misunderstood and sometimes don't share with their social and professional environment their condition. As a result, they often feel isolated and misunderstood, thus seeking a community of people with the same condition to engage in social activities, to share experience, to generate awareness, or to advocate for access to treatment or better reimbursement of drugs. About a quarter (26%) of all identified postings were invitations to attend meetings, social events, webinars, symposia or other gatherings of HAE patients. These were organized by the international patient association (HAEi), respectively by its subchapters in the different countries or states (such as for example the one for Australasia https://www.facebook.com/HAEAustralasia). HAEi specifically established the "HAE Day" every year on May 16th, with the participation and sponsoring by the scientific community and the pharmaceutical industry. This day is promoted through http://www.haeday.org and includes social gatherings, scientific and educational sessions, a walk (e.g. "Camino Walk") where steps are measured and other activities. Local chapters further foster the sense of community through other events such as dinners spread around the year, publishing pictures and shared experiences which appear to have a positive QoL (section 3.7.19) effect on the patients. Such events are an example of patients taking their destiny and well-being in their own hands, possibly as a response to the fact that physicians and payers cannot fulfil all their needs as part of the agency framework described in section 2.3.

5.3.1.2 HAE experience sharing

The second most frequent type of posting representing 20% of posts was about seeking and sharing of experiences in coping with HAE. This could be specific experiences on

treatments, their efficacy and side effects, or also more personal ones sharing specific day-to-day challenges and how the patient coped with them. Patients shared how they are dealing with anxiety and depression, sometimes receiving words of encouragement and appreciation from other members. Various posts were from patients sharing about their experiences with specific treatments, which could be both positive (e.g. good clinical results from novel treatments such as Takhzyro® or negative (e.g. side effects), including asking fellow patients for advice. Patients shared online their experience with treating physicians, for example when there are communication barriers or disagreements on the treatment to pursue Posts could also be found where patients and caregivers shared their frustrations or inability to obtain the needed medication reimbursed by the insurance companies, despite the physician writing a prescription in line with clinical needs and guidelines. A recurring theme was the patient's attempts to lead a normal life, with normal interactions, without missing out on opportunities professionally, educationally or socially.

5.3.1.3 Raising funds for HAE activities

To improve awareness on the condition and its treatments, patients organized activities (see section 5.3.1.2) or issued publications and distributed materials which required funding. About 15% of the identified posts had as objective to raise funds in the form of donations for the cause.

5.3.1.4 HAE education

About 9% of posts were about disease education in the form of webinars, links to websites, articles, study outcomes, or dinners. HAE education concerns newly diagnosed patients and their caregivers by making them aware of current trends and knowledge. HAE education was in layman's language and covered all topics from the selection of the right treatment based on the patient profile, how to recognize attack triggers and potentially avoid them, and how to treat comorbidities. Physicians and key opinion leaders made themselves available and, in some cases, these offerings were sponsored by academic institutions, by the pharmaceutical industry, or by donations.

5.3.1.5 Information about HAE treatments

Posts containing information about treatments represented 7% of the total. They could be both links to official publications such as promotional statements or clinical results (see section 3.2.1) and real-life observations (see section **Error! Reference source not found.**). T hey covered specific drugs, treatment regimens and diagnostic tools. Patients posting information related to their own experience or sharing links contributed to improving the efficiency of the healthcare systems closing the gaps inherent to the agency theory (described in sections 3.6.1 and 3.6.4) and the therapeutic decision-making (described in sections 3.6.5 and 3.6.6). In some cases, patients advised each other on which medications to switch to in case of a specific disease profile. Some doctors have shown to be open to listening to treatment proposals coming from the patients and willing to experiment with different drugs as not all patients react the same way.

5.3.1.6 HAE life advice and support

About 5% of the posts were from participants who offered life advice and support, either by sharing grief, sharing advice on how to cope with specific situations such as stressful events and triggers, or simply through some words of inspiration and motivation. These posts were frequently met with 'likes' similar to those found on a social media platform. Similarly, signs of appreciation and even a small sign of caring and positive comments between strangers with the same rare condition possibly mitigate the pain of these diseases and help to offer a more positive outlook.

5.3.1.7 Invitations to clinical trials, surveys, registries

About 2% of the posts were calls to patients, and sometimes caregivers, to participate in clinical trials, survey or registries, that have as an objective to gain new knowledge on the condition, possible treatments and other ways to improve the situation. These posts are made by pharmaceutical companies, contract research organizations, academic institutions, consultants and other entities which engage social media to recruit patients.

5.3.1.8 Selling/offering of goods and services related to HAE

Another group of postings with free offers, such as digital publications, participations to webinars, discussion, and commercial offers, represented 2% of all posts on HAE. Commercial offers were more suited to patients with HAE and often consisted of comprehensive toolkits that include educational material, posters and gimmicks to be used during the HAE day in order to educate and generate awareness. Other more standard items included T-shirts or other wearables with logos and simple messages for awareness generation.

5.3.1.9 Sharing of other information

Lastly, there was a share of about 14% of the postings that included a wide range of messages where other information or simple content was shared. These could be links to magazines, wishes for the HAE day, organizational announcements within HAEi, special holiday wishes (e.g. Mother's Day), announcements that specific websites had been translated into other languages, progress made or milestones achieved in improving access to drugs in some healthcare systems, welcoming of new members, and more. This kind of postings appeared to address the need of having a form of bulletin board for HAE patients widely dispersed globally or within geographies. Some postings were anonymous, and some indicated names and showed pictures of individuals.

5.3.2 Twitter

Twitter can be researched in a similar way as Facebook, as it provides easy access to posts through a search capability. The major differences are that posts are limited in their number of characters and that there are no closed interest groups of users where the posts are not made accessible to the general public. The limitation on the size of the posts that can be shared forces users to be succinct and prevents them from sharing directly more details (such as experience sharing, educational content, etc.). Latter can still be achieved by way of hyperlinks leading to other websites. The impossibility to constrain postings to limited and selected users (for example fellow patients carrying the disease) might be a reason why Twitter postings on HAE appear in general less personal and detailed. These characteristics of Twitter seem to lead to a slightly different type and distribution of posts by category. Similar to the study on Facebook, the thesis identified and catalogued a couple of thousands of postings over several years and across different geographies until data saturation became prominent and beyond which new content seemed to add only marginal, if any, additional insights that could be used to answer the RQs or change the findings of the thesis. The same nine posting segments were identified as with the search on Facebook, yet with a different rank and weight.

5.3.2.1 Invitations to HAE events and activities

The share of postings in this segment was 51%, which was about twice as high as in Facebook. The vast majority of posts in this category took place around HAE Day on May 16th of every year and was about invitations to awareness events (such as the HAE walk) and other social events for HAE patients and their families and friends to gather. These invitations were dominantly posted by patient organizations such has “HAE International”, HAE UK”, or “HAE Australasia”, and, as they were for specific on-site events, focused on the country where the condition was more known, diagnosed and treated. Virtually all content in this category was sourced in the US, Europe, Australia and from a couple of Latin American countries. No content could yet be found coming from Asia, Middle East or Africa (which represent the majority of the world population), supporting other observations suggesting a significant disparity between advanced Western Healthcare systems and the rest of the world.

5.3.2.2 Other information

About 13% of Twitter posts on HAE were about sharing other types of information such as awards being given, wishes for public holidays, recommendations, or updates on the patients’ organizations meetings, congress participation or similar activities and links to articles. These postings were per se not specific to the condition, to treatments or any particular person.

5.3.2.3 HAE Experience sharing

The third most frequent type of post could be categorized as experience sharing with patients telling about their personal experience with diagnosis, a new treatment, or a particular life challenge that previously was unsolvable or intimidating and that thanks to new treatments

they could overcome. All postings were biased towards the positive, showing enthusiasm and a promising outlook that could inspire other patients. Used in this way, social media fulfilled their mission of bringing people together that have things in common. The participants were HAE patients and their commonality was their rare disease combined with their strive to lead a normal life professionally and socially. Patients sharing their positive experience may lead and inspire others to do the same.

5.3.2.4 HAE education

Similarly to what was found in the study on Facebook posts related to HAE, also on the Twitter platform about 9% of posts were about disease education. Users posted short messages suggesting details about symptoms that could indicate a diagnosis might be warranted, prodromes that could indicate an impending attack, how to deal with co-morbidities. As Twitter is significantly limited in the length of the posts that can be published, the majority of the ones with the objective of providing educational links to webpages, presentations, or speeches that could be followed on Youtube.

5.3.2.5 Information about HAE treatments

Immediately after HAE education followed the category of the posts providing information about treatments. Some posts were promoted by pharmaceutical companies, most by the HAE patients' organizations and individuals who aimed to spread the news and provide new hope to patients who still had unmet medical needs that could not be fulfilled by current treatments. One part of the posts shared new clinical data of novel compounds (such as Lanadelumab) through links to official study communications. Some posts aimed to raise awareness about the new WAO (World Allergy Organization) guidelines (see 3.1.10, 0), which was relevant as they moved C1-inhibitors to first-line treatment replacing androgens. Another type of posts which fell into this category was when a product achieved reimbursement status in a specific country. A concrete example took place when Firazyr® obtained reimbursement status in South Korea, which was announced officially in Q3 2018, and the word spread via Twitter and other channels fast.

5.3.2.6 Selling/offering of goods and services related to HAE

About 4% of posts on Twitter were offering goods and services for patients with HAE, which could be divided into three sub-categories. From a number of perspectives, the most frequent offering was for "HAE kits to generate awareness". During the year these were concentrated mainly in the weeks and months before the HAE Day on May 16th. The HAE kits were assembled and offered by the patient organizations, and contained different material (T-Shirts, brochures, posters) and content, which patients and caregivers could utilize to generate awareness and create the commitment to identify the condition, diagnose the disease and offer/reimburse the existing treatments. Some of the awareness material was scientific and educational in nature, sometimes also utilized by patients to update their treating physicians on the latest treatment guidelines, drugs or scientific data. Other offerings were low cost, generic and informative (such as access to newsletters) or tailored and significant in monetary terms (such as scholarships).

5.3.2.7 Raising funds for HAE activities

It appears that when searching under the HAE keyword on Twitter, only around 3% of posts were made with the intent to raise funds. All of the invitations were for donations to HAE patients' organizations in order to fund activities such as awareness events, educational events, social events, material for disease education or participation at congresses or other events.

5.3.2.8 HAE life advice and support

Only a small share of around 2% of posts on Twitter fell into the category of HAE patients or other stakeholders offering life advice or support. These posts, which sometimes were made of quotes and links to other inspirational websites or writings, could be seen as generic in nature, in that they could be applied to a large variety of life situations. Possibly posters use other channels or user groups to post life advice and support in order to have a wider reach. It was observed that retweets do rarely targeted HAE-specific groups or users.

5.3.2.9 Invitations to clinical trials, surveys, registries

The smallest group of posts, with about 1% of posts on Twitter, was composed of invitations to HAE patients to enroll in clinical trials, to participate in surveys, or to share their medical profiles with registries. Overall in Twitter few mentions of clinical trials could be found, however for sharing results and not for recruitment purposes. The few posts found in this category were mainly for surveys or asking patients to participate in registries, which are both a part of RWE (see section 3.3).

5.4 Study 3 – Meta-analysis results

5.4.1 HAE Patient population, epidemiology

The HAE condition selected for the thesis has a prevalence between1:10,000 and 1:50,000. HAE rare diseases, therefore, affect fewer than 8,000 individuals in the United States, less than 15,000 in Europe, and less than 200,000 worldwide (Lumry, 2018).

5.4.1.1 Onset of HAE

A search through the databases identified 30 studies which mentioned and measured the onset of HAE, that is the first time that the condition manifests itself by an attack.

# of sources	30
Sources	(Aabom, 2017), (Agostoni, 2004), (Andrejevic, 2017), (Bork, 2003), (Bork, 2006), (Bork, 2010), (Bork 2015), (Bouillet, 2013), (Bygum, 2009), (Bygum, 2015), (Caballero, 2014), (Christiansen, 2016), (Deroux, 2016), (Devercelli, 2018), (Farkas, 2002), (Farkas, 2010), (Huang, 2014), (Karkasharif, 2015), (Lei, 2011), (Nanda, 2015), (Nygren, 2016), (Psarros, 2014), (Riedl, 2015), (Riedl, 2017), (Roche 2005), (Steiner 2016), (Tourangeau, 2012), (Xu, 2013), (Zanichelli, 2013),
Total # of patients	2,934
Weighted average	Age of first HAE attack 13.3 years
Range	4-27 years

Table 5.4.1 - Median age at onset of HAE

Table 5.3.1 summarizes that all studies combined reported data for 2,934 patients with a resulting weighted average of the age when patients reported their first attacks at about 13 years.

5.4.1.2 Diagnosis of HAE

Using the same approach, 33 studies were identified as illustrated in Table 5.3.2, which amongst others, the median age of diagnosis was reported. Altogether, these studies aggregated data of almost 4,300 patients. As illustrated, the weighted median age of diagnosis of HAE resulted to be about 23 years. This figure is about ten years older than the average onset of the condition.

# of sources	33
Sources	(Aabom, 2017), (Banerji, 2017), (Bernstein, 2013), (Bernstein, 2014), (Bonner, 2015), (Bouillet, 2013), (Bygum, 2009), (Caballero, 2014), (Caminoa, 2013), (Christiansen, 2016), (Deroux, 2016), (Devercelli, 2018), (Farkas, 2002), (Farkas, 2010), (Huang, 2014), (Karkasharif, 2015), (Lei, 2011), (Lumry, 2010), (Nanda, 2015), (Nygren, 2016), (Psarros, 2014), (Riedl, 2016), (Riedl, 2017), (Roche 2005), (Steiner 2016), (Tourangeau, 2012), (Zanichelli, 2013), (Zanichelli, 2015), (Zuraw, 2010), (Zuraw, 2015)
Total # of patients	4,298
Weighted average	Age of HAE diagnosis 23.4 years
Range	3-42 years

Table 5.4.2 - Median age at diagnosis of HAE

5.4.1.3 Misdiagnosis and unnecessary procedures

Several articles and studies mentioned the issue of HAE patients being misdiagnosed. The thesis was able to identify one study by Banerji (2015) which attempted to quantify the percentage of patients who had been misdiagnosed before obtaining the right diagnosis.

# of sources	1
Sources	(Banerji, 2015)
Total # of patients	186
Weighted average	65% of HAE patients have been misdiagnosed
Range	-

Table 5.4.3 - Percentage of HAE patients that have been misdiagnosed

As illustrated in Table 5.3.3, about two-thirds of patients had been misdiagnosed before. Once misdiagnosed, the patients were likely exposed to unnecessary medical procedures, as their treating physicians were attempting to improve the clinical situation. Two studies were identified that reported the percentage of patients who underwent medical procedures that were later shown to have been unnecessary.

# of sources	2
Sources	(Banerji, 2015), (Bouillet, 2013)
Total # of patients	379
Weighted average	22% of HAE patients underwent unnecessary procedures
Range	19% - 24%

Table 5.4.4 - Percentage of HAE patients that went through unnecessary procedures

Combined the two studies reported data on 379 patients of which more than a fifth (22%) underwent unnecessary procedures as illustrated in Table 5.3.4.

5.4.2 Distribution of HAE attacks

5.4.2.1 Abdominal HAE attacks

Abdominal HAE attacks have been found to be most mentioned in articles for mainly two reasons: they are the most painful (see section 3.8), and they are also prone to lead to misdiagnosis (for example acute abdominal pain) with likely unnecessary procedure and treatments that do not lead to improved medical outcomes. The thesis identified 28 articles which combined used data from more than 2,500 patients.

# of sources	28
Sources	(Aabom, 2017), (Agostoni, 1992), (Agostoni, 2004), (Andrejevic, 2017), (Bernstein, 2013), (Bernstein, 2014), (Bonner, 2015), (Bork, 2006), (Bork, 2009), (Bork, 2010), (Bygum, 2009), (Bygum, 2015), (Deroux, 2016), (Farkas, 2002), (Farkas, 2010), (Huang, 2014), (Karkasharif, 2015), (Lei, 2011), (Nanda, 2015), (Narissara, 2018), (Nygren, 2016), (Nzeako, 2001), (Psarros, 2014), (Riedl, 2015), (Steiner 2016), (Wilson, 2010), (Xu, 2013), (Zuraw, 2015)
Total # of patients	2,522
Weighted average	66% of HAE patients suffered from abdominal attacks
Range	18%-100%

Table 5.4.5 - Percentage of HAE patients suffering from abdominal attacks

As illustrated in Table 5.3.5 on average about two-thirds of HAE patients suffered from abdominal attacks.

# of sources	15
Sources	(Banerji, 2017), (Bork, 2009), (Bouillet, 2013), (Caballero, 2014), (Caminoa, 2013), (Federici, 2018), (Jolles, 2014), (Levi, 2006), (Lumry, 2010), (Perego, 2017), (Steiner 2016), (Tourangeou, 2012), (Zanichelli, 2010), (Zanichelli, 2015)
Total # of patients	2,670
Weighted average	47% of HAE attacks are abdominal attacks
Range	32%-58%

Table 5.4.6 - Abdominal attacks as a percentage of all HAE attacks

The thesis also searched for how frequent abdominal attacks affect patients, and 15 studies reported this variable with an overall average of almost half the HAE attacks being abdominal (see Table 5.3.6).

5.4.2.2 Peripheral cutaneous HAE attacks

Peripheral cutaneous HAE attacks are the most prevalent and 25 studies have been found to report on how many patients suffer them. Table 5.3.2.2.1 illustrates that on over 2,000 patients, about four out five patients have suffered this type of attack.

# of sources	25
Sources	(Aabom, 2017), (Agostoni, 1992), (Agostoni, 2004), (Andrejevic, 2017), (Bernstein, 2014), (Bonner, 2015), (Bork, 2006), (Bork, 2009), (Bork, 2010), (Bork, 2015), (Bygum, 2015), (Deroux, 2016), (Farkas, 2002), (Farkas, 2010), (Huang, 2014), (Karkasharif, 2015), (Lei, 2011), (Nanda, 2015), (Narissara, 2018), (Nygren, 2016), (Psarros, 2014), (Riedl, 2015), (Steiner 2016), (Wilson, 2010), (Xu, 2013)
Total # of patients	2,034
Weighted average	82% of HAE patients suffered from peripheral cutaneous attacks
Range	41%-100%

Table 5.4.7 - Percentage of patients suffering from peripheral cutaneous HAE attacks

When searching for the share of total attacks, 25 sources could be identified which in the aggregate report that almost half of the attacks are peripheral and cutaneous, as illustrated in Table 5.3.8.

# of sources	15
Sources	(Banerji, 2017), (Bork, 2006), (Bork, 2009), (Bouillet, 2013), (Caballero, 2014), (Caminoa, 2013), (Federici, 2018), (Jolles, 2014), (Levi, 2006), (Perego, 2017), (Steiner 2016), (Tourangeou, 2012), (Zanichelli, 2010), (Zanichelli, 2015)
Total # of patients	2,434
Weighted average	45% of HAE attacks were peripheral cutaneous attacks
Range	24%-62%

Table 5.4.8 - Peripheral cutaneous attacks as a percentage of all HAE attacks

5.4.2.3 Laryngeal HAE attacks

Laryngeal attacks were of particular interest as they can be lethal if not treated properly, and therefore are also the main source for the comorbidities anxiety and depression (see section 3.8).

# of sources	36
Sources	(Aabom, 2017), (Agostoni, 1992), (Agostoni, 2004), (Andrejevic, 2017), (Bernstein, 2013), (Bernstein, 2014), (Bonner, 2015), (Bork, 2001), (Bork, 2003), (Bork, 2006), (Bork, 2009), (Bork, 2010), (Bork, 2015), (Bouillet, 2013), (Bygum, 2015), (Farkas, 2002), (Farkas, 2010), (Gower, 2011), (Huang, 2014), (Jolles, 2014), (Karkasharif, 2015), (Lei, 2011), (Longhurst, 2012), (Lumry, 2010), (Nanda, 2015), (Narissara, 2018), (Nygren, 2016), (Nzeako, 2001), (Ohsawa, 2015), (Psarros, 2014), (Riedl, 2015), (Steiner 2016), (Wilson, 2010), (Winnewisser, 1997), (Xu, 2013)
Total # of patients	4,011
Weighted average	36% of HAE patients have suffered from laryngeal attacks
Range	7%-90%

Table 5.4.9 - Percentage of HAE patients suffering of laryngeal attacks

A search through the databases identified 36 studies which reported data on more than 4,000 HAE patients and resulting in an average that more than a third of patients have experienced this type of attacks before, as presented in Table 5.3.9.

The frequency of laryngeal attacks was of particular interest and the thesis determined that less than half (16) studies reported such data, extracted from more than 2,000 patient profiles, as illustrated in Table 5.3.10.

# of sources	16
Sources	(Bork, 2006), (Bork, 2009), (Bouillet, 2013), (Caballero, 2014), (Caminoa, 2013), (Federici, 2018), (Jolles, 2014), (Karkasharif, 2015), (Levi, 2006), (Longhurst, 2012), (Perego, 2017), (Steiner 2016), (Tourangeou, 2012), (Zanichelli, 2010), (Zanichelli, 2015)
Total # of patients	2,040
Weighted average	4% of HAE attacks were laryngeal attacks
Range	1%-8%

Table 5.4.10 - Laryngeal attacks as a percentage of all HAE attacks

With a variance between 1% and 8%, on average 4% of HAE attacks appear to be laryngeal.

5.4.3 Severity of attacks (with treatment)

Measuring the severity of an attack is challenging as there is no universally accepted definition of severity, and the assessment of the severity of an attack can be subjective and different patient to patient. With HAE there is the additional complication of two dimensions: pain during an attack and frequency of attacks, which do not always correlate. Prior (2012) proposed a set of criteria to describe the severity of HAE attacks. For instance, 'Asymptomatic', when the patient reports no angioedema episodes and is not taking any treatment. The term 'Mild' is preferred when the patient has non-life-threatening HAE episodes. less than six attacks per year and is not taking long term prophylactic treatment. Similarly, 'Moderate' is used when the patient has less than 12 not life-threatening attacks per year, without taking into account long term prophylactic treatment, or more than six attacks per year with long term prophylactic treatment. "Severe" if the patient suffers life-threatening HAE attacks and/or more than 12 attacks per year with long term prophylactic treatment. Using different terminologies, Zanichelli (2012) suggested that 55% of patients fell into the mild category, 25% in to moderate and 20% into the severe category. From a patient's perspective, the severity of each attack is also measured from uncomfortable skin swelling to life-threatening laryngeal edema (Lei, 2011). In the following meta-analysis, the studies had either no definition or not a consistent definition of severity according to these scholars.

Between eight and ten studies could be found that report the distribution of the severity of the HAE attacks as illustrated in Tables 5.3.11, 5.3.12 and 5.3.13.

# of sources	8
Sources	(Blasco, 2013), (Caballero, 2014), (Federici, 2018), (Lumry, 2010), (Perego, 2017), (Riedl, 2015), (Wilson, 2010), (Zanichelli, 2015)
Total # of patients	2,432
Weighted average	28% of HAE attacks are mild
Range	16%-37%

Table 5.4.11 - Mild attacks as a percentage of all HAE attacks

# of sources	8
Sources	(Blasco, 2013), (Caballero, 2014), (Federici, 2018), (Lumry, 2010), (Perego, 2017), (Riedl, 2015), (Wilson, 2010), (Zanichelli, 2015)
Total # of patients	2,432
Weighted average	48% of HAE attacks are moderate
Range	45%-56%

Table 5.4.12 - Moderate attacks as a percentage of all HAE attacks

# of sources	10
Sources	(Blasco, 2013), (Bouillet, 2013), (Caballero, 2014), (Caminoa, 2013), (Federici, 2018), (Lumry, 2010), (Perego, 2017), (Riedl, 2015), (Wilson, 2010), (Zanichelli, 2015)
Total # of patients	2,818
Weighted average	25% of HAE attacks are severe
Range	17%-32%

Table 5.4.13 - Severe attacks as a percentage of all HAE attacks

Taking the average across all published research, it appears that about half the attacks are considerate “moderate”, and a quarter each “mild” and “severe”.

5.4.4 Frequency of HAE attacks per year

The thesis identified 27 publication reporting the number of attacks HAE patients can have in one year, measured over 3,700 patients as illustrated in Table 5.3.14.

# of sources	27
Sources	(Aabom, 2017), (Banerji, 2015), (Banerji, 2017), (Bork, 2006), (Bork, 2008), (Bork, 2009), (Bork, 2015), (Bouillet, 2011), (Bouillet, 2013), (Bygum, 2009), (Bygum, 2014), (Caminoa, 2013), (Deroux, 2016), (Federici, 2018), (Levi, 2006), (Lumry, 2010), (Perego, 2017), (Riedl, 2015), (Riedl, 2017), (Steiner 2016), (Tourangeau, 2012), (Wilson, 2010), (Zanichelli, 2010), (Zanichelli, 2015), (Zuraw, 2010)
Total # of patients	3,747
Weighted average	19 HAE attacks per year
Range	4-94 attacks

Table 5.4.14 - Total frequency of HAE attacks per year

The frequency of attacks appeared to be highly variable among different patients, with reports ranging between four and 94 attacks per year, and a total average of 19 attacks per year. Aabom (2017) reported that 7% of patients had zero attacks within a year and Inhaber (2019) reported that attack rates and severity of attacks appear not to depend on body weight. The literature mentions in addition, that a patient's experience of attack frequency can also vary over time depending on a number of factors such as the attack triggers, which occurred in a wide range for annual frequency.

The thesis was able to extract more details, for example, that about 40% of HAE patients suffer less than one attack every two weeks (illustrated in Table 5.3.15), and 31% of patients suffer less than one attack per month (Table 5.3.16).

# of sources	4
Sources	(Agostoni, 2004), (Banerji, 2015), (Banerji, 2017), (Federici, 2018)
Total # of patients	844
Weighted average	40% of HAE patients have less than one attack every two weeks
Range	18%-54%

Table 5.4.15 - Percentage of HAE patients with less than one attack every two weeks

# of sources	10
Sources	(Aabom, 2017), (Agostoni, 2004), (Andrejevic, 2017), (Banerji, 2015), (Banerji, 2017), (Caballero, 2014), (Federici, 2018), (Nordenfelt, 2014), (Steiner 2016), (Zilberberg, 2011)
Total # of patients	1,299
Weighted average	31% of HAE patients have less than one attack every month
Range	18%-82%

Table 5.4.16 - Percentage of HAE patients with less than one attack per month

On the other side of the spectrum, four studies have reported in average that about one-fifth of patients suffer more than one attack per week, as illustrated in Table 5.3.17.

# of sources	4
Sources	(Andrejevic, 2017), (Banerji, 2015), (Caballero, 2014), (Steiner 2016)
Total # of patients	110
Weighted average	21% of HAE patients have more than one attack per week
Range	10%-28%

Table 5.4.17 - Percentage of patients with more than one attack per week

5.4.5 Duration of HAE attacks

The duration of HAE attacks is a key indicator for the severity and length in time HAE patients have to suffer, which directly affects the productivity and the QoL of a patient. The longer the attack, the longer the probable absence from work, education or social life. The thesis found six studies with a combined total of 409 patients.

# of sources	6
Sources	(Bork, 2005), (Bork, 2008), (Bygum, 2009), (Zanichelli, 2010), (Zanichelli, 2013), (Zuraw, 2010)
Total # of patients	409
Weighted average	Duration of attacks 2.3 days for HAE patients not treated
Range	1.7-3.8 days

Table 5.4.18 - Duration of untreated HAE attacks

As illustrated in Table 5.3.18 the attacks in untreated patients would last about 2.3 days on average.

# of sources	2
Sources	(Zanichelli, 2010), (Zanichelli, 2013)
Total # of patients	256
Weighted average	Duration of attacks 1.5 days for patients treated with androgens
Range	1.5 days

Table 5.4.19 - Duration of HAE attacks with androgen therapy

# of sources	2
Sources	(Zanichelli, 2010), (Zuraw, 2010)
Total # of patients	125
Weighted average	Duration of attacks 1.3 days for patients treated with C1-inh
Range	1.1-2.1 days

Table 5.4.20 - Duration of HAE attacks with C1-inhibitor therapy

Patients treated with androgens or with C1-inhibitor benefit from significantly shorter durations of attacks, 1.5 days and 1.3 days as illustrated in tables 5.3.19 and 5.3.20 respectively.

5.4.6 Triggers of HAE attacks

HAE attacks are variable in location and severity, as well as unpredictable, which contributes to the burden of the condition. While it has been recognized that the deficiency of functional C1-inhibitor is the cause of most forms of HAE, the specific mechanism that triggers attacks has not been definitively described. Agostoni (2004) reported that in some patients the absence of spontaneous attacks despite strong deficits of C1-inhibitor, indicating the possibility that multiple biological events have to take place for HAE attacks to happen. Patients are naturally keen to be able to predict when attacks occur, to be able to identify what triggers them, in order to possibly avoid such behaviors and events and thus the attack themselves. This part of the search aimed to consolidate from the available studies which activities and events could trigger attacks.

5.4.6.1 Trauma

Trauma as a trigger had been studied in 14 articles of research, as illustrated in Table 5.3.21, which collected the data of 778 HAE patients who recognized trauma as a trigger for an attack.

# of sources	14
Sources	(Bonner, 2015), (Bork, 2009), (Farkas, 2010), (Howlett, 2019), (Javaud, 2015), (Karkasharif, 2015), (Lei, 2011), (Nanda, 2015), (Narissara, 2018), (Psarros, 2014), (Read, 2014), (Riedl, 2015), (Steiner, 2016), (Winnewisser, 1997)
Total # of patients	778
Weighted average	52% of HAE patients reported trauma to trigger attacks
Range	10%-75%

Table 5.4.21- Percentage of HAE patients who reported trauma as an at attack trigger

The variability across studies is relatively high, possibly suggesting that this variable could be dependent on the cohort of patients.

5.4.6.2 None/not sure

The nine studies illustrated in Table 5.3.22, which measured the percentage of HAE patients not able to trace their attacks to specific triggers reported on average that about half the patients are unable to do so.

# of sources	9
Sources	(Bonner, 2015), (Karkasharif, 2015), (Lei, 2011), (Nygren, 2016), (Nzeako, 2001), (Psarros, 2014), (Riedl, 2015), (Steiner, 2016), (Winnewisser, 1997)
Total # of patients	454
Weighted average	49% of HAE patients are not sure or cannot trace their HAE attacks back to specific triggers
Range	16%-95%

Table 5.4.22- Percentage of HAE patients who report no attack trigger or are not sure

Similar to the report in section 5.3.6.1, the variability between the studies is relatively high.

5.4.6.3 Stress

Stress as a psychological trigger for an HAE attack was studied in 13 publications which combined included 674 HAE patients as illustrated in Table 5.3.23.

# of sources	13
Sources	(Bonner, 2015), (Bork, 2009), (Farkas, 2010), (Javaud, 2015), (Karkasharif, 2015), (Lei, 2011), (Nanda, 2015), (Narissara, 2018), (Psarros, 2014), (Read, 2014), (Riedl, 2015), (Steiner, 2016), (Winnewisser, 1997)
Total # of patients	674
Weighted average	47% of patients reported stress to trigger attacks
Range	14%-79%

Table 5.4.23- Percentage of HAE patients who reported stress as an at attack trigger

On average about half the patients reported stress to be a factor that could trigger an attack.

5.4.6.4 Pregnancy, menstruation, hormonal factors

Approximately the same number of articles than in sections 5.4.6.1 and 5.4.6.3 reported female HAE patients suffering from attacks when triggered by pregnancies, menstruations, or other hormonal factors.

# of sources	11
Sources	(Bonner, 2015), (Bork, 2009), (Bork, 2010), (Deroux, 2016), (Farkas, 2010), (Howlett, 2019), (Javaud, 2015), (Karkasharif, 2015), (Lei, 2011), (Psarros, 2014), (Steiner, 2016)
Total # of patients	745
Weighted average	47% of female HAE patients reported pregnancies, menstruations or other hormonal factors to trigger attacks
Range	18%-95%

Table 5.4.24 - Percentage of female HAE patients who reported pregnancy, menstruation, hormonal factors as an attack trigger

On average about half the female HAE population is affected by attacks triggered by such common situations, as presented in Table 5.3.24.

5.4.6.5 Emotions

Emotions are also psychological factors, however, only two studies, illustrated in Table 5.3.25, appear to have measured how frequently they could trigger HAE attacks.

# of sources	2
Sources	(Bonner, 2015), (Nanda, 2015)
Total # of patients	64
Weighted average	32% of HAE patients reported emotions to be possible trigger factors for HAE attacks
Range	13%-42%

Table 5.4.25 - Percentage of HAE patients who reported emotions or being upset as an attack trigger

The two studies reported in aggregate that about one-third of patients, when subject by negative emotions such as being upset, could be facing an impending HAE attack.

5.4.6.6 Infections

Infections have been studies in ten articles over 549 patients as illustrated in Table 5.3.26.

# of sources	10
Sources	(Bonner, 2015), (Farkas, 2010, (Javaud, 2015), (Karkasharif, 2015), (Lei, 2011), (Nanda, 2015), (Narissara, 2018), (Psarros, 2014), (Read, 2014), (Steiner, 2016)
Total # of patients	549
Weighted average	28% of HAE patients reported infections to be possible trigger factors for HAE attacks
Range	13%-50%

Table 5.4.26 - Percentage of HAE patients who reported infections as an attack trigger

Combined across the studies in about 28% of HAE patients' infections could trigger attacks.

5.4.6.7 Specific foods

Undiagnosed patients having their first attacks often seek help from the family physician or general practitioners, whom when observing the swelling, incorrectly assume it was caused by allergies. If the attack is abdominal (see section 5.4.2.1), then the hypothesis of food poisoning or allergy would appear plausible. The nature of the disease is not an allergic reaction (see section 3.8), nevertheless some foods could trigger HAE attacks in patients, as it has been studied in five articles, as illustrated in Table 5.3.27.

# of sources	5
Sources	(Bonner, 2015), (Bork, 2009), (Karkasharif, 2015), (Narissara, 2018), (Psarros, 2014)
Total # of patients	194
Weighted average	24% of HAE patients reported that specific foods could trigger HAE attacks
Range	9%-40%

Table 5.4.27 - Percentage of HAE patients who reported certain foods as an attack trigger

Over close to 200 patients, the studies reported that on average one-quarter of the patients could suffer from HAE attacks triggered by specific types of food.

5.4.6.8 Dental procedures

Trauma as a trigger has been studied as described in section 5.4.6.1, where about half the patients reported it to be a trigger of attacks. Anecdotal evidence seemed to indicate that dental procedures could trigger the laryngeal attacks which are particularly feared as they could become lethal. The thesis identified five studies over 250 patients, illustrated in Table 5.3.6.8, which specifically analyzed these factors.

# of sources	5
Sources	(Bonner, 2015), (Bork, 2009), (Karkasharif, 2015), (Narissara, 2018), (Psarros, 2014)
Total # of patients	251
Weighted average	22% of patients reported that dental procedures could trigger HAE attacks
Range	5%-33%

Table 5.4.28 - Percentage of HAE patients who reported dental procedures as an attack trigger

As illustrated in Table 5.3.28 dental procedures could trigger HAE attacks in 22% of the patients.

5.4.6.9 Lack of sleep

During the research, two articles reported lack of sleep as a trigger factor for a share of the HAE population studied, illustrated in Table 5.3.29.

# of sources	2
Sources	(Bonner, 2015), (Nanda, 2015)
Total # of patients	64
Weighted average	17% of patients reported that lack of sleep could trigger HAE attacks
Range	13%-19%

Table 5.4.29 - Percentage of HAE patients who reported lack of sleep as an at attack trigger

These studies reported in aggregate that about 17% of HAE patients can suffer from attacks due to lack of sleep.

5.4.6.10 Prodromal symptoms

Prodromal symptoms are sensitive non-specific manifestations that patients feel hours or days before HAE attacks. They can include localized tingling, itching, tightness, pain, and rashes (like erythema marginatum), urticaria, fatigue, malaise, flu-like symptoms, irritability, mood changes, hyperactivity, thirst, or nausea. Prodrome can last from an hour to several hours and can also include mental states like unexplainable sudden anxiety, feelings of impending doom. Depression, mental confusion, suicidal thoughts or just difficulties in managing basic daily tasks, like struggles to unlock a door. Prevalence is variable, Dagen (2010) reported that nine out of ten patients had a prodrome before attacks and that therefore they could be used as an indicator to predict an attack. Kemp (2008) suggested that as the reproducibility of prodromes varies, they may not be sufficient indicators to initiate therapy. Magerl (2014) reported that over 90% of the patients reported being able to predict the onset of an attack with a higher than 50% certainty, although it is still unclear how many truly lead to an attack.

5.4.7 Comorbidities of HAE patients

Comorbidities are other medical conditions that a share of HAE patients suffer from possibly as a direct or indirect result of the condition itself. They can arise through the condition itself overall, by the treatment, the lack thereof, or indirectly. Agostoni (2004) reported that they need to be understood and considered as they might be avoidable. In some cases, they require diagnosis and treatment by other medical specialties beyond immunology (e.g. for depression). Co-morbidities not only exacerbate the negative impact of the primary condition on the QoL, but they can also add significant additional financial burden to the patient, the caregiver, the payer and society.

5.4.7.1 Depression

Of the published literature on HAE, nine studies reported the prevalence of depression in patients living with HAE, as presented in Table 5.3.30.

# of sources	9
Sources	(Banerji, 2017), (Bernstein, 2013), (Devercelli, 2018), (Fouche, 2013), (Gower, 2011), (Lumry, 2010), (Steiner, 2016), (Tachdjian, 2017), (Zilberberg, 2011)
Total # of patients	3,365
Weighted average	34% of HAE patients suffered from depression
Range	19%-44%

Table 5.4.30 - Percentage of HAE patients with depression as a comorbidity

With 3,365 HAE patients studied, about a third also suffered under depression. Lumry (2010) applied the Hamilton Depression Inventory–Short Form to HAE patients and reported that 43% of them had scores indicating a clinically significant depressive symptomatology, which is more than twice the 16% of an unaffected population. Fouche (2014) reported patients showing a sense of helplessness and emotional distress and disappointment even before they got an accurate diagnosis of HAE. Kargasharif (2015) reported that many patients develop feelings of guilt passing the disease to their children as HAE is hereditary. Fouche (2014) also mentioned that a further exacerbation of the condition is that patients not only can feel depression and anxiety as a result of attacks, but that vice versa feelings of depression and anxiety can and do play a causative role in the initiation of the attacks themselves. It follows that substantial shares of patients receive treatment for depression or anxiety, reflecting the additional disease burden beyond HAE attacks (Tachdjian, 2017). Lumry (2010) finally reported that close to one-fifth of patients with HAE take psychotropic or antidepressant medication, which is nearly double the national average.

5.4.7.2 Anxiety

Anxiety as a comorbidity was measured in four studies and over 1,032 patients as illustrated in Table 5.3.31.

# of sources	4
Sources	(Banerji, 2017), (Devercelli, 2018), (Fouche, 2013), (Psarros, 2014)
Total # of patients	1,032
Weighted average	43% of HAE patients suffered from anxiety
Range	15%-53%

Table 5.4.31 - Percentage of patients with anxiety as a comorbidity

Anxiety affected about 43% of patients and Winnewisser (1997) reported that at least one-third of patients live in continuous apprehension of an attack. When Quincke (1882) first described HAE, he originally labeled the condition as “angioneurotic” edema, based on the suspicion that the condition was in part “neurotic”, due to the high prevalence of depression and anxiety coming with it. Only in recent decades, thanks to a better understanding of the pathogenesis, has this label fallen out of usage (Henao, 2016). While it is biochemically not resulting from the genetic mutation causing HAE, it comes as a result of the condition and can vary over time and across individuals. The unpredictability of attacks and their potentially life-threatening nature is still the greatest source of worry for both patients and physicians (Jain, 2018). Bygum (2014) reported that 85% of patients are concerned about the inherent risk of sudden suffocation through a laryngeal attack. This can be explained with 12% of patients experiencing the death of a family member due to airway closure as reported by Huang (2004) from a survey.

5.4.7.3 Autoimmune disorders

Table 5.3.32 illustrates that autoimmune disorders as a comorbidity of HAE were reported only in two publications with 77 patients in total.

# of sources	2
Sources	(Agostoni, 2004), (Nygren, 2016)
Total # of patients	77
Weighted average	12% of HAE patients suffered from autoimmune disorders
Range	12%-12%

Table 5.4.32 - Percentage of HAE patients with autoimmune disorders as a comorbidity

Relatively few studies have reported this comorbidity describing the propensity of HAE patients to develop autoimmune disease, which can manifest as inflammatory bowel disease, systemic lupus erythematosus or thyroiditis. Levy (2019) reported that the frequency of autoimmune diseases appears to be almost triple (>12% vs. 4.5%) in patients with HAE compared to the general population. Frank (2018) recommended that although these diseases are usually mild, they should be considered by the treating physician. They can add further burden and costs to the condition.

5.4.7.4 Other comorbidities

Nanda (2015) reported in a study of over 21 patients that 15% of HAE patients could also be subject to atopy.

Bernstein (2013) in another study over 457 HAE patients reported that 71% suffered also of weight gain due to their condition. Anecdotal discussion with specialist treating the patients indicated obesity to be a co-morbidity, resulting probably from a lower propensity of patients to engage in high impact physical activities and sometimes even sport in general, for fear of triggering an attack through trauma or distress. As studies show the positive

impact of physical activity on the psychological well-being, a lack of the first might not only contribute to weight gain, but also to depression and possibly self-loathing mentioned above. In the same study Bernstein (2013) also reported that 60% of the HAE patients were exposed to mood changes, possibly driven by the disruptive nature of HAE attacks on daily life and long-term prospects. Lastly, Bernstein (2013) reported that 46% of HAE patients were also subject to sleep disturbances, which might be linked to anxiety and depression as illustrated in sections 5.4.7.1 and 5.4.7.2.

Additional co-morbidities have been mentioned in the literature, however, it appears not yet exhaustively and quantitatively been studied. Sexton (2019) reported in one of the analyses as part of the HELP study for lanadelumab on the cardiovascular risk of the treatment. He reported that up to 24.4% of the enrolled HAE patients had a history of hypertension. Nielsen (1996) reported that women with HAE were showing increased symptoms of urinary tract infections in conjunction with the attacks. The same study mentioned also women with HAE experiencing more spontaneous abortions or premature labors than healthy ones.

Savarese (2018) reported that children with HAE were showing an impaired ability to recognize and describe their feelings (alexithymia), which is common when they suffer from chronic diseases. This comorbidity is exacerbating the HAE condition as children with alexithymia have reduced abilities to cope with stress, which can result in increased perceived stress and therefore more trigger factors for additional attacks. Abdominal attacks cause pain ranging at the top of the scale and often require the use of narcotic analgesics. Zuraw (2008) reported that frequent abdominal attacks may have led to addiction and some patients have been inappropriately considered to be “drug seeking” having developed narcotic dependence as described by Hemperly (2013). Lastly, Nielsen (1996) mentioned that patients with HAE have also been more frequently reported showing symptoms of heartburn or peptic ulcers, rheumatic complaints, while Steiner (2016) reported dyslipidemia, deep vein thrombosis, coronary heart disease, and diabetes.

5.4.8 Patient engagement of health care services

Patients with HAE display a relatively high utilization of health care resources including hospitalizations and ER visits. Tachdijan (2018) reported in a US study on a cohort of commercially insured HAE patients, that on a per year-basis 18% had claims for HAE-related ER visits, and 11.5% had claims for HAE-related inpatient stays.

5.4.8.1 Hospitals visited

# of sources	3
Sources	(Bygum, 2009), (Petraroli, 2015), (Zhi,2018)
Total # of patients	204
Weighted average	7.5 hospital visits per HAE patient over lifetime
Range	5.5 – 16.8

Table 5.4.33 - Average number of hospitals visited per HAE patient

Studies which included more than 200 HAE patients indicated that on overage they had over 7.5 hospital visits over their lifetime, as illustrated in Table 5.3.33.

5.4.8.2 Doctor visits

One study over 159 HAE patients reported that on average untreated HAE patients sought the help through more than 11 doctor visits when having attacks, but not having been diagnosed yet, as illustrated in Table 5.3.34.

# of sources	1
Sources	(Zhi,2018)
Total # of patients	159
Weighted average	11.4 doctor visits by untreated HAE patients seeking treatment
Range	-

Table 5.4.34 - Average number of doctors visited seeking treatment per HAE patient

Two studies reported the same variable (doctor visits) when HAE patients were diagnosed and under treatment as illustrated in table 5.3.35.

# of sources	2
Sources	(Banerji, 2015), (Zhi,2018)
Total # of patients	345
Weighted average	4.6 doctor visits per year when under treatment
Range	4.0 – 5.2

Table 5.4.35 - Number of doctor visits per year per HAE patient

The frequency of doctor visits for such patients was on average 4.6 per year for example to monitor the evolution of the condition or renew or change the prescription of the medication to take.

5.4.8.3 ER visits

The more severe the pain of a medical condition, the higher the utilization of medical resources. Studies have confirmed that the higher the intensity of the pain during an attack, the lower the productivity, the greater the absenteeism and the higher the likelihood of visiting an ER for treatment. Ayggören-Pürsün (2014) reported that 19% of attacks with severe pain led to ER visits, while 16% did so with moderate pain and only 2% with mild or no pain. Seven studies over combined close to 1,200 HAE patients and their visits to ERs were identified.

# of sources	7
Sources	(Bouillet, 2011), (Bouillet, 2013), (Federici, 2018) (Javaud, 2015), (Tourangeau, 2012), (Wilson, 2010)
Total # of patients	1,191
Weighted average	10% of HAE patients visit ERs
Range	2% - 16%

Table 5.4.36 - Percentage of HAE patients visiting ERs

As illustrated in Table 5.3.36, on average around 10% of patients with HAE have visited ERs. The thesis found another group of studies which measured ER visits by HAE patients that were yet undiagnosed vs. patients that were already diagnosed. Two publications reported on average that the former visit ERs 3.2 times per year, as illustrated in Table 5.3.37.

# of sources	2
Sources	(Huang, 2014), (Zhi, 2018)
Total # of patients	222
Weighted average	3.2 ER visits by undiagnosed HAE patients per year
Range	2.6 – 4.7

Table 5.4.37 - Number of ER visits per year per undiagnosed HAE patient

Another seven publication reported the average number to be 2.9 visits per year for diagnosed patients as illustrated in Table 5.3.38.

# of sources	7
Sources	(Banerji, 2015), (Bernstein, 2013), (Blasco, 2013), (Bygum, 2014), (Javaud, 2015), (Nanda, 2015), (Petraroli, 2015)
Total # of patients	1,567
Weighted average	2.9 ER visits of diagnosed patients per year
Range	1.0 – 4.7

Table 5.4.38 - Number of ER visits per year per diagnosed HAE patient

5.4.8.4 Assistance by caregiver

Both on-demand and prophylactic treatments of HAE are administered intravenously or subcutaneously. This can become a challenge for pediatric, elderly or otherwise impaired patients, especially during an attack.

# of sources	1
Sources	(Aygören-Pürsun, 2014)
Total # of patients	164
Weighted average	52% of HAE patients use assistance by a caregiver
Range	-

Table 5.4.39 - Percentage of HAE patients using assistance by a caregiver

Aygören-Pürsün (2014) quantified (see Table 5.3.39) that about half the patients were using the assistance of caregivers which could be family members.

5.4.8.5 Tracheotomies

Laryngeal attacks and their resulting risk of causing death were discussed in section 5.4.2. The tracheotomy is an intervention of last resort to keep patients suffering a laryngeal attack alive.

# of sources	6
Sources	(Bouillet, 2013), (Bygum, 2009), (Javaud, 2015), (Psarros, 2014), (Roche, 2005), (Wilson, 2010)
Total # of patients	1,321
Weighted average	4% of patients
Range	2% - 10%

Table 5.4.40 - Percentage of HAE patients who had a tracheotomy performed on them

Six publications covering 1,321 HAE patients established that about one patient in 25 had undergone such intervention, as illustrated in Table 5.3.40.

5.4.8.6 Fatalities

The discussion in section 5.4.2 on laryngeal attacks possibly affecting HAE patients also highlighted the possibility of fatal outcomes. An HAE attack causing the death of a patient is the ultimate burden of the disease afflicting the family and society socially and economically. One group of studies illustrated in Table 5.3.41 reported such outcomes affecting 10% of undiagnosed HAE patients.

# of sources	3
Sources	(Agostoni, 2004), (Bork, 2012), (Winnewisser, 1997)
Total # of patients	833
Weighted average	10% of undiagnosed patients
Range	7% - 28%

Table 5.4.41 - Percentage of undiagnosed HAE patients who died due to asphyxiation

The second group of studies, illustrated in Table 5.3.42 reported that diagnosed HAE patients had a probability of a fatal outcome of 3%, suggesting that on average the risk of death could be reduced to less than a third by diagnosis and proper treatment.

# of sources	8
Sources	(Blasco, 2013), (Bork, 2015), (Bygum, 2014), (Karkasharif, 2015), (Kim, 2014), (Lei, 2011), (Zanichelli, 2015), (Zilberberg, 2011)
Total # of patients	1,960
Weighted average	3% of diagnosed patients
Range	0% - 6%

Table 5.4.42 - Percentage of diagnosed HAE patients who died due to asphyxiation

Some research indicated that zero diagnosed patients were succumbing because of an attack, possibly proving the great progress of modern therapy in improving QoL and preserving life itself.

5.4.9 Treatment in general

Section 3.8 mentioned that HAE can be treated on demand, when an attack occurs, or prophylactically with the aim to prevent attacks from occurring.

5.4.10 On-demand treatment of HAE

On-demand treatment is taken when an attack is occurring or about to occur. Effective on-demand treatment can make the difference between severe pain and loss of productivity, absenteeism or not. It may make the difference between death by asphyxiation or not in the case of a laryngeal attack.

5.4.10.1 Total percentage of HAE patients treating attacks

The thesis identified six studies which covered 1,073 HAE patients and reporting the treatment of attacks with on-demand drugs.

# of sources	6
Sources	(Banerji, 2015), (Bygum, 2014), (Caballero, 2014), (Howlett, 2019), (Nanda, 2015), (Wang, 2015)
Total # of patients	1,073
Weighted average	67% of HAE patients treated their attacks
Range	40% - 88%

Table 5.4.43- Percentage of HAE patients treating attacks

As illustrated in Table 5.3.43, on average 67% of patients treat their HAE attacks with on-demand treatment, confirming the medical need and the positive outcome.
Jain (2018) reported on surveys that have shown that patients sometimes are unwilling to administer rescue medications, preferring to use them only if an attack was "bad enough". For example, a US survey reported by Castaldo (2019) and conducted exclusively with patient members of the HAEi organization, reported that the 37.3 patients using only on-demand therapy leave 31% of their attacks untreated. Such behavior can be linked to the relatively high price of the medication. While the guidelines state that every attack should be treated, Federici (2018) reported in Italy that 21% of the attacks on average were not treated (Federici, 2018).

5.4.10.2 C1-inhibitors

The first category of on-demand treatment for HAE patients researched for this thesis is the C1-inhibitors.

# of sources	8
Sources	(Aabom, 2017), (Bygum, 2014), (Howlett, 2019), (Jolles, 2014), (Ohsawa, 2015), (Riedl, 2017), (Steiner, 2016), (Wilson, 2010)
Total # of patients	1,364
Weighted average	37% of HAE patients used C1-inhibitors to treat acute attacks
Range	6% - 75%

Table 5.4.44 - Percentage of HAE patients treating attacks with C1-inhibitors

Eight studies spanning different healthcare systems (illustrated in Table 5.3.44) were found measuring the use of C1-inhibitors for on-demand treatment of HAE attacks as illustrated in Table 5.3.44. The weighted average of over 1,364 patients suggests that 37% take C1-inhibitors such as Cinryze® or Berinert®).

The treatment with plasma-derived C1-inhibitors is also called “replacement therapy” as it replaces the protein in the body, which is causing the attacks. Nzeako (202) reported strong efficacy of this therapy, as 69% of the attacks responded with relief after 30 minutes and 95% after two hours, compared to only 12% after four hours by taking only a placebo. Studies also reported that 99% of laryngeal attacks improved within 30 to 60 minutes (Agostoni, 2004), and that the duration of an upper airway obstruction can be substantially reduced (Bork, 2001). Bork (2001) also reported that none of the patients who took C1-inhibitors on demand, required additional emergency procedures such as tracheotomies or cricothyrotomies. Overall, Craig (2013) also reported that early treatment with C1-inhibitors within six hours after the start of the attack leads to better treatment responses. These results confirmed the lifesaving impact these drugs can have. For example, in a later study, Bork (2008) showed that that treatment of non-life-threatening skin swellings with C1-inhibitors can substantially reduce the time to relief from 50h to 1h and the duration of attacks from 3.2 days to 1.7 days.

On the other hand, Prior (2012) reported that treatment with plasma-derived C1-inhibitors could also lead to adverse events and contraindications, such as from the potential transmission of infectious and/or pathogenic viruses, infections at injection sites or thrombosis associated with indwelling catheters. To minimize risks, and to ensure safety, Hemperly (2013) listed that for example in the US only licensed sources can collect plasma whereas each blood donor is tested for antibodies against human immunodeficiency virus (types 1 and 2), hepatitis C virus, and hepatitis B surface antigen. Additionally, specific nucleic acid tests and polymerase chain reaction assay for hepatitis A virus, hepatitis B virus, and hepatitis C virus, human immunodeficiency virus type 1, and human parvovirus are performed. to test all serologically negative plasma. This is then followed by pasteurization and nanofiltration.

5.4.10.3 Icatibant

Icatibant is synthetic decapeptide, structurally similar to bradykinin, which acts as a potent selective competitive antagonist of the bradykinin B 2 receptor and has been brought to the market (trademark Firazyr®) in 2008. Since then both patients and physicians had the opportunity to gain more than ten years of experience benefiting from this drug. Several studies and the Icatibant Outcome Survey (IOS) have analyzed the efficacy, the safety and its use since its launch (Andresen, 2019)

Table 5.3.45 illustrates the result of five studies over 714 patients indicating that about 23% of them use Icatibant to treat the HAE attacks on demand. The high variability of its usage is driven by the selection of the eligibility criteria and the primary objective of the different bodies of research.

# of sources	5
Sources	(Bygum, 2014), (Howlett, 2019), (Jolles, 2014), (Riedl, 2017), (Steiner, 2016)
Total # of patients	714
Weighted average	23% of HAE patients used Icatibant to treat acute attacks
Range	6% - 100%

Table 5.4.45 - Percentage of HAE patients treating attacks with icatibant

Lumry (2011) reported that Icatibant improved within two hours by 50% the symptoms of HAE such as debilitating pain and swelling in cutaneous and abdominal attacks. Cicardi (2010), on the other hand, reported with the FAST study that within 8-10 hours symptoms of HAE in cutaneous and abdominal attacks were completely relieved as reported by. Icatibant is administered by subcutaneous injection, which is preferred to intravenous therapy. Administration can more easily be taught to patients for home use, and Degan (2010) observed that adverse events associated with poor technique are minimal. A noted minor side effect persists in the form or injection site reactions (Banerji, 2013) which can be self-limited erythema, pruritus or pain in the injection area (Prior, 2012).

5.4.10.4 Tranexamic acid

Tranexamic acid is one of the older drugs which originally was used to treat HAE for prophylaxis, but with less efficacy and a less compelling safety profile (Prior, 2012). The average share of patients using this drug for on-demand use across six studies is 6%, as illustrated in Table 5.3.46.

# of sources	5
Sources	(Aabom, 2017), (Bygum, 2014), (Howlett, 2019), (Wilson, 2010), (Zanichelli, 2015)
Total # of patients	890
Weighted average	6% of HAE patients used tranexamic acid to treat acute attacks
Range	0% - 23%

Table 5.4.46 - Percentage of HAE patients treating attacks with tranexamic acid

5.4.10.5 Fresh frozen plasma

Fresh frozen plasma (FFP) has been used historically as the only therapy with the potential to arrest an acute attack and is still administered for acute treatment in healthcare institutions where modern treatments such as icatibant or C1-inhibitors are not available. Christiansen (2015) mentioned in her study, that because FFP is not virally inactivated, there is still a relatively high risk of transmitting infectious agents and blood-borne pathogens, exposing the patient to the risk of a blood-borne illness. C1-inhibitors, which are also plasma-derived, do not carry this risk as they are virally inactivated and nano-filtered. Agostoni (2004)

reported that FFP requires a larger dosing volume and therefore a longer infusion time, which can become an issue in emergency situations such as when there is imminent risk of asphyxiation during a laryngeal attack. Additionally, Hemperly (2013) associated FFP with several adverse effects, including urticaria, anaphylactic shock, and hemolysis. FFP is also known to potentially aggravate the severity of HAE attacks through an increase of bradykinin, alloimmunization, anaphylactic or allergic reactions, excessive intravascular volume with the risk of hypervolemia and heart failure.

# of sources	2
Sources	(Tachdjian, 2017), (Wilson, 2010)
Total # of patients	1,186
Weighted average	6% of HAE patients used FFP to treat acute attacks
Range	4% - 7%

Table 5.4.47- Percentage of HAE patients treating attacks with FFP

Kalaria (2014) additionally reported that 12% of patients being treated with FFP experienced a worsening of the attack, with 68% of these deemed related to the administration of the drug itself. Such a mixed profile explains why the two studies mentioned in Table 5.3.47 have reported relatively and significantly lower use of FFP by on average 6% of the HAE patients.

5.4.10.6 Other treatments

Ecallantide is an acute treatment available only in the US, with associated adverse events such as headache, diarrhea, pyrexia, nasal congestion, and an infrequent but serious risk of anaphylaxis (which made a commercial use in Europe not viable (Banerji, 2013). Due to the severe pain, pain relievers and narcotics are used as an alternative as well. Banerji (2013) reported the use of psychotropic medication to treat anxiety and depression. Hemperly (2013) also reported the historic acute treatment of HAE attacks being restricted to supportive measures such as intravenous fluids administration and pain management. Use of corticosteroids, epinephrine, and antihistamines, all not having efficacy for this ailment, had also been reported.

5.4.11 Prophylaxis treatment

While on-demand treatment aims to treat an immediately impending or already ongoing HAE attack, prophylaxis treatment aims to prevent the attacks from happening altogether. Longhurst (2010) reported that that patients' access to prophylactic treatment can reduce the severity and duration of attacks, improve QoL, reduces time off work, education or other social activities, while being safe. On the other hand, with prophylaxis treatment come additional burdens such as significantly increased frequency of drug intake by infusion or injection resulting in higher costs. Cicardi (2012) raised in his article that for these reasons, before deciding if to start a patient on prophylaxis, physicians, patients and payers should assess if the benefits outweigh the downsides, including also potential side effects. Riedel (2017) added as a factor the need for assistance at home in preparing and administering infusions, finding usable veins or getting the infusions to work properly. Reasons to switch to prophylaxis stem mainly from the overall burden of disease measured through attack frequency and the history of severe debilitating or life-threatening attacks. Daniel (2019) measured a reduction of attacks per year from 49 with no prophylaxis to four when taking C1-inhibitors following 19.7 months of therapy. Other factors driving a switch to prophylaxis can include the limited access to urgent care or the lack of efficient access to acute treatment – in these cases, prophylactic therapy could potentially be lifesaving.

5.4.11.1 Total percentage of patients using prophylactic drugs to prevent attacks

The thesis identified 15 studies over 2,719 patients and which measured to use of prophylaxis drugs. Virtually all studies were conducted in advanced healthcare systems where the diagnosis of the rare condition is established, and treatment is available.

# of sources	15
Sources	(Andrejevic, 2017), (Banerji, 2015), (Banerji, 2017), (Bouillet, 2011), (Bygum, 2014), (Federici, 2018), (Karkasharif, 2015), (Nanda, 2015), (Nygren, 2016), (Read, 2014), (Riedl, 2017), (Roche, 2005), (Wilson, 2010), (Zanichelli, 2010), (Zanichelli, 2015)
Total # of patients	2,719
Weighted average	56% of HAE patients take prophylactic HAE drugs
Range	16% - 94%

Table 5.4.48 - Percentage of HAE patients using prophylactic drugs to prevent attacks

The weighted average illustrated in Table 5.3.48 suggest that 56% of HAE patients follow a prophylactic HAE treatment. A US survey conducted exclusively with patient members of the HAEi organization reported 62.7% receiving prophylaxis therapy (Castaldo, 2019).

5.4.11.2 C1-inhibitors

C1-inhibitors (for example Cinryze®) are called "replacement therapy" as they replace the protein that is missing in the human body due to the genetic condition that defines HAE. Plasma-derived C1-inhibitors are very effective for acute and prophylactic treatment of HAE, while at the same time displaying a better safety profile than androgens. The most common side effects reported with C1-inhibitors include pruritus, rash, headache, lightheadedness, fever (Banerji, 2013), chills, faintness, vertigo, and paresthesia (Krassilnikova, 2008). A survey covering over 856 patients (taking the intravenous formulation of C1-inhibitors) through their treating physicians reported that only 0.6% experienced a thromboembolic episode (Kalaria, 2013).

# of sources	8
Sources	(Banerji, 2017), (Howlett, 2019), (Javaud, 2015), (Jolles, 2014), (Read, 2014), (Riedl, 2017), (Steiner, 2016), (Wilson, 2010)
Total # of patients	1,676
Weighted average	24% of patients
Range	0% - 94%

Table 5.4.49 - Percentage of HAE patients using C1-inhibitors to prevent attacks

Eight studies researching prophylaxis treatment have been identified as illustrated in Table 5.3.49. Combined over 1,676 patients on average they report a quarter (24%) of the HAE patients were using C1-inhibitors to prevent attacks.

5.4.11.3 Androgens

A relatively large number of studies (21) that included 5,415 patients was identified measuring the use of androgens for prophylaxis therapy, as shown in table 5.3.50. The average use of androgens was reported to be by 38% of HAE patients for prophylaxis. The variability is once larger and depending on the same factors as identified for C1-inhibitors.

# of sources	21
Sources	(Aabon, 2017), (Agostoni, 1992), (Andrejevic, 2017), (Aygören-Pürsun, 2014), (Banerji, 2017), (Bernstein, 2013), (Howlett, 2019), (Javaud, 2015), (Jolles, 2014), (Karkasharif, 2015), (Lei, 2011), (Levi, 2006), (Lumry, 2010), (Perego, 2017), (Psarros, 2014), (Steiner, 2016), (Tachdjian, 2017), (Wilson, 2010), (Zanichelli, 2010), (Zanichelli, 2015)
Total # of patients	5,415
Weighted average	38% of patients
Range	0% - 77%

Table 5.4.50 - Percentage of HAE patients using androgens to prevent attacks

5.4.11.4 Tranexamic acid

Tranexamic acid, an antifibrinolytic agent, that can be utilized as prophylactic treatment of HAE, despite its lower efficacy compared to androgens and the increased risk of thromboembolic events as reported by Bork (2001). Eight publications quantified their usage by HAE patients and reported it at around 8%, as illustrated in Table 5.3.51.

# of sources	8
Sources	(Aygören-Pürsun, 2014), (Javaud, 2015), (Levi, 2006), (Ohsawa, 2015), (Psarros, 2014), (Steiner, 2016), (Zanichelli, 2010), (Zanichelli, 2015)
Total # of patients	926
Weighted average	18% of patients
Range	1% - 50%

Table 5.4.51 - Percentage of HAE patients using tranexamic acid to prevent attacks

5.4.11.5 Lanadelumab

Lanadelumab (Trademark Takhzyro®) is a monoclonal antibody launched in the Summer of 2018 in the US and in early 2019 in Europe. Compared to the other described therapies, RWE is still limited, however, the clinical data from the HELP study has shown significant reductions in HAE attack rates compared to placebo (Banerji, 2019). Busse (2019) reported a reduction of the mean monthly attack rate of 62.5% vs. placebo as a result of the HELP study over 28 weeks. In the same study, a rollover over 132 weeks was performed as an open-label extension leading to a reduction of the mean attack rate by 94.9% vs. baseline. An important share of patients is achieving an attack-free state, 57% of patients after three months as reported by a survey (Castaldo, 2019). The HELP study also reported around 97% attack-free days as a result of the treatment (Inhaber, 2019). Patients who were not responders in the HELP study continued in an open-label extension (OLE) and reported improvements driving them to choose to remain enrolled (Jacobs, 2019). Riedl (2019) reported that patients who had used C1-inhibitors for prophylaxis previously, reduced on average attack rates by up to 98.9% thanks to the treatment with lanadelumab. In the third phase of the HELP study, it was also demonstrated that patients can achieve a “biological steady state” where the inhibition of plasma kallikrein suppresses the production of bradykinin, which prevents the triggering of HAE attacks (Wang, 2019).

5.4.11.6 Oral drugs

Oral kallikrein inhibitors (for example BCX7353) have been under development during the execution of the thesis. An oral mode of administration (for example one capsule daily) was a new proposition as it would provide more convenience and have been preferred by patients compared to an infusion or an injection. The ZENITH-1 Phase 2 study had shown significant improvements in reduction of attack severity and reduced need for on-demand treatment compared to placebo (Longhurst, 2019).

5.4.12 Other types of treatment

Historically and in healthcare systems with low disease awareness, the capability to diagnose and low access to modern medicine, corticosteroids and antihistamines had been and were still being prescribed. Agostoni (2005) reported these treatments to be usually ineffective, leading them to be part of the section on misdiagnosis and wrong treatments 5.1.2.2). A number of physicians have been reported in studies to prescribe pain relievers and narcotics mainly to mitigate the pain of HAE.

# of sources	2
Sources	(Bernstein, 2013), (Wilson, 2010)
Total # of patients	914
Weighted average	39% of patients
Range	32% - 46%

Table 5.4.52 - Percentage of HAE patients using pain relievers and narcotics

The two studies illustrated in Table 5.3.52 reported that close to 40% of patients were being prescribed pain relievers and narcotics, with the inherent risk of addiction (see the section on co-morbidities 5.4.7). The studies on comorbidities have highlighted the high prevalence of depression among patients suffering under HAE.

# of sources	3
Sources	(Bernstein, 2013), (Tachdjian, 2017), (Wilson, 2010)
Total # of patients	914
Weighted average	41% of patients
Range	20% - 55%

Table 5.4.53 - Percentage of HAE patients using psychotropics and antidepressants and narcotics

Three studies over 914 patients have reported about 41% of them were using antidepressants and narcotics, as illustrated in Table 5.3.53. These drugs possibly lead to additional burden and costs as a different set of healthcare specialists needs to be consulted.

5.4.13 Treatment costs

5.4.13.1 Cost overview

Although the per-patient treatment costs for rare diseases are often high, the perception that orphan treatments as a whole have an inordinate impact on total pharmaceutical expenditures and health care costs is inaccurate. As discussed in section 3.7.1, rare diseases affect about 8–10% of the population. EvaluatePharma (2015) analyzed the overall market and reported that orphan indications represented less than 10% of the pharmaceutical expenditures and only 1% of the total healthcare expenditures. Despite this, Lumry (2018) noted that it appeared that payers in the US and around the world, healthcare authorities put an inordinate number of barriers to limit the use of specific therapies for new diseases. Federici (2018) analyzed the composition of total treatment costs and reported that drug type was the most relevant cost driver. However, the share of the different cost drivers could vary significantly, as Wilson (2010) explained that more efficacious treatments result in fewer inpatient and outpatient costs, leading the drug costs to contribute proportionally higher to the overall cost. Wilson also reported that ER visits and hospitalizations were major contributing factors to the cost of treating and managing HAE. One study also included the drug costs and severity of attacks as main drivers of cost and resource use (Bhasin, 2014). Rasmussen (2016) reported the cost of emergency department visits and hospital admissions to account for 68% of the costs when treating a patient with severe HAE.

5.4.13.2 Direct vs. indirect costs

There are two types of costs: (A) Direct costs such as treatment costs (drugs, interventions, e.g. tracheotomies), hospital ER visits, primary care visits, specialist visits, hospital admissions, ICU admissions or also some nonmedical costs such as transportation to the hospital/ER that can be directly linked. (B) Indirect costs are defined as those incurred from labor productivity losses (e.g. patients' or caregivers' working hours), costs of missed workdays or cost of missed school days. In case of death, indirect costs also include the labor costs of lost labor, estimated by multiplying the years the patient could no longer work and contribute to the national wealth. Indirect costs are difficult to generalize and quantify as they can be individual and depending on life choices that have also an impact on QoL. For example, even between attacks, patients and caregivers might change their behaviors, might incur in additional costs to be close to acute treatment infrastructure, or might miss out on income-generating opportunities due to the burden of HAE.

5.4.13.3 Cost factors in HAE

With increasing severity of the condition, the costs of treatment increase dramatically. Banerji (2013) reported annual treatment costs in Europe increased from mild to moderate to severe from USD 14,400, to USD 26,900 to USD 96,500 respectively. Wilson (2010) reported similarly for the US the figures USD 3,700, USD 9,800 and USD 76,400 respectively. Castaldo (2019) conducted a survey exclusively with patient members of the US HAE patient organization and reported that patients on acute treatment only incurred direct medical costs (treatment, ER, and co-morbidities) of USD 364,500 and indirect costs

(missed work, reduced wages, under-employment) of USD 52,600 for a total of USD 417,100 per year. The major drivers that exponentially drove the costs with increasing severity were caused by additional needs for ER and hospitalizations.
The attacks that concerned HAE patients the most were the potential fatal laryngeal attacks. Zilberberg (2010) estimated that in the US every hospitalization cost on average USD 4,000. Manson (2013) attempted to quantify in more detail the costs and reported that, in addition to the cost of an ER visit, there could be costs resulting from intubation of USD 146 and artificial respiration of USD 14,809 for less than 96 hours, which could leap to USD 32,709 if more than 96 hours were needed.

5.4.13.4 Lifetime costs of HAE

ICER (2018) calculated the average total lifetime direct costs for a patient with no prophylaxis to be around USD 9.95 million (mainly driven on-demand drug costs, but also USD 750,000 for ER visits, hospitalizations, and emergency procedures for those with laryngeal attacks). Patients who received prophylaxis treatment incurred lifetime costs between USD 10.3 million and USD 14.4 million depending on the treatment chosen. Depending on the prophylaxis drug, patients needed more or less on-demand treatment. Over a lifetime, patients taking C1-inhibitors consumed USD 4.6 million on additional on-demand treatment and USD 1.2 million if on Takhzyro®.
Using QALYs, the same analysis reported lifetime QALYs of 17.5 without prophylaxis and between 18.2 and 18.7 for patients taking prophylaxis treatment. Such differences combined with the cost differences between treatments could lead to incremental cost-effectiveness ratios ranging from USD 0.33 million to USD 5.95 million per QALY. Over a lifetime, patients had been estimated to experience 1,703 acute attacks without long-term prophylaxis, and between 223 attacks for patients receiving Takhzyro® and 843 for patients receiving a C1-inhibitor. Combining with the lifetime costs of the different therapies, this would lead to incremental costs per attack avoided between USD 273 and USD 5,168 depending on the therapy selected (ICER, 2018).
The thesis identified five publications which quantified the yearly treatment costs for HAE patients based on the type of therapy that they follow, as illustrated in table 5.3.54.

	On-demand	Prophylaxis	
	Not defined	C1-inhibitors	Androgens
Sources	(Banerji A. , 2013), (Manson, 2013), (Bhasin, 2014)	(Rasmussen, 2016), (Lumry W. R., 2018)	(Rasmussen, 2016)
Average (USD)	38,790	334,915	494
Range (USD)	16,108-93,194	182,829-487,000	494

Table 5.4.54 - Yearly HAE treatment costs by type of therapy

HAE patients that treated attacks only when they occurred, generated average yearly treatment costs of around USD 39,000. Patients that took prophylaxis medication aiming to

reduce or eliminate attacks from occurring, generated average yearly treatment costs of USD 335,000.
In addition, HAE patients that had access to modern treatment options were still at risk of requiring hospital treatments, as described in section 5.4.8.1), for example in case of severe attacks. Bouillet (2011) reported an average annual cost for hospital treatments at about USD 5,000 in selected European countries, while Lumry (2018) reported USD 8,134.
In section 5.4.3 different degrees of severity of HAE attacks have been analyzed. Two studies that quantified the dependence of the yearly treatment costs on the severity of the condition have been identified and the results illustrated in Table 5.3.55.

	Severity of condition		
	Severe	Moderate	Mild
Sources	(Banerji, 2013), (Lumry, 2018)		
Average (USD)	92,600	21,600	9,900
Range (USD)	76,400-104,900	9,800-28,800	3,700-14,400

Table 5.4.55- Yearly treatment costs by the severity of the HAE condition

These studies indicate that treatment of patients with a severe form of the condition could cost up to tenfold compared to the mild form.
Zilberberg (2010) attempted to quantify the average hospital and ER cost per attack depending on the severity and reported USD 65,500 for severe attacks, USD 5,000 for moderate and USD 600 for mild ones. These publications measured the direct healthcare system costs. Lumry (2018) additionally attempted to measure indirect costs, quantifying the reduced productivity to cost the patient USD 5,200 p.a., the reduced income USD 6,400 p.a., and the impact of missed work USD 4,300 p.a.

5.4.13.5 Payers perspective and their concept of value

In the section 3.1.16 on EBM, the shared decision-making between physician and patient was discussed against the background of agency theory described in section 3.6 with the role of the payer described with the double agency theory detailed in section 3.6.4. The disconnect between the three parties became obvious when on one side physicians and patients selected therapies that provided clinical outcomes and convenience, but on the other hand, payers were not concerned about ease of use or convenience. As long as treatments cost the same, mode of administration and convenience (for example through less frequent dosing or less painful administration) were perceived as added values freely available. However, when pharmaceutical companies began to demand a higher price for more innovative modes of administration (for example oral administration instead of subcutaneous, or biweekly instead of daily dosing), misalignment arose. Payers were interested in and were ready to fund solutions that limited costs and ideally kept the patients out of the costly ER. Therefore, payers could also question the value of expensive prophylaxis therapy with fewer side effects, if on-demand treatments achieved the same objective.

5.4.13.6 Challenges from novel treatments

Over the past few years, there has been a rapid increase in drug development and launches which brought many benefits to the patients and all stakeholders, as described in sections 5.4.10 and 5.4.11. These novel treatments could reduce the burden of the condition while at the same time decrease the need for emergency treatments and hospitalizations. However, Lumry (2018) pointed out that these modern life-changing and potentially life-saving therapies were much more expensive and raised concerns with payers leading to access and reimbursement limitations. The orphan status described in section 3.7.3 may not always have been considered in economic analyses, resulting in orphan treatments not being deemed cost-effective and the treatment not reimbursed. Pharmaceutical companies needed to consistently emphasize the orphan status of their innovative drugs when submitting to the payers the value dossiers with the intention of obtaining reimbursement for their patients. Kanavos (2018) reported that the consideration of orphan status may have contributed to US long-term prophylactic therapies for HAE to cost more than USD 30,000 per month, adding up to annual costs of more than USD 400,000. Such costs were well above the threshold of USD 150,000 which had usually been used as an upper bound for the cost-effectiveness of treatments. It has been estimated that 70% of the 6,500 HAE patients in the US were being treated with long-term prophylaxis, suggesting total yearly costs of close to USD 2 billion for drugs alone.

5.4.13.7 Implications on costs, reimbursement and prices

ICER (2018) analyzed the reimbursement procedures of US private payers and reported that all require a confirmed diagnosis of HAE. Most additionally require that patients suffer a minimum number of attacks per month, before they can be prescribed and reimbursed prophylaxis treatment (for example Aetna specifies that the patient must at least one attack per month, Cigna at least two attacks per month, Health Net more than one severe event per month or be disabled for more than five days per month).

EvaluatePharma (2015) estimated that in the US the total expenditures on orphan drugs represents less than 10% of pharmaceutical expenditures and only 1% of the total healthcare expenditures. Schey (2011) quantified the share of orphan drugs to be 3.5% of the total pharmaceutical market, suggesting that their impact on the budget is limited and that fears that their expenditures will be unsustainable in the long run are not justified. Despite these facts, Lumry (2018) analyzed the HAE situation and determined that payers and healthcare authorities sometimes perceive orphan drugs to cause an excessive economic burden on their payment systems and put barriers in place to limit the use of new disease-specific therapies. Over the past years, there has been a wave of high-cost orphan drugs which augmented the payer's sensitivity to cost, resulting in increased formulary restrictions (Hyde, 2010). Cohen (2014) found that orphan drugs appear to have more reimbursement restrictions than non-orphan drugs. These restrictions could be in the form of requiring additional diagnostic tests before the drugs can be prescribed, to ensure the patient positively has the condition justifying the expensive medicine, or additional clinical data, authorizations or approvals before reimbursement is given. Bennett (2013) observed that in the Netherlands in some

cases healthcare authorities asked pharmaceutical companies to voluntarily reduce prices to 'acceptable' price levels.

5.4.13.8 Challenges during the review of new HAE treatments

A dilemma arises when physicians and patients are keen to get access to a new promising drug, but long-term data does not yet exist. Agboola (2019) reported that for example when reviewing Takhzyro®, the CTAF panel decided that the evidence at the time of the meeting was not yet sufficient to prove that the drug's net health benefit is superior to on-demand therapy only, when used as indicated for the long term. This was justified by the fact that the trials, which lasted 4-26 weeks, were not sufficiently long to prove the treatment's long-term effectiveness and safety (ICER, 2018). The comparison of HAE drugs led to the following results for acute treatments. Reimbursement decisions for HAE treatments became difficult when modern treatments were introduced into the market. These modern treatments were the results of significant research and development, producing significantly improved results, but not having any meaningful comparator to demonstrate cost-effectiveness. For example, fresh frozen plasma used to be the only treatment for acute attacks of HAE (it was still being used in countries where modern drugs were not yet available). As discussed in section 5.4.10, FFP had questionable efficacy, imposed risks, had to advantage of being low cost, but did not even have the explicit indication for the treatment of HAE attacks. The guidelines at the time recommended physicians prescribing licensed treatments rather than FFP and a comparison of cost-effectiveness with modern treatments was impossible. Additional challenges for HAE treatments occurred when dosing of one drug was weight-dependent (for example Berinert®), while the other one was not (for example Firazyr®). Sabharwal (2013) assessed that depending on the weight of the patient one drug could become cost-effective while the other did not and vice versa. While some computation suggested Berinert® to be more cost-effective, it did not take into account that in real life, once a vial had been opened, all medication that had not been administered had to be discarded, as it could not be kept in sterile conditions until the next attack. This wastage did not occur with weight-independent dosing of Firazyr®. Therefore, for the cost-effectiveness comparison, the full cost of every opened vial needed to be factored in, and not just the amount infused.

5.4.13.9 Additional challenges with prophylaxis HAE treatments

For prophylaxis treatment, the situation was different, requiring the inclusion of more considerations. The cost-effectiveness of prophylactic treatments needed to be compared between themselves and with the costs of on-demand treatment that could be avoided by reducing acute attacks. Prophylactic treatments for HAE must be administered regularly resulting in substantial treatment costs. Attacks, hospitalizations and ER visits may be partially or even completely offset, but even combined, these were unlikely to outweigh the costs of treatment which can exceed several hundreds of thousands of dollars per year. ICER (2018) compared the three most prescribed prophylaxis drugs in the US (Cinryze®, Haegarda® and Takhzyro®) and benchmarked them against the commonly accepted willingness-to-pay thresholds between USD 50,000 and USD 150,000 per QALY. Cinryze®

would have cost USD 5.95 million per QALY, Haegarda® USD 0.33 million per QALY, and Takhzyro® USD 1.11 million per QALY. Clinical trials and current pricing provided the following comparison:

	% reduction # attacks	% attack free	USD per dose	Source
Cinryze®	-50.5%	18.2%	$2,012	(Zuraw, 2010)
Haegarda®	-84.0%	40.0%	$2,090	(Longhurst, 2017)
Takhzyro®	-86.9%	44.0%	$16,520	(Banerji, 2017)

Takhzyro®, a monoclonal antibody and the latest prophylaxis drug for HAE, had a label for an initial biweekly administration which resulted in more than USD 1 million per QALY. However, clinical data and the FDA label also indicated that once patients reach a steady state of prophylaxis, measured in having been six months attack free, they could move to every four-week dosing. Such a switch may have been considered for about 87% of patients and the halved consumption would make consumption of Takhzyro® more cost-effective than existing treatments (ICER, 2018). An ICER analysis confirmed that long-term prophylaxis with these modern drugs resulted in fewer acute attacks and improved QoL, yet all three were estimated to be well above the threshold, and therefore should not be prescribed or reimbursed.

5.4.13.10 Impact of disease variability

HAE is highly variable and if a patient had a more significant QoL reduction due to the number of attacks and the clinical outcome of the treatments was the same, then cost-effectiveness may have been achieved. ICER (2018) also reported that decision-makers needed to be aware that even minor adjustments in the key assumptions (e.g., frequency of attacks) could have resulted in substantially different cost-effectiveness results. For example, when changing the base assumptions of the number of attacks per month from 3.52 to 3.32, the cost-effectiveness of prophylactic treatment with Haegarda® would have increased from $50,000 per QALY to $500,000 per QALY. Another assumption that played an important role was dosing. Takhzyro® can be dosed every two weeks or every four weeks depending on the patient's profile. Assuming 75% of eligible patients could switch to the less-frequent dosing would make the drug meet the cost-effectiveness thresholds. Concretely for these drugs, Agboola (2019) used the above cost-effectiveness threshold to determine that Haegarda® would have become cost-effective at a monthly baseline attack rate of 3.43, compared to Takhzyro® at 3.78, and Cinryze® at 5.85. From a payer perspective, this meant that only patients that had more than 3.43 attacks should have been prescribed modern prophylaxis with Haegarda® and accordingly for the other treatments. Zuraw (2019) reported that in real life and with the reported frequencies of attacks reported in section 5.4.4, for the majority of HAE patients, approved prophylactic medications would not be cost-effective. Agboola (2019) also reported that when a panel assessed the clinical benefits of the three drugs, it determined that all significantly reduced the number and severity of HAE attacks without significant adverse events. However, on average and at

current pricing, all three were judged to represent low or intermediate long-term value for money. In other words, the treatments would have needed to be priced substantially lower than the then-current net price to reach cost-effectiveness thresholds. ICER (2018) reported that for Cinryze® to achieve a QALY threshold cost of USD 150,000, a price discount of approximately 60% from the list price would have been necessary. The same analysis showed there was no difference in survival among the different prophylaxis treatments, since death had become a rare outcome with appropriate treatment and the correct use of on-demand drugs.

5.4.13.11 Patient perspective

Patients are not only affected by their conditions causing a burden on life. Depending on the healthcare system the burden extends into a financial burden due for example to deductibles and co-payments. The meta-analysis on the payers' perspective in section 5.4.13.5 and the review of the HAE treatments from a cost perspective in section 5.4.13.8 explained the possibility that patients may have been denied access to certain orphan drugs, if the payer decided not to reimburse them or if they have not yet been reviewed. In some cases, depending on the healthcare and reimbursement system, treatment might have been technically approved and reimbursed. However, patients needed to navigate their insurance systems to obtain coverage, which could cause delays. In some cases, insurers demanded evidence (such as the patients having been reportedly symptomatic or providing laboratory data) before funding the required treatment. To help bridge the time until the drug is given and funded, some pharmaceutical companies supported the patients with access programs which could include free of charge drugs (ICER, 2018). Despite such programs, Sanger-Katz (2018) reported that more than a third of seriously ill patients had spent all or most of their savings due to their conditions, even with health insurance. The same research also suggested that over half of the patients had faced financial difficulties due to the compounding burden of medical bills and due to work interrupted by illness. Calculations estimated going to the hospital could mean an average income reduction of 20% that persisted for six years or more. Section 5.1.3 showed data in line with the concept that debilitating chronic conditions affect also family members and caregivers. Such indirect impact may result in those taking care of ill relatives also facing financial challenges. Sanger-Katz (2018) reported in this context from the US that, as a result of caring for an ill person, 23% of friends or family members ran into financial strain, and 15% had to quit or change their jobs.

5.4.14 Quality of life

Since treatments had become available during the last decade, QoL has substantially improved. Anderson (2019) reported that highly effective HAE therapies have influenced the guidelines to increasingly emphasize QoL as a key aspect of HAE management. Christiansen (2015) reported that despite the rapid and significant treatment advancements, a substantial burden of illness still remained.

5.4.14.1 Measures of QoL

Numerous studies analyzed in the sections from 5.4.1 to 5.4.5 have described the significant clinical burden that HAE patients carry, despite the considerable progress of treatment options. Banerji (2015) conducted a QoL analysis on HAE patients to prove that improvement in the care was still needed. The psychological burden was significant due to the immediate impact of attacks and the psychological impact of living with a chronic unpredictable disease. This burden could be deducted from the high prevalence of comorbidities such as anxiety and depression discussed in section 5.4.7, largely stemming from the constant fear of the next attack. It could be supposed that HAE patients have a lower QoL than the general population, and possibly so inversely proportional to the increasing severity and frequency of the attacks. Banerji (2015) reported from Europe that QoL worsened when patients were exposed to more than five attacks per year. Devercelli (2018) reported from a survey that 86% of patients perceived that more than three-quarters of their attacks were severe enough to negatively impact their QoL. These publications suggested that QoL scores were generally lower with patients with a higher number of attacks and with patients whose most recent attack was laryngeal. Lumry (2018) advanced a hypothesis from his data that QoL is not only a relevant measure in its primary purpose, quality of life, but should also be seen as the single most meaningful way to measure how well a prophylactic treatment for HAE worked.

5.4.14.2 Differences and inconsistencies across QoL measures

Agboola (2019) compared QoL measures across trials and reported that they were used infrequently and inconsistently, and none of the trials used a QoL measuring instrument specific to HAE. This could explain why Gomide (2013) could not measure any difference in relation to gender, age, education level, or disease severity when using the SF-36 instrument. In sections 3.4.5 and 3.4.6 the thesis determined that to measure the QoL impact of the symptoms and the treatment of a disease, tailored instruments are required. Historically such instruments had not been in existence for HAE, therefore some scholars used other questionnaires to measure the impact of treatments, such as DLQI (a validated dermatology QOL questionnaire) or more general QOL assessment tools such as the SF-36 (Bygum, 2009). In his work on HAE, Lumry (2019) utilized yet other instruments such as the HADS (Hospital Anxiety and Depression Scale), the WPAI (Work Productivity and Activity Impairment) or the TSQM (Treatment Satisfaction Questionnaire for Medication). Nordenfelt (2017) utilized a combination of different QoL instruments such as HR-QoL: EQ-5D-5L, RAND-36, AE-QoL to gain comprehensive information. This approach raised the risk of introducing redundant questions, and significantly increasing the amount of work

for the patients and the treating physicians. A next step in order to develop appropriate QoL measurement tools took place when researchers leveraged surveys which had measured different aspects such as anxiety, depression, stress, and other concerns regarding the HAE attacks, the methods of administration, or the ability of patients to infuse or inject themselves the medication (Wang, 2015). They grouped the impacts by physical manifestations, ability to perform daily roles, emotions, social life, appearance and morbidity to better understand how HAE patients are affected in their QoL. Anderson (2019) conducted qualitative interviews to identify concepts that characterized the QoL of patients with HAE, and which were used to compare different treatments from the patient's perspective.

5.4.14.3 AE-QoL, a QoL measure specific for angioedema

Weller (2016) described the development of a questionnaire specific to angioedema called AE-QoL (Weller, 2016). AE-QoL was developed to cover 17 items and to be self-administered by HAE patients, with each item measured over a five-point response scale ranging from 1 (never) to 5 (very often). This questionnaire, when completed, provided an overall score plus four domain scores that were regarded as relevant: (A) Functioning, measuring the impairment of work, physical activity and social relations, (B) Fatigue and mood, measuring the difficulties in falling asleep, waking up during the night, feeling tired during the day, challenges in concentrating or feeling down; (C) Fear and shame from having swellings and the shame of visiting public places, measuring the embarrassment by the appearance during attacks and the fear of possible long-term negative drug effects, (D) Nutrition, measuring the limitations in the selection of food and beverages that can be consumed. Weller (2016) also reported the total AE-QoL score to be proportional with the disease activities and, while being sufficiently sensitive to changes within patients over time, making it a valuable tool to assess changes of QoL impairment over time or due to treatment.

5.4.14.4 Burden during HAE attacks

For this section, the thesis researched data on day-to-day life implication resulting from the suffering of HAE. The HAE patient organization HAEi (2015) reported that more than 80 per cent of the patients who experience severe attacks reported dysfunctions and pain which impacted the time they would utilize for daily activities. Seven studies on cumulatively more than 1,500 patients measured that on average patients miss almost seven weeks of working- or school days per year due to HAE attacks, as illustrated in Table 5.3.56.

# of sources	7
Sources	(Aygören-Pürsun, 2014), (Bernstein, 2013), (Jolles, 2014), (Lumry, 2010), (Petraroli, 2015), (Tourangeau, 2012)
Total # of patients	1,529
Weighted average	32.8 working or school days lost per year
Range	7.1 – 128.5

Table 5.4.56 - Working- and school days lost per year due to HAE attacks

Included in the number of working and school days lost reported in Table 5.3.56 was at least half a day per attack necessary to travel to a medical facility for acute treatment. Lumry (2010) reported in his research over 457 patients that on average they missed 3.3 days per attack. When asked about their most recent HAE attack, 51% of all patients who were employed missed at least one day of work, 44% of students missed at least one day of school, and 59% of respondents reported that they did.

# of sources	4
Sources	(Aygören-Pürsun, 2014), (Bernstein, 2013), (Nordenfelt, 2014), (Ohsawa, 2015)
Total # of patients	895
Weighted average	38% of patients of HAE patients missing work or school days due to attacks in a year
Range	29% – 56%

Table 5.4.57 - Percentage of HAE patients missing working- and school days due to attacks

Four studies over combined close to 900 patients reported that 38% of patients on average missed working- or school days due to their HAE attacks as reported in table 5.3.57. However, the picture appeared more differentiated: Bonner (2015) reported that some patients learned to cope with milder attacks in order not to let them affect their life too much. Caballero (2014) reported that the impact of HAE on daily activities did not vary significantly by which part of the body was affected. In section 5.4.10 data was analyzed highlighting that a number of attacks were left untreated. While they there less visible to the health-care system (no drugs consumed, no health care services used), they can still be disabling and disrupt work, education and family life (Manson, 2013), as when patients suffer an attack, often they are unable to perform and are forced to take time off from their activities (Bygum, 2015). Longhurst reported that in ERs, patients with HAE attacks may not have been prioritized over competing emergencies (e.g. heart attacks, stroke or severe injury) which led to further delays and absenteeism.

5.4.14.5 QoL impact of treatment

Lumry (2014) measured QoL using the SF-36 instrument during a clinical trial with patients taking C1-inhibitors or placebo. Patients who took C1-inhibitors scored the best. Nordenfelt (2017) however relativized these results and reported that QoL was not significantly affected by prophylaxis. QoL was mapped against disease activity and increased disease activity was associated with a deterioration of the QoL, independent of which the patients were on prophylactic treatment or not. This more differentiated results suggested that it was not so much the treatment per se which reduced QoL, but rather the effect of reduced disease activity when taking the treatment. Kavalec (2013) compared the QALY increase of two C1-inhibitors, Ruconest® and Berinert® and reported for both virtually identical QALYs gains vs. placebo.

On the other hand, treatments do not lead only to improvements. Current modern therapies for HAE such as C1-inhibitors are in the form of a subcutaneous injection or intravenous

infusions (the first oral medication is expected towards the end of 2020). Riedl (2016) reported in a study on a C1-inhibitor that the most common adverse events were injection site reactions (reported by 84% of patients), fatigue (9%) and headache (5%).
All mentioned studies implicitly presumed or did not raise the question if patients could be treated differently. Jain (2018) reviewed dialogues between patients and doctors during the assessment phase in order to determine and decide the treatment. Communication gaps between physicians and patients when discussing the burden of the disease where identified, remained. As discussed in the context of the agency theory in section 3.6.7, they pose a hurdle to achieve the optimal clinical outcome and a better QoL.

5.4.14.6 HAE Burden on health and productivity

In section 5.4.1 the thesis analyzed the significant delay between onset of disease and diagnosis. This delay leads to high anxiety and uncertainty in addition to the unmet medical need of patients suffering under the attacks. During the period where patients have HAE attacks but no diagnosis, they don't know what condition they have, and are likely getting the wrong treatment that either does not work or possibly creates an additional burden. Even after diagnosis and with correct treatment (described in sections 5.4.10 and 5.4.11) patients continued to experience attacks, maybe with lesser frequency and lower severity. Banerji (2017) reported that a substantial burden affecting the HAE patient persisted. In his work, Lumry (2010) had already confirmed that the QoL of HAE patients was significantly impacted by the episodic and chronic nature of the disease, their overall mental and physical health scores were significantly lower than for the normative populations. In his study, Bernstein (2013) concluded that patients living with HAE displayed significant decreases in physical and mental health, impaired work productivity, and a significantly greater amount of depression.

5.4.14.7 HAE leading to lost opportunities and missed activities

Along the same line, Bygum (2014) reported that the significant psychological impact of the HAE condition restricted the lives and the activities in more than half of the patient population. Gomide (2013) summarized, using the QoL questionnaire SF-36, that the most affected domains which impaired the life of the patients were related to vitality. The thesis identified only a few studies that quantified the amount of time lost by HAE patients. Zhi (2018) performed research on 159 HAE patients and determined that 96% lost, on average, 21 days of social life per year due to their HAE condition. These patients could not participate in social activities due to intensive pain, fear of attacks, or to avoid the embarrassment resulting from the disfigurement in case of swellings of the face. Caballero (2014) quantified by type of HAE attack how many hours of daily activities are prevented. HAE attacks at the face, neck and abdomen impacted between two and four hours, attacks affecting the airways, genitals, or extremities could take between 4-12h, and if more than one site was affected, then the impact increased. The QoL factors that constrain the life of patients have been further analyzed and research has determined that 53% of patients develop a phobia of not having drugs available when they would get the next attack. 48% of HAE patients feared possible death at the next laryngeal episode. This fear was driven by

the possibility of not being able to reach the next ER or hospital in time in the event of a laryngeal attack (Bygum, 2015). Patients may be well taken care of where they normally live. However, when traveling, they might encounter situations during an attack where a competent physician is not available, where they have to articulate to a foreign healthcare professional who is unfamiliar with the disease their condition and how it should be treated. Agostoni (2004) reported that such additional anxiety prevented HAE patients from traveling altogether.

5.4.14.8 HAE impact of family life and future outlook

One-third of the patients admitted having problems in the family due to anxiety, fear, feelings of guilt and psychological stress. The combination of fear and feelings of guilt led 50% of the HAE patients to avoid marriage. 44% of patients avoided trips away from home and 47% reported problems in their social lives. Hirose (2017) reported HAE patients in Japan having a fear of genetic discrimination, highlights a broader challenge for all rare diseases.

Psarros (2014) reported that HAE impacted children and adolescents, for example when 20% of them selected sports and activities with a reduced risk of injury. The study also found that 30% were frequently absent from school, and that 22% felt marginalized because they could not participate in certain school activities.

On the other hand, Lumry (2014) measured the MCS (Mental Component Score) when administering a QoL questionnaire, enabling the observation that a significant share of patients was not lacking impairment, had learned to cope, and have accepted the burden of having HAE as a regular part of their life. While coping was the only option before efficacious treatments existed, currently, a better outlook could be provided to patients living with HAE. Christiansen (2015) compared the negative psychological and emotional impact that HAE had on patients before and after having had access to prophylaxis treatment in the form of C1-inhibitors. The study reported that 53% of patients suffered before or without treatment, and 17% did so with HAE treatment. Bewtra (2012) had already reported earlier that having a treatment available made more than half the HAE patients feel better and gave more than 80% of patients a better outlook on the future, feeling more secure about the danger of life-threatening attacks.

The most modern treatments recently launched, for example, Takhzyro® discussed in section 5.4.11.5, opened new opportunities and appeared to offer a possibility of a life with zero attacks for many patients. Zuraw (2019) stated that this could be the first time since the existence of the condition, that HAE patients could hope and possibly expect to live normal life.

5.4.14.9 Burden on career and education

In addition to the effects of the HAE attacks themselves discussed in the sections 5.4.1 to 5.4.5, HAE patients are additionally exposed to comorbidities (see section 5.4.7) and intensive use of healthcare services (see 5.4.8). All of these take a direct toll on the time that patients can spend on work and education. HAE is a chronic, debilitating, disfiguring condition, and therefore can affect all aspects of a patient's life. For example, when attacks affect the feet, HAE patients cannot wear shoes, when the hands are concerned, simple tasks such as typing on a computer can become impossible (Banerji, 2013). Bernstein (2013) reported that half the HAE patients missed 47 days of work on average per year. Such figures were significantly higher than migraine sufferers (7 days per year) or severe asthmatics (10 days per year). Jolles (2014) reported a rage for absenteeism between zero to 43 days. The large variance might have depended on the cohort, the eligibility criteria, or the healthcare systems which display different processes and criteria for patients having access to certain types of treatment. With many patients experiencing HAE work and activity impairment, the impact was observed not only on immediate lost work, education and leisure. Education and long-term career perspectives were negatively impacted as well. Manson (2013) observed that multiple family members were also likely to be affected as HAE is hereditary, which further compounded the issue. Lumry (2010) conducted a survey in the US, reporting that 69% of HAE patients were excluded from certain jobs due to their illness, 48% reported that it had hindered their education, and 58% that it inhibited their career advancement. Even when HAE patients were attending their work or education duties, they were often less productive and unable to achieve the educational and career goals, compared to if they were healthy (Lumry, 2018).

Three pieces of research on a combined 1,078 patients reported that on average 44% of them believed that they suffered from hindered education due to their condition, see Table 5.3.58.

# of sources	3
Sources	(Aygören-Pürsun, 2014), (Bernstein, 2013), (Lumry, 2010),
Total # of patients	1,078
Weighted average	44% of HAE patients suffered from hindered education
Range	41% - 48%

Table 5.4.58- Percentage of patients suffering from hindered education due to HAE

Two of the studies over 621 patients reported that three patients out of five were not applying to certain positions and roles due to their conditions, suggesting reduced freedom in their professional life (illustrated in Table 5.3.59).

# of sources	2
Sources	(Aygören-Pürsun, 2014), (Lumry, 2010),
Total # of patients	621
Weighted average	61% of HAE patients were not applying for a certain job due to the disease
Range	40% - 69%

Table 5.4.59 - Percentage of patients not applying to certain jobs due to HAE

This limitation might have been a contributing factor to half the HAE patients reporting their careers were not advancing due to their condition, as illustrated in Table 5.3.60).

# of sources	2
Sources	(Aygören-Pürsun, 2014), (Lumry, 2010)
Total # of patients	621
Weighted average	52% of patients
Range	36% - 58%

Table 5.4.60 - Percentage of patients prevented from advancing their career due to HAE

Lane (2012) reported in his research examples of HAE patients being involuntarily discharged from the army, having had to leave a job because the working environment generated triggers (e.g. fumes in a refinery), having had to work for a family member as only they fully understand the disease and the impact of attacks, living in seclusion because minor events could trigger attacks, or needing to live and work within short distance of a hospital due to frequent attacks (Lane, 2012). In his research on 457 HAE patients, Lumry (2010) determined that 16% of them were unable to work full time. Two studies illustrated in Table 5.3.61 reported that 12% of HAE patients had lost their last position due to HAE, and one study by Aygören-Pürsun (2014) found that another 9% of HAE patients had to change their jobs due to the condition.

# of sources	2
Sources	(Aygören-Pürsun, 2014), (Psarros, 2014)
Total # of patients	280
Weighted average	12% of HAE patients left or lost their last position due to HAE
Range	10% - 14%

Table 5.4.61 - Percentage of patients who left or lost their last position due to HAE

Weller (2012) observed and reported that HAE patients with recurring attacks were being perceived to be unreliable, confirming it to be a possible contributing factor to the challenge of advancing their career progression. Aygören-Pürsün (2014) reported a correlation

between attack frequency and the likelihood of HAE patients not applying for certain jobs, leaving jobs, or switching jobs.

5.4.14.10 Caregivers

The role and the impact of caregivers on HAE patients was discussed in sections 5.4.9 and 5.4.13.11 in the context of treatments and costs. Aygören-Pürsün (2014) reported that on average 52% of HAE patients receive assistance from a caregiver, with 69% of the patients with severe pain requiring such help. These results suggested that family and friends of HAE patients also need to be included when studying QoL implication of the disease. For example, when HAE patients have an attack with severe pain, their caregivers often miss time from work or activities to assist them. Longhurst (2016) reported that that absenteeism of caregivers was comparable to that of HAE patients.

When the patients are children, the lives of the parents are particularly impacted. Nygren (2016) recorded that the parents of 73% of the children with HAE had taken parental leave to care for their children when they had attacks. In addition to the time that has to be given, for the caregivers there is also the emotional burden of needing to be ready at any time to take the patient for urgent treatment. Bygum (2015) recorded that being a caregiver implied also providing help in administering injections or infusions or taking on additional responsibilities and tasks at home when the HAE patient had attacks. Longhurst (2016) additionally noted that the help and assistance provided by caregivers takes time and was mostly unpaid, indicating that the full cost of the condition to society was underestimated.

5.4.14.11 Patient associations

Sections 5.4.14.4 to 5.4.14.10 covered the multiple ways in which HAE impacts on patients and their caregivers. The condition is pervasive through all aspects of life and can lead patients into isolation, possibly initiating vicious circles as stress, for example, is known to be a trigger. Agostoni (2004) reported that since HAE is a rare condition, patients were mostly scattered widely across the territory and the Internet had proven to be an effective tool to facilitate patients' first contact with the patient association and establishing such links. Patient associations were found to play a prominent role for patients so that they could not only share their experience with treatments and how to cope in life, but also to provide a sense of belonging to a community. Castaldo (2004) as president of the global patient association HAEi published that these associations provide a sense of community, information, analysis, and guidance on key issues regarding HAE management, diagnosis, and the direction of future research.

6 CHAPTER SIX - DISCUSSION OF RESULTS

6.1 Stakeholders

The survey with physicians described in section4.3, with results in section 5.1.1, confirmed the patients as the single most important stakeholder in the therapeutic decision-making process. However, the second most mentioned stakeholders in the survey were the payers. As physicians recognize, the payers play a critical role as they decide which drugs and treatment to reimburse (see section 3.5.5, 3.5.14), which is also in line with the theoretical framework (see section 2.3) and double agency theory (see section 3.6.4 with the decision-making process described in section 3.6.5). The search on social media with the results presented in section 5.3 also substantiated that patients and physicians are the key stakeholders, surrounded by other influential stakeholders such as patient advocacy groups, payers (insurance companies), family members, caregivers, other healthcare professionals (e.g. nurses, pharmacists), pharmaceutical companies, regulatory bodies, and media, as suggested in section 4.2.1. Patients and their organization were the dominant source of posts confirming the roles within the application of agency theory extended to all stakeholders which are part of the healthcare system.

The role of patient's associations was discussed in section 5.4.14.11. They work as advocates and collectively have a stronger voice with payers, authorities and pharmaceutical companies. Patient associations lobby with governments and health authorities to increase awareness and recognize HAE as a serious disabling, potentially life-threatening and chronic condition where patients need to be diagnosed, need to get access to treatments and be treated in a timely manner. This is achieved through education in the form of expert groups, speaker engagements at conferences, and groundwork where individual patients help other patients. Patient associations also foster cooperation within the scientific community with the objective of advancing research and clinical trials, improving treatments and ultimately possibly developing a gene therapy which would become the cure for HAE.

6.2 Diagnosis

6.2.1 Profile of HAE condition

HAE has been selected as the rare condition to be studied in depth to answer the RQs. It is a genetic disease, described in section 3.8 affecting about one in 40,000 people. It manifests through mostly unpredictable swellings of different frequency and severity, affecting different parts of the body and all these characteristics vary across patients and within the same patient over time.

6.2.1.1 Abdominal and peripheral HAE attacks

In section 5.4.2 the thesis aggregated different studies and the distribution of attacks was extracted based on self-reported diaries, surveys or medical claims. HAE attacks can be abdominal, laryngeal and peripheral/cutaneous.

As illustrated in section 5.4.2.1, two-thirds of the reported patients suffered from abdominal attacks and they represent 47% of the total. Cicardi (2014) reported that they typically manifest as severe cramping pain and last typically 2–5 days. This type of attack is the most frequent, the most painful and the most likely to lead to misdiagnosis. Craig (2009) for example reported that recurrent abdominal attacks can be associated with biliary or pancreatic obstruction and lead to gallbladder disease or pancreatitis, leading to hospitalizations and unnecessary surgical procedures.

Peripheral attacks are the second most frequent, representing 45% of all attacks and affecting 82% of the HAE patient population, as reported in section 5.4.2.2. These swellings manifest in the patients' extremities or on their face. They are disruptive because they may be functionally disabling, causing, for example, an inability to operate a keyboard or work with the hands, or making it impossible to wear shoes. Banerji (2013) reported that facial attacks can be disfiguring, resulting in social stigmatization, isolation, and depression as patients may elect to reduce or cancel social interactions, staying homebound owing to the change in overall appearance.

6.2.1.2 Laryngeal attacks

Laryngeal attacks have been studied in section 5.4.2.3 and are the most dangerous as well as main source for comorbidities such as anxiety and depression, described in section 5.4.7. Bork (2003) reported that each laryngeal attack is potentially life-threatening and its course unpredictable. These attacks carry a 30% risk of death due to asphyxiation if untreated, however, with treatment, death is rare. Episodes last, comparably as long as abdominal attacks, between two to five days, and are usually self-limited (ICER, 2018). For this reason, Longhurst (2010) reported, attacks affecting head and neck should always be treated because of the risk of rapid progression and asphyxiation, even if the symptoms are initially mild. Section 5.4.8.5 discussed the ER interventions called tracheotomy. The frequency of use of this last-resort intervention depends on the maturity of the healthcare system measured for example in terms of how many patients have access to prophylaxis medicine or have access and can administer acute treatment at home. Especially the latter has contributed to almost eliminate the need for tracheotomies in Western European countries. Agostoni (2004)

reported that in some severe cases the airway cannot be unobstructed with a tracheostomy as the laryngeal attacks extend deep into the thorax, requiring immediate ER intervention. Tachdjian (2017) analyzed insurance claim data and determined that about a quarter of treated patients with HAE had claims for asphyxiation. Although representing less than one attack out of 20, about a third of HAE patients have experienced at least a laryngeal attack in their lifetime. However, the frequency distribution is very wide. Bork (2003) reported in one study of 61 patients, the number of episodes ranged from one to 200 in the lifetime of the patients. The initial symptoms of a laryngeal attack can be a sensation of a lump in the throat, a feeling of tightness, voice changes such as hoarseness and roughness (Bork, 2001). An HAE patient feeling those symptoms should trigger rapid action. Usually, from the onset of symptoms, there is sufficient time to allow for appropriate emergency procedures, as reported by Longhurst (2012), as the symptoms might be mild and slowly progressive for several hours before a rapid progression leading to asphyxiation takes place. On the other hand, Bork (2003) reported fatalities occurring within 20 minutes of the first symptoms. These extreme cases, despite the relatively low frequency of laryngeal attacks and the low case fatality of each attack, could partially explain why the HAE disease presents itself with many patients suffering also from anxiety and depression. Longhurst (2010) reported a still significant lifetime mortality and ICER (2018) calculated an estimated monthly probability of death from a laryngeal attack to be 0.0022%. Bork (2012) estimated that undiagnosed patients have their lifespan shortened by 31 years on average due to the risk of death by asphyxiation. In the same study, Bork reported that despite the clear mortality data, 31% of patients with fatal laryngeal attacks did not receive any emergency life-saving care and that of the remainder, 40% received an emergency cricothyrotomy, and intubation was attempted for the rest. Most of this pain, risk of death and costs could have been avoided if on-demand treatment would have been given at the first signs of a laryngeal attack. In conclusion, any HAE patient can virtually expect a laryngeal attack to take place at any time and patients should be carefully educated to recognize the first symptoms of upper airway obstruction, having available and taking on-demand medicine as described in section 5.4.10. When children have been diagnosed before their first symptoms as part of the family screening, it is important to generate awareness of the possibility that the first HAE attack might be laryngeal and fatal. Farkas (2002) noted that the emphasis is of high priority as children have smaller airway diameters in comparison to adults, asphyxia may ensue more rapidly, and laryngoscopy is more difficult to perform.

6.2.1.3 Distribution of HAE attacks by severity

The severity of attacks depends on a combination of the location of the attack, duration of the attack and level of pain caused. In section 5.4.3 the thesis discussed the categorization of the severity into mild, moderate and severe, with about half the attacks being moderate, and a quarter each being mild or severe. In addition to the statistical distribution, Aabom (2017) for example reported that there seemed to be no correlation between the age at which the first HAE attack occurred, and the disease severity measured later in life. Bouillet (2011) reported that 87% of patients had already experienced at least one severe life-threatening HAE attack in their life.

Section 5.1.3 attempted to show how especially severe HAE attacks could be detrimental to the patients' ability to work and study, leading to absenteeism and impacting his or her social life. Xu (2013) reported how severe cases of HAE could also provoke opiate dependence. Beyond the clinical and QoL consequences of severe attacks, the treating physicians would attempt to mitigate the symptoms and the number of attacks suffered by the patients by prescribing prophylaxis medicine described in section 5.4.11. This type of treatment is linked to significantly higher costs. Additionally, patients suffering severe HAE attacks require more use of healthcare services, raising the HE questions discussed in section 5.4.13. Lastly, these patients may often be exposed to increased indirect costs which are not borne by the payers.

6.2.1.4 Risk of fatality of HAE attacks

Despite effective treatment having been available to HAE patients for more than a decade, a risk of fatality still persists, as described in section 5.4.8.6. Kim (2014) estimated that HAE caused about 50 deaths in the US each year, which was a reduction to a quarter from the early to late 2000s. Jolles (2014) reported 55 deaths in 33 families, ranging from one to three deaths per family. Ohsawa (2015) indicated that 12% of patients had experienced a death in the family due to an HAE attack. Zuraw (2008) reported that before the introduction of modern therapy about one-third of HAE patients used to die of asphyxiation. The reduction of the death rates could be explained also by higher awareness, faster and more accurate diagnosis, in addition to improved treatments. Aabom (2017) observed that death due to asphyxiation could occur at any age and has been reported in children as young as two weeks old and in patients as old as 78 years (Nzeako, 2002). The time between the onset of a laryngeal edema and asphyxiation suggests a mean of seven hours. However, there have been reported cases of up to 14 hours, and as short as 20 minutes, which was the time it took a 9 year-old-boy to lose his life from his first attack (Bork, 2000). Undiagnosed patients are the reason for the majority of deaths due to HAE attacks, as the treating physicians might not have the awareness to recognize the condition, provide the right therapy and possibly not have the right medication on hand in the first place. Longhurst (2007) reported that a share of HAE-induced deaths could be avoided, reinforcing the recommendations on early diagnosis, self-administration of acute treatment (5.4.10) and the proactive preparation of ER visits. Patients and their caregivers should closely monitor laryngeal attacks for a change in voice, difficulty in swallowing or breathing, which could be signs of an impending airway

closure and possibly asphyxiation, requiring urgent preparations for intubation and possible tracheotomy (Zuraw, 2008).

6.2.1.5 Frequency of attacks and acceptability threshold

In section 5.4.4 the thesis consolidated available data from multiple research studies which have quantified the frequency of HAE attacks that patients had to endure. The overall average is 19 attacks per year as illustrated in table 5.3.41. Subsequent analysis showed the high variability across patients.

The survey with physicians presented in section 5.1.2.3 reported that physicians perceived only 21% of the patients having the most selected frequency of attacks per year. The dispersion of the perceptions of the frequency of the attacks was very wide, including that 42% of patients were thought to suffer fewer than one attack every three months.

The survey also asked the treating physicians what number of HAE attacks would be considered an “acceptable stable condition”. Section 5.1.2.10 reported that the majority of physicians considered fewer than three attacks per year to be acceptable. This figure is much lower than the average number of 19 attacks per year derived from the meta-analysis and suggests that many more patients need to be treated with effective prophylaxis medicine, in order to attain an “acceptable state”. A caveat for the answers to these questions is that there was no consensus definition of “acceptable” or “in control”. While for one patient it is acceptable to go through a few extremity attacks over the year, for another even a single attack is too much. With the advent of new treatments with the prospect of ensuring zero attacks (as described in section 5.4.11.5), the definition of “acceptable stable condition” could be likely to shift further to fewer attacks per year.

6.2.1.6 Variability of HAE, its drivers and knowledge limitations

All combined, this data confirms the high variability and unpredictability of HAE attacks which could also be linked to the high prevalence of depression and anxiety which are mentioned as co-morbidities and potentially as triggers for attacks.

A limitation of most studies is that they did not specify if the patients were under treatment and which, if any, drugs they were taking. From the way the studies were presented, it was unclear how much this plays a role. On the one hand research such as that done by Zuraw (2010) showed that the use of prophylaxis could reduce the attack frequency by half (for example from 12.7 attacks to 6.3 attacks over a 12-week period. On the other hand, other studies such as Winnewisser (1997) showed that for certain patients and therapies (e.g. tranexamic acid or attenuated androgens) the attack rate was the same as that of untreated patients.

6.2.1.7 Dependency of attack frequency or factors, and impact on comorbidities

Additionally, most studies reported only the aggregated attack frequency for both genders. Steiner (2016) reported that women were more affected by the intensity and frequency of HAE attacks than men. This might be explained by the fact that women have more attack triggers as described in section 5.4.6. Another limitation on the data collected might have been that studies reported the attack frequencies aggregated across all the age segments. Bygum (2014) noted that population selection could introduce a bias. Lastly, the studies identified measuring the impact of treatment on attacks did not segment the patients by how many attacks they had before treatment and/or did not randomly allocate treatment. Such omissions could have allowed the patients suffering more severely to have a different treatment, causing the end results to be less comparable.

The data collected by this thesis and presented in section 5.1.2.4 could be seamlessly reconciled with the outcomes of clinical studies. Given that for the survey performed for this thesis, the term "treated" has been used in broad way, characterizing a blend of all types of treatments. These include modern prophylaxis which reduces the number of attacks (see section 5.4.11), a modern on-demand treatment which mitigates the impact of an attack but does not directly reduce the attack frequency in a patient (see section 5.4.10), and other legacy treatments with questionable or no efficacy data available. An improvement when comparing untreated patients with treated patients was visible in the higher attack frequencies in figure 5.1.2.4.2. A possible explanation could be that patients suffering a higher attack frequency were considered to be more severe (see section 5.4.3) and as a consequence were more likely to be prescribed the significantly more expensive prophylaxis treatment with the consequent positive clinical result. Possibly reduction of attack frequencies occurred in the more severe patients as a result of therapeutic treatment, with the results suggesting that lower attack frequencies are similar, while higher attack frequencies could be reduced. With all the restrictions and limitations, responses to the two questions on attack frequency in the survey suggested that attack frequencies are widespread across all patient segments both if treated or not.

All combined, the data collected as part of this thesis confirms the high variability and unpredictability of HAE attacks. Such a reality combined with the findings discussed in section 5.4.7, could help explain the high prevalence of depression and anxiety which are mentioned as co-morbidities, and potentially as triggers, for attacks.

6.2.1.8 Duration of HAE attacks

The meta-analysis described in section 5.4.5 quantified that on average HAE attacks last about two and a half days. The duration can be significantly reduced by one day or more if HAE medication is taken, or reduced to zero (no attack) in some cases where prophylactic therapy is taken as described in section 5.4.11. As highlighted in section 5.4.14.10 not only the HAE patients, but also their caregivers are impacted. In his study, Henao (2016) provided a more differentiated view, reporting that HAE attacks develop gradually, worsen over the first 12–24 hours and slowly resolve within 2–5 days. The on-demand treatment described in section 5.4.10 significantly shortens the duration of the attacks, as shown by Maurer (2013).

The duration of attacks is used to measure the efficacy of drugs or when drugs should be taken. Studies such as for example Zanichelli (2015) have reported that the time from onset of attack to treatment administration had a significant impact on the total attack duration. If treatment was administered within an hour from the onset of the HAE attack, then its duration could be reduced to about six hours. Attacks treated within two hours were significantly shorter compared with those treated after four hours which is a strong argument in favor of home administration of the drugs where possible. Treating attacks later and allowing them to develop for more than an hour resulted in reduced response and delayed resolution. For this reason, self-administrators are more likely to treat, and therefore suffer, shorter attacks than those treated by a healthcare professional, which could make the difference between missing a day of work/school or not.

6.2.1.9 HAE attack triggers

Section 5.4.6 has collected data on possible situations, behaviors or other factors that can trigger HAE attacks. As reported in section 5.4.4, HAE attacks are considered mainly unpredictable which is a considerable driver for comorbidities such as anxiety and depression. Exposure to certain temperatures, trauma, activities, lack of activities, chemicals, food, emotions, procedures, menstruation, infections, medications and stress have been mentioned, yet none consistently and unequivocally provoke attacks every time. HAE can also occur spontaneously without any clear triggers, as reported by Kargarsharif (2015).

Given the risk of provoking life-threatening attacks and pain, ethical concerns prevent a systematic study by provoking attacks with different possible triggers. Retrospective studies and real-world evidence are the sources to better understand triggers. With greater clarity on triggering factors, patients can be counseled towards suitable modifications of their lifestyle in order to avoid triggers, attacks and therefore potentially unnecessary consequences such as surgery or worse. For example, if trauma is identified as a likely trigger, advice could be given to children suffering from HAE not to participate in certain types of sport. Some triggers on the other side may be unavoidable in life, such as emotional stress, surgery, hormonal changes, or certain drug treatments. In such cases prophylaxis treatment, if accessible, might help to alleviate the burden as described in section 5.4.11. Despite well-documented experience with a number of trigger factors, about half the patients are still not able to trace back their attacks to specific triggers, as described in section 5.4.6.2. Banerji (2017) reported this to be one of the key reasons for the dominant comorbidities anxiety and depression.

6.2.1.10 Mechanical trauma as a trigger for HAE attacks

The research analyzed in section 5.4.6.1 suggests that mechanical trauma is one of the most common precipitating factors. Trauma in the form of pressure (rather than sharp trauma) can already cause an attack. Patients who stand in one spot for a long time may be exposed to foot swelling, or patients who use a tool or mow the lawn may precipitate an attack in their hands as reported by Frank (2018). To reduce the risk of HAE attacks, patients and their physicians or caregivers could decide on restrictions (for example refraining children and adolescents from participating in certain activities). Such choices might have to be well considered as on the one hand they reduce the probability of HAE attacks with all of their negative consequences, but on the other hand, they reduce the freedom of patients, their execution of activities, their participation in social life, fostering potential social isolation and stigma.

6.2.1.11 Stress as a trigger for HAE attacks

Section 5.4.6.3 reported that stress had been mentioned as a trigger factor across several studies. Nygren (2016) even reported stress as the prominent trigger factor for abdominal attacks. Another scholar identified the possibility of a negative self-reinforcing cycle where the condition causes stress, which is a risk factor for attacks and so forth (Fouche, 2014). Stress being recognized as a risk factor means that attacks are more likely to occur during intensive moments at work or during exams. A possible implication might be that patients and their families might, as a result, face employment and educational disadvantages. Avoidance of stress is not always possible. However, as Savarese (2018) reported, helping patients to improve their ability to recognize when such situations arise and how to deal with them might be beneficial to achieve attack reduction.

6.2.1.12 Dental procedures as a trigger for HAE attacks

Of the possible triggers of HAE attacks, dental procedures as described in section 5.4.6.8, needs special mention, as they have been repeatedly mentioned in the context of the feared and potentially fatal laryngeal attacks. This type of trigger has also been studied in terms of behavioral changes by the patients. Singh (2019) reported that HAE patients had less frequent routine dentist visits and were more likely to use anti-bacterial toothpaste. The findings suggested that HAE patients were less inclined to seek dentists for routine dental care out of concern about triggering an attack. HAE patients undergoing surgical or dental procedures have also the option of taking short-term prophylaxis (STP) medication (e.g. C1-inhibitor described in section5.4.11.2) one to two hours prior. Valerieva (2019) reported that 97% of HAE patients who administered a C1-inhibitor for STP before undergoing dental procedures such as dental extractions, abscess draining, root canal or dental impaction, remained attack-free for two days.

6.2.1.13 Prodrome

Next to triggers, research has also been conducted to identify symptoms or signs that appear before the attacks, called prodromal symptoms. Examples such as itching or tingling sensations, sore joints, nausea, feeling tired, red rings or spots on the skin have been reported as warning signs (Bonner, 2015). A recent survey conducted in Canada reported that the majority of HAE patients are knowledgeable in identifying their triggers and managing their attacks (Howlett, 2019). However, the link between prodromes and attacks might be heavily reliant on patients' recall, thus possibly biased. As a result, initiating on-demand therapy following prodrome might lead to over-treatment, but the benefits of having avoided the attacks and improved QoL might still outweigh risks and costs.

6.2.1.14 Comorbidities of HAE

Section 5.4.7.1 reported that a third of HAE patients additionally suffer from depression, which adds not only to the burden of disease, but to also to the costs, as the treatment of this condition might require attention by specialists from many therapeutic areas and additional medication. The survey conducted for this thesis reported in section 5.1.2.11 that depression seems to have been observed by only 8% of treating physicians. The most frequently appearing comorbidity (43%) appearing in HAE patients is anxiety, as quantified in section 5.4.7.2. The survey reported that anxiety was observed by the participating physicians to have occurred in about 22% of the patients. Based on the literature, one would expect a much larger share of physicians observing these co-morbidities, especially as most physicians see more than just a few patients. The discrepancy could be explained by a communication gap between physicians and patients (described in section 3.6.7) thus not enabling the former to identify the conditions. When the co-morbidities were observed, the participating physicians referred the patients to other specialists - in 75% of the cases with depression and in 46% of the cases with anxiety, indicating that additional specialized medical help was warranted.

6.2.1.15 Anxiety and depression

Undiagnosed and untreated patients show additional risks of depression and anxiety, as they don't know what is happening to them when they have an attack, and their physicians cannot help. With the first diagnosis, there might come relief from learning about what has been causing the swelling attacks, followed by fear of loss of independence and worry about the future. Savarese reported that the unpredictability of the HAE attacks can cause more distress than the symptoms and the pain of the attacks themselves. The unpredictability of the disease causes patients to feel that their career choices are limited, especially as they already experienced setbacks such as being able to work only part-time, being unable to perform certain tasks, or being unable to keep up with work due to frequently missed days as discussed in sections 5.4.14. Outside of work, uncertainty about the next attack could further complicate everyday life and make the planning of any activity more difficult, impacting significantly on QoL and the social functioning of the patients. Fear of dying may combine with a fear of lifetime dependence on the family, which can cause self-loathing and depression. Other reasons may also cause anxiety: HAE patients are anxious about having

to suffer intolerable pain during an attack or about transmitting HAE to their children. Bygum (2015) reported that anxiety about having children led some to choose not to have children or to have fewer than desired, which might have caused further emotional distress and possibly contributed to marital problems. Agostoni (2004) recorded in his work that patients developed ongoing anxiety concerning access to treatment when they have an attack, which caused some to be reluctant to travel or not to travel at all, or to refrain from pursuing certain hobbies. Huang (2014) reported patients who avoided activities and social life altogether due to fear of sudden attacks causing severe psychological distress. Zanichelli (2015) concluded that anxiety is potentially triggering more attacks and Craig (2009) reported that this comorbidity is therefore both a result and a trigger of attacks, requiring the physician to help the patients manage it. In addition to the strict management of HAE and its attacks, a more holistic view might include psychiatric care. Such an approach could positively impact patients both in the short-term in daily life and in the long term, possibly allowing for higher education and better career prospects. Besides the clinical and QoL impact, the overall results could also be financially positive through higher and more sustainable incomes.

6.2.1.16 Other comorbidities

The survey with treating physicians conducted for this thesis found other comorbidities have been observed as described in section 5.1.2.11, consistent with the literature in section 5.4.7. Forty per cent of physicians treated the observed additional autoimmune disorders themselves, in line with the fact that the vast majority of physicians treating HAE are immunologists and allergists. For the pain indication, the share is 46% suggesting that this was standard practice across specialties. The above-mentioned discrepancy between the co-morbidities observed by the participants versus what is reported in the literature appears to be a common theme. The literature reports weight gains affected more than 70% of patients, suggesting that the majority of, if not all, physicians should be cognizant of this. The survey, however, indicated that only 14% of the participating physicians were aware of this comorbidity. A possible explanation could be differing criteria to define weight gain and obesity.

6.2.1.17 Use of healthcare services and hospitalizations

Zilberberg (2011) reported for the US that hospital costs are responsible for approximately one-third of the health care expenditures. An understanding of their drivers in the context of rare diseases and the understanding of how to optimize and contain them becomes an important element of this thesis. Patients living with HAE have swelling attacks that can be disfiguring, painful and even life-threatening. In some occasions and especially if they have no drugs for self-administration, they may seek help in hospitals, as analyzed in section 5.4.8.1. The range of the number of hospital visits required by HAE patients is relatively high and could be explained by the fact that the studies did not factor is different parameters such as age, time since diagnosis, changes in the availability of self-therapy and variability of the condition during the lifespan of individual patients. One of these factors has been studied separately and is indicative of a major source of variance: on average patients who

were taught to self-administer HAE treatment were able to reduce the mean number of hospitalizations from 16.8 to 2.1 (Petraroli, 2015). Hakl (2015) additionally reported that effective HAE treatment could reduce the share of attacks requiring hospitalization from 2.85% to 0.93%. Ohsawa (2015) reported that around one-fifth of patients had to be admitted to the hospital for more than a day per year. While still a significant number, it appears to be an improvement compared to the time before modern therapies have been made available. Winnewisser (1997) had reported that three-quarter of patients suffered severe attacks and half of them sought hospital care when that happened.

6.2.1.18 Cost impact of hospital stays

Besides the disruption resulting from HAE attacks that require hospital stays, there are additional costs involved. Zilberberg (2010) reported with data from US hospitals that stays caused by HAE cost around USD 2,000 per day. A similar study conducted in Europe (Helbert, 2013), reported the mean length of stay for an HAE event to be 2.8 days and an average yearly cost per patient of approximately USD 3,500. While different costs of hospitalization persist between healthcare systems, the total figures are significant and there are opportunities for improvements. Martinez-Saguer (2012), for example, reported a reduction of the mean annual number of hospital days from 15.9 to 0 when HAE switched from an androgen to a C1-inhibitor therapy. The latter is an important consideration when considering the impact of long term HAE prophylaxis treatments.

6.2.1.19 Visits to physicians and Centers of Excellence

In some cases, patients suffering attacks see doctors instead of hospitals, as quantified in section 5.4.8.2. Undiagnosed HAE patients sought on average 11 doctor visits and diagnosed ones see a doctor on average 4.6 times per year. This figure can vary significantly across healthcare systems. For example, anecdotal evidence indicates a frequent use of automatically renewing prescriptions for chronic diseases in the Netherlands, allowing patients in control to see their physician only once a year, while in other systems (such as China) prescriptions can be written for maximally one month or one acute treatment at the time, forcing a patient to see his or her physician 12 or more times per year. Such differences have subsequent repercussions on the respective healthcare costs and the burden of disease. Riedl (2015) reported that 97% of physicians treating HAE are allergists and immunologists, with the former being involved mostly because HAE symptoms present as allergic reactions. While this situation could change depending on the healthcare system, the insurance coverage or the culture, it has to be noted that patients of rare diseases face additional challenges which explain the relatively high number of visits. For example, Bonner reported of patients seeking treatment for HAE attacks but having been given inappropriate treatment because doctors were unfamiliar with the condition. In some cases, unnecessary surgery was performed or attempted to be performed, for example, to treat abdominal attacks, which ultimately exacerbated the attacks. Section 5.4.1 discussed misdiagnosis and unnecessary procedures, confirming how an improved awareness and education of the rare disease condition not only would improve clinical outcomes and QoL but might also decrease health care costs.

The rarity of the conditions leads to a high concentration of HAE patients around relatively few physicians, mostly specialists. Riedl (2015) studied this phenomenon and reported that for example in the US 70.4% of physicians see less than five HAE patients per year, while another 19.3% see between six and ten patients per year. Such concentrations reinforce the establishment of centers of excellence like in Germany, where hundreds of patients are treated by highly trained and specialized physicians.

6.2.1.20 Visits to Emergency Rooms

When HAE patients are suffering potentially life-threatening laryngeal attacks or the pain becomes unbearable, they might visit Emergency Rooms (ER). In section 5.4.8.3 the thesis found that 10% of HAE patients had already had the need to do so. Craig (2009) reported in the US 15,000 to 30,000 ER visits annually associated with HAE attacks. While the condition is rare, the number of visits to ERs, the number of hospital stays and the costs are relatively high (Zilberberg, 2011). It would be expected that patients undergoing a prophylaxis treatment would visit ERs less frequently. However, grouping the data by undiagnosed and diagnosed (and more likely treated) patients, Perego (2017) and others suggested the difference to be merely marginal. Javaud (2015) attempted to explain the result through different factors such as the patients running out of acute drugs. Manson (2013) noted that despite prophylaxis treatment, HAE patients could still suffer so-called breakthrough attacks requiring urgent ER care. Although the use of medications might prevent emergencies and hospitalizations, laryngeal (potentially fatal) and complex attacks may still require emergency care and visits to the ER. As discussed in sections 5.4.2.3 and 6.2.1.1, the evolution of laryngeal attacks can be especially unpredictable and can lead to death. Cicardi (2012) recommended, based on clinical experience, that if the symptoms persisted despite the initial treatment, the patients should immediately report to the hospital in such cases.

A discussion on ER treatments of HAE patients requiring urgent help needs to include the fact medical staff may be unfamiliar with their rare condition. Manson (2013) reported this unfamiliarity with the condition to have led to long waiting times. HAE (and other rare conditions) require unique treatments. Banerji (2015) advised treating physicians and patients to proactively communicate with local hospitals and ERs to share their medical record and discuss action plans in anticipation of an urgent situation that is likely to happen. Such preparation would both improve the patient's control over the condition, as well as ensure that a robust mechanism for emergency treatment is in place to provide appropriate and timely treatment while eliminating or minimizing side effects. For a patient to have to visit the ER is not ideal not only for the burden and the costs, but also because of the time between attack onset to ED arrival and treatment. Javaud (2015) reported that the median time between attack onset and arrival to the ER was 5.6 hours. This compared unfavorably to self-administration, which has also been shown to lead to faster resolution of attacks.

6.2.2 Diagnosis

6.2.2.1 First steps and initial challenges to achieve an HAE diagnosis

The studies discussed in section 5.4.1.1 spanned over 15 years and over 2,900 patients, found that HAE manifested itself for the first time through an attack. The large data range for this variable could be explained by the fundamental challenge of rare diseases. Sample populations for any type of study are rarely representative and the cohorts of study subjects are not always comparable. This and several of the other variables were determined based on the memory of the subject, trying to remember events that took place many years, or even decades, earlier. Recollection bias and possibly different interpretations of "onset" (first real attack vs. symptoms) added further noise to the data. Despite the limitations, the weighted average of age of onset in the early teens was not conflicting with the assessments of most authors identified and used as a reference for the thesis. While HAE was already described by Osler in 1888, its diagnosis continued to be challenging as well as its main appearance.

6.2.2.2 Lack of HAE disease awareness

One of the challenges of rare conditions such as HAE is the lack of awareness of the condition and its treatment within the general population and within the medical community. This has been researched (see discussion in section 3.7.7) and shared through real-life examples, for example when patients share their experiences on social media platforms as described in section 5.3.1.2. The search on Twitter postings discussed in section 5.3.2.1 Twitter reported that 51% of the postings made by and into HAE accounts were invitations to HAE events and activities. As noted for Facebook and when discussed with the patient organizations (for example see section 5.3.1.1) these events served to both generate disease awareness (a major challenge discussed in sections 3.7.7 and 5.4.1) and to foster a sense of community which is particularly important for patients suffering from rare diseases, who are often isolated and sometimes misunderstood in their suffering. These events contributed to improving their QoL while also generating attention in the media which influenced the medical and the payer community, thus enhancing and expanding funding and treatments for better clinical and RWE outcomes. The consequences of the lack of awareness of a condition could be delayed diagnosis or misdiagnosis (described in section 5.4.1) and in daily life a lack of understanding by employers, school, friends and in some cases, stigma.

6.2.2.3 Patients contributing to spreading disease awareness

The research on social media identified and described in section 5.3.1.3 found that numerous patients, directly or through the patients' association, attempted to improve awareness of the condition. This is achieved by means of publications and activities. For example, the thesis found that the most frequent postings on Facebook were by patients and social media users inviting the readers to attend HAE events and activities as described in Section 5.3.1.1. Section 5.3.1.4, described the posts inviting the readers to HAE education events, which could be an example of patients and other stakeholders aiming to overcome hurdles specific to rare conditions and to close information asymmetries (described in section 3.6.7) which are the basis of the challenges described in the double agency theory (see 3.6.4). Section 5.3.1.5 described postings offering information about HAE treatments to prepare the patients for discussions with their physicians, covering specific drugs, treatment regimens and diagnostic tools. Lack of knowledge on diagnostic tools is a characteristic of some rare diseases as they are difficult to diagnose with doctors sometimes not knowing or not having access to the latest tests (see sections 3.7.7 and 3.7.11). In some cases, patients advised each other on which medications to switch to in case of a specific disease profile (see high variability of the symptoms across patients and within the same patients over time 5.4.2, 5.4.3, 5.4.5, 5.4.6 and 5.4.7).

6.2.2.4 Need for funding

Such activities require funding, and the research on social media also measured (for example on Facebook), that about 15% of the postings had as objective to raise funds, mainly in the form of donations. This could be constructed as another instance where the agency theory underlying this thesis (see section 3.6.4) or the healthcare systems in our society (described in section 3.5.5) are not entirely efficient or sufficient. Due to the funding or drug access constraints and tradeoffs discussed in section 3.5.6, patients are forced to take a higher share of responsibility to improve outcomes. On Twitter, as reported in section 5.3.2.7 only about 3% of postings aimed to raise funds and only generic invitations to donate, shared with the whole platform community, were visible. It was therefore not possible to assess the impact, for example in relation to personal invitations being sent to individual members of the organization, or to pharmaceutical companies active in the specific field.

6.2.2.5 Disease education

On Twitter, the research on social media found that about 9% of posts were about disease education. Twitter is a platform for the general public and most of the content is communicated in a language suitable for the layman. However, rare diseases differ from most primary care diseases in that the general level of knowledge is much smaller, less widespread, and less established. Given the highly debilitating nature of the condition, its potentially lethal consequence, and the fact that it cannot be cured, only mitigated by treatments. Possibly for these reasons, patients appeared quite committed to learning about the most recent scientific advances, in the hope to gain early access to new medicines, either by prescription or by participating in clinical trials. This may explain why some of the

educational posts linked directly to scientific literature and presentations given at scientific events. These posts were made by both patient organizations and by individual users.

6.2.2.6 Additional burdens due to clinical manifestations of HAE

Kim (2014) reported that the swellings that HAE patients have, do initially not point toward a specific etiology. HAE is diagnosed based on the physician's assessment of a patient's signs and symptoms, family history and results of laboratory testing. However, in many cases, HAE could easily be confused with angioedema (AE), for which prevention and treatment are different (Zilberberg, 2010). The clinical presentations can range from an occasional skin edema to one or more attacks of swelling every month, from attacks with debilitating abdominal pain, to whole extremity swellings, and to potentially fatal laryngeal edemas that obstruct the airways (Krassilnikova, 2008). HAE could impair the patients' ability to perform their daily activities increasingly with the level of severity of the attacks as described in sections 5.4.3 and 5.4.14.4. Such experiences cause significant psychological burden such as anxiety or depression and impairment that continues also between swelling episodes as covered in the sections on comorbidities 5.4.7 and 6.2.1.14. During attacks, patients are often absent from their jobs or education which could result in lower productivity and missed opportunities for advancement. Pagnier (2015) reported that with pediatric patients' diagnosis of HAE is made more challenging as numerous differential diagnoses need to be considered. Kavalec (2013) reported that many people suffering under HAE had such infrequent attacks and of such moderate strength, that the symptoms were not recognized by physicians, especially when they were not aware of the disease of if they had never seen HAE patients before. The theoretical framework utilized for this thesis, agency theory, discussed in section 3.6.7, discussed the risk of communication gaps between physicians and patients. Consistent with theory, Jain (2018) reported the misalignment on symptom assessment and difficult communications and interactions between HAE patients and non-specialist physicians.

6.2.2.7 Time from onset of disease to diagnosis

The World Allergy Organization (WAO) issued guidelines for the diagnosis of HAE, which included the identification of recurrent episodes of angioedema without urticaria, recurrent episodes of abdominal pain and vomiting, a family history, and the performance of laboratory tests to measure serum C4, C1-inhibitor protein and functional C1-inhibitor to differentiate HAE from other types of angioedema, reported by Maurer (2018). Despite well-documented descriptions of different symptoms, and existing procedures for testing and issued guidelines, the time between the onset of symptoms and the diagnosis of the HAE condition is significant and can span several decades (Bygum, 2014). Data collected for a population close to 4,300 patients and 33 research studies discussed in section 5.4.1.2, indicates an average time to diagnosis of over 23 years. The survey with HAE physicians conducted as part of this thesis and described in section 5.1.2.2, concluded that about a third of physicians estimated that less than 10% of patients had been diagnosed with HAE. This result falls in line with the meta-analysis outcome that the median age of onset of the condition is at about 13.3 years, however, the median age of diagnosis is at 23.4 years (see Section 5.4.1).

6.2.2.8 Differences across healthcare systems

Factoring in that most of the studies have been performed in Europe and North America, the data is skewed towards earlier and more widespread diagnosis rates. The range of the diagnostic delay was significant as well. Zanichelli (2013) reported that Germany and Italy showed ranges of diagnostic delay of two years and fifteen years respectively. The survey noted that more advanced healthcare systems in Europe and North America had a higher likelihood for patients born there to be diagnosed. Possible explanations could be the differences in maturity of the healthcare systems, their ability to identify and diagnose rare diseases, the proximity of patients to state of the art clinical facilities and labs, patient demographics, differences in HAE awareness among health care professionals, and patient selection bias. While the substantial burden of the condition is acknowledged in most countries, recognition of HAE as a burdensome condition may still be lower in somewhere other much more prevalent and life-threatening conditions are still not properly managed.
Kargarsharif (2015) raised the hypothesis that children may benefit from shorter diagnostic delays when whole families are tested for the condition, or when the clinical manifestations of HAE are better known among clinicians. Jolles (2014) suggested that in some cases children with HAE can even be identified and diagnosed before their first attack strikes. On the other hand, Jolles (2011) reported that 25% of patients without a family history or with novel mutations, continued to remain exposed to longer delays before obtaining the right diagnosis.

6.2.2.9 Role of family history

HAE is a hereditary condition that is mostly transmitted across generations. According to scholars including Andrejevic (2015), Bonner (2015) and Lei (2011) reported that 77%, 33% and 100% of their observed patients had a family history of HAE. Riedl (2025) reported that a third of the enrolled relatives of HAE patients in his research had lab results indicative of HAE, reinforcing the importance of testing family members. Other research by Bernstein (2013) indicated that HAE patients had an average of two immediate and two extended family members also diagnosed with HAE. The same scholar reported that about half (48%) of their immediate family members and a quarter (26%) of extended family members had never been tested before. Despite the real risk and the guideline that early diagnosis and treatment are highly recommended, the data suggests that many family members of diagnosed HAE patients often do not seek evaluation diagnosis or treatment. Further communication of the guidelines and potentially systematic screening of family members could possibly alleviate delays in and incorrect diagnoses (Lunn, 2010). Once family members have been identified and diagnosed, the follow-up should be made with all family members including caregivers to include treatment, methods of emergency help, advice on the most suitable means of lifestyle modification, addressing risks and prevention of social stigmatization, engagement with self-help groups and patient organizations (Agostoni, 2004). The full range of activities can lead to improved clinical outcomes and improved QoL.

6.2.2.10 Misdiagnosis of HAE

Banerji (2015) reported in her research over 186 patients that 65% had been misdiagnosed prior (see section 5.4.1.3). Read (2014) reported that half of the centers treating children with HAE in the UK reported initial misdiagnosis. The number of studies on this variable is small and, given the high variability of the numbers, it is difficult to make more precise statements. Three studies quantified HAE attacks affecting patients before they were diagnosed with HAE: for instance, Aabom (2017) and Psarros (2014) reported that out of a total of 138 patients, 51% suffered abdominal attacks. Similarly, Aabom (2017) and Zanichelli (2010) reported that out of a total of 125 patients, an average of 48% experienced peripheral attacks. In this context, it has been described that HAE, often obscures its diagnosis due to its tendency to mimic other dissimilar conditions (Agostoni, 2004). Patients with HAE frequently require hospitalizations and there is a high rate of ER (Emergency room) visits as described in section 5.4.8. Rizk (2013) reported that when patients show up at the ER with large, painful and potentially life-threatening attacks, staff may not recognize the symptoms and proceed with the appropriate triage. This can be partially explained by the fact that ER staff rotates relatively frequently, with a resulting lower probability that a specific physician has seen and treated an HAE patient before.

6.2.2.11 Unnecessary procedures due to misdiagnosis

The consequence of misdiagnosis could be that abdominal symptoms, which mimic acute appendicitis or other forms of acute abdomen, can lead to unnecessary abdominal surgery (Gower, 2011). Other likely differential diagnostic factors for misdiagnosis of abdominal attacks include acute appendicitis, intussusception, mesenteric lymphadenitis, strangulation ileus. With young children, it becomes even more difficult as 'belly ache' is a common symptom with a multitude of possible causes (Farkas, 2002). Patients with an angioedema attack are easily mislabeled as having an allergic reaction or anaphylaxis. When the right diagnostic test is unknown, not available, or beyond the reach of the patient, the right diagnosis becomes impossible. Zilberberg (2011) reported that such challenges in recognizing the disease likely leads to an overall underestimation of the full burden and costs of hospitalizations. Banerji (2013) reported that some patients had also been misdiagnosed as having psychosomatic symptoms and were subsequently referred for psychiatric evaluation. Bernstein (2013) also noted erroneous diagnoses of HAE patients suggesting they were suffering from a psychosomatic illness instead. In addition to leading to inappropriate pharmacologic therapies, a misdiagnosis could lead to unnecessary surgical procedures and to an increased risk of death. Bork (2000) calculated that undiagnosed and untreated patients have a permanent risk of dying of asphyxiation that is 2.7 higher than diagnosed ones.

Section 5.4.1.3 found that about 22% of patients had undergone unnecessary surgery due to misdiagnosis. Kargarsharif (2015) had reported that acute abdominal pain resulted in an urgent surgery in 34% of the patients and Henao (2016) reported that as many as one-third of the patients had undergone abdominal operations before being diagnosed with HAE. When patients presented with severe cramps, nausea, and vomiting, it could easily have been mistaken for an acute abdomen, especially if unaccompanied by cutaneous symptoms. ER physicians might have decided to perform unnecessary surgical abdominal explorations and the excision of otherwise normal gallbladders and appendixes. Nzeako (2002) reported that patients with abdominal HAE attacks had been left undiagnosed for decades despite presenting themselves repeatedly to the emergency department with the same complaints. Huang (2004) reported in his work of 27% of HAE patients who had gone to the ER during an attack to have been treated for anaphylaxis or other disorders, with one half being given epinephrine injections resulting in less than a third showing a positive response. Roche (2005) listed other cases where patients were given antihistamine or corticoid treatments which were completely ineffective for resolving HAE attacks. Such low outcomes led to 40% of surveyed HAE patients reporting that they had no trust in ER physicians, as reported by Banerji (2013). Repeated misdiagnosis and erroneous intervention not only failed to treat the condition and may have added additional risk for the patients but may also have added an element of stigma.

6.2.2.12 Patients sharing personal experience to mitigate issues

The search on social media conducted for this thesis illustrated the results in section 5.3.1.2 where the second most frequent type of postings was experience sharing (about 20% of the HAE-related posts on Facebook). Besides sharing their experience with the symptoms and how to cope in daily-life, HAE patients also shared their experience with the physicians, for example when there are communication barriers or disagreements on the treatment to pursue. These postings seemed to provide concrete examples of the challenges of the agency theory describing the relationship between patients and doctors (see sections 3.6.1, 3.6.5 and 3.6.7), which could lead to wrong treatment decisions.

Jaiganesh (2012) raised that beyond the ability to diagnose, ERs need to have access to the correct treatment and be trained to administer them. In his study, he found that 94% of ERs in the UK had a supply of C1-inhibitors (discussed in section 5.4.10 to be highly effective for treating HAE attacks, but only 49% had any guidance with regard to their use. Patients could be facing the challenge of getting the correct treatment even when the drug is available.

6.2.2.13 Learning from disease attributes and diagnosis

Section 6.2.2.10 suggests that focusing on early and effective diagnosis would allow patients to have early access to effective treatments and help ensure that HAE attacks are shorter and less severe, as discussed in section 6.2.1.3. In addition, early and correct diagnosis is also both cost-effective and lifesaving. Beyond the duration and the severity of the attack, undiagnosed patients are at a much greater risk of mortality from a laryngeal attack than those who are diagnosed (Riedl, 2015). The rare incidence of the HAE condition could be a force for both clinicians and researchers to pool their experiences and data, with the aim of attaining statistically significant insights that subsequently allow for more effective diagnosis and treatment. Medical education and the raising of disease awareness among physicians could lead to more timely and accurate diagnosis, resulting in earlier treatment and improved clinical outcomes and resulting in positive QoL impact, as suggested by Zanichelli (2013). Zanichelli (2015) also reported that HAE patients have a shorter life expectancy compared to the general population. Earlier diagnosis and effective use of modern treatments could help close this gap.

6.3 Treatments

6.3.1 Treatments in general

6.3.1.1 Drivers for the use of guidelines

The survey conducted as part of this thesis reported in section 5.1.2.13 that two-thirds of physicians believe a reduction in frequency and severity of HAE attacks is critical. This perspective was in line with the historic focus of EBM discussed in section 3.1 on clinical outcomes. Improving QoL and enabling patients to conduct a normal life were assessed to be critical for about a third of the physicians in about equal proportion. These are factors that are critical or highly important for over 90% of participants suggesting that modern medicine has moved beyond the narrow scope of clinical outcomes to encompass the holistic view of patients' QoL and roles in society. Treatment of HAE has increased over the past decade thanks to more widespread awareness and diagnoses, but also thanks to launches of drugs that have proven to be effective, as discussed in sections 5.4.10 and 5.4.11. Currently, guidelines described in sections 3.1.10, 3.1.12, 3.1.13, assist physicians and patients in making decisions about appropriate treatment of HAE in specific clinical circumstances. Principles that lead to practical and credible guidelines have been applied by WAO (World Allergy Organization) when devising HAE guidelines through their cycles and updates following a multidisciplinary process and scheduled reviews: Validity (strong evidence, ideally through RCTs), reliability, reproducibility, clinical applicability and flexibility and clarity.

6.3.1.2 HAE-specific challenges for the preparation of guidelines

Compared to other more widespread, historically better researched and well-known conditions, rare diseases and especially HAE faced a few challenges. Modern HAE treatment became available after 2008. Cicardi (2012) noted that prior to that, there were also few controlled studies and consensus guidelines were mainly based on limited case series, observational studies, and expert opinions leading to treatments which were based mostly on empiric evidence. It is still difficult to directly compare drugs as part of the preparation of the guidelines. The ethical concerns of possibly giving less effective drugs to patients with high severity of disease and induce significant health risks and possibly mortality, inhibit the willingness to execute head to head studies. Another reason for the lack of head-to-head comparisons is the difficulty to recruit sufficient patients due to the rarity of the condition. An alternative option is to conduct indirect treatment comparisons, which once more due to small patient numbers, are exposed to considerable uncertainty around the outcomes and their interpretation. A multi-disciplinary steering group of clinicians, nurses and a patient representative has been assembled in 2012 to develop a consensus with 48 recommendations, which were distributed to relevant clinicians and a representative group of patients to be scored for agreement on a Likert scale (Longhurst, 2015).

6.3.1.3 HAE guidelines agreed during the writing of the thesis

Consistently with the profile of the disease and the high variability of the manifestations, some statements had been agreed upon early on (Cicardi, 2012). (1) The reduction of morbidity and mortality in HAE must begin with early and accurate diagnosis, (2) HAE patients should have a specialist familiar with the disease involved in their care, (3) Treatment for HAE must be individualized to the patient's needs and request to provide optimal care and restore a normal quality of life. A UK consensus on HAE reinforces patients' rights and possibilities which take into account different aspects discussed above (Longhurst, 2015). "Each C1 inhibitor-deficient patient should be able to manage his or her symptoms proactively in such a way that they maintain personal safety and minimal disruption in living a healthy and productive life" emphasizes the importance of QoL. "All disabling attacks irrespective of location are eligible for treatment as soon as they are clearly recognized" addresses QoL and enables the patient to take medication at the earliest signs for better clinical outcomes. "Patient self-treatment is the ideal service model in line with government policy" acknowledges both the importance of early treatment to shorten the attack and the fact that self-administration is more cost-effective than visits to the ER or hospital stays. "Every patient should hold a safe quantity (minimum of one) of acute treatment doses at home dependent on individual needs" addresses the permanent risk that the next attack could be laryngeal and potentially fatal if not treated in time. The last update and revision of the global WAO guideline for HAE was published in 2017 and provides up-to-date consensus recommendations for the management of HAE (Maurer, 2018). The goal of the guideline update and revision was to provide clinicians and their patients with guidance on making rational treatment decisions for HAE. The guidelines issued recommendations on how to define and classify HAE, how to diagnose HAE, which treatment option (prophylactic and/or on-demand treatment to prescribe), should HAE management be different for special patient groups such as pregnant/lactating women or children and lastly should HAE be self-administered.

6.3.1.4 Specific situations not covered by the HAE guidelines

Bygum (2014) reported that despite the guidelines, different patients choose different approaches to treatment, in terms of which drug they take and when they take it: some patients opt to take their drugs at the earliest signs of a forthcoming attack, while others first want to ensure the impending attack would be very painful or significantly interfere with their daily life before administering treatment. The former might be the result of high anxiety and could lead to overtreatment (and unnecessary costs) in case of false prodromes, the latter might lead to longer attacks and unnecessary burden of disease (see also impact of taking on-demand medication earlier vs. later (5.4.10). Riedl (2017) noted the flexibility in the way treating physicians prescribe therapies, when reporting that 74% of patients had an individual treatment plan. The same study reported that 78% of patients were satisfied with the care prescribed by their doctor. A possible alternative and partial explanation for the high satisfaction could also be that newly prescribed treatments had higher efficacy and fewer side effects.

6.3.1.5 The role of social media in informing patients on treatments

The search on social media found for example on Twitter, that a significant share of postings was about informing the public on HAE treatments, as described in section 5.3.2.5. For example, for many patients updates of the guidelines could open up new treatment opportunities as when in 2018 C1-inhibitors had been lifted to the status of first-line treatment. Having demonstrated better efficacy and improved safety profile compared to androgens, and being listed as first line, C1-inhibitors could be prescribed by the physicians and reimbursed by their insurance. On-demand treatment with this product in case of one HAE attack could cost between several hundred and several thousand USD depending on the healthcare system, as discussed in section 5.4.13. If the potentially life-saving products were not reimbursed but accessible as self-pay only, it would have posed an unsurmountable affordability barrier and put most patients at risk. The news that the pharmaceutical company and the healthcare authorities, respectively the payers, were able to negotiate and agree on a reimbursement price, could be significant news and even live-altering for all affected patients. Social media could become an excellent and rapid communication channel for all stakeholders involved.

6.3.1.6 The role of the patients' organization

The patient advocacy group HAEi has also issued principles for the treatment of HAE which could be adapted and generalized to all rare diseases within the scope of this research (HAEi, 2015). They include the ambition for every patient to live as normal a life as possible via an optimal individualized treatment plan. They acknowledge that HAE can successfully be managed with modern therapies which should be made accessible, and demand that the treatment choice should be taken together by patient and physician. Given the hereditary nature of the condition, they recommend that family members of patients with HAE should be screened so that appropriate therapy can be available for treatment. While the guidelines, the consensus and the principles issued by HAEi are general, they provide flexibility in their execution, which is also required due to the high variability of the condition.

6.3.1.7 Criteria for therapy selection

The survey conducted for this thesis reported in section 5.1.2.5 that the most important criteria for physicians when selecting the therapy for their HAE patients is the previous history of laryngeal attacks. This criterion was followed by efficacy and safety profile of the drugs, and subsequently by the costs of the treatment. These results confirmed the focus on treating and possibly preventing laryngeal attacks which occur in only about 4% of all attacks (see section 5.4.2), affecting approximately 36% of patients, but with a significant probability of becoming lethal if not treated properly. With the high variability of the HAE disease symptoms combined with the different levels of patient experience in terms of QoL (see section 5.4.14), it followed that different drugs are prescribed for different situations. Self-administration at home offers benefits, but intravenous administration is more difficult, requires more training and might not be suitable for everybody, when compared for example with oral administration. Dosing frequency played an increasingly important role as newer prophylactic drugs required only biweekly (and in some cases monthly) dosing, compared to twice weekly with the older C1-inhibitors.

The survey reported also that the age of patients was critical or highly important for 63% of the physicians. This figure could possibly be driven by the physicians and the caregivers' objective to minimize disruption through attacks for young patients in their education and professional development phase, which could be achieved by prescribing a higher share of prophylaxis drugs. Another influencing factor could have been that older drugs like androgens are significantly more likely to cause side effects in young patients in their growth phase (see section 5.4.11). The distance of the patient's domicile from the next hospital was reported as being highly important or critical for 60% of the treating physicians, confirming the high urgency for treatment in case of attacks, especially in case of laryngeal attacks described in sections 5.4.1 and 5.4.8. Timeliness for last resort ER treatment needed to be factored in to reduce and possibly eliminate otherwise likely fatal situations. Patients who could not reach an ER within a short time period during a laryngeal attack are at imminent death risk, unless they have effective on-demand medication at hand, or even better, are on prophylaxis therapy aiming to avoid a priori such situations.

For the physician and patient to make the right informed therapeutic decision, which might also change over time, they need to factor in all of the above considerations.

6.3.2 On-demand treatment

6.3.2.1 Share of treatments and results

In section 5.4.10 the thesis focused on on-demand treatments of HAE and in section 5.4.10.1 it illustrated that two-thirds of HAE patients treated their attacks. The remaining patients who did not treat their attacks could be partially explained by their attacks having been predominantly mild or moderate overall, or that these patients have gotten used to coping with these symptoms or that simply they did not have access to the needed medicine. A US survey conducted exclusively with patient members of the HAEi patient organization reported 37% of patients using only on-demand therapy and treating on average 69% of their attacks (Castaldo, 2019). Several studies, amongst which Maurer (2013) have demonstrated that on-demand treatment, if taken early enough after first symptoms of an attack, can significantly reduce the duration from 16.8 hours to 6.1 hours. Zanichelli (2015) reported a reduction of angioedema-related morbidity from 26 to five days per year for patients being administered modern treatment.

6.3.2.2 Differences and gaps in treatment and results

Despite the strong evidence of a positive clinical outcome if on-demand treatment is taken early, research has shown that not all attacks have the same likelihood of getting treated. More severe attacks are more debilitating on daily activities and/or can have more dramatic consequences (for example the laryngeal attacks described in section 5.4.2.3). Caballero (2014) reported that face-, neck- and laryngeal attacks were treated 100% of the time, while cutaneous attacks involving the genitals or buttocks were treated only 58% of the time. Modern on-demand treatment effectively reduces the HAE-related disability. Zanichelli (2010) reported that if success was incomplete, it appeared not to depend on the limited efficacy of the drugs, but rather on them not having been used to their full potential. Such observations reinforce the need for improved awareness of the condition and especially of the available treatment options.

There are differences in the way patients with HAE are treated by various physicians, and analysis has demonstrated there are gaps between the availability of treatments and their actual use (Agostoni, 2004).

6.3.2.3 Possible solutions to close gaps

To close these gaps, the establishment and training on the guidelines could be a necessary initial step, followed by individual therapy plans for patients that should include training in recognizing prodromal symptoms, recognize (and avoid as much as possible) trigger factors, and ultimately self-administering on-demand therapy during acute episodes. Steiner (2016) suggested that beyond improved clinical outcomes, such an approach would enhance the patient's independence, self-responsibility and QoL. The value of self-administration has been recognized in several healthcare systems, and in Italy for example, Zanichelli (2015) reported that more rigorous adherence to the guidelines has led to an increase of the use of on-demand treatment to 50% of HAE attacks. A more detailed analysis showed that the real use depended on the type of attack: 89% in laryngeal and 37% in peripheral attacks. Sections

5.4.10.2 to 5.4.10.6 analyzed usage and profiles of the different on-demand treatments. C1-inhibitors have, for example, been reported to effectively reduce the days of absenteeism and the inability to engage in social life by half. Icatibant on the other hand, with its subcutaneous mode of administration, could contribute to reducing the need for medical administration and emergency room visits, offering opportunities to reduce healthcare costs (Blasco, 2013) while at the same time improving QoL.

6.3.2.4 Conclusion on demand treatment

The survey executed as part of this thesis determined that icatibant and C1-inhibitors were the most prescribed on-demand therapies and that 40% of physicians prescribed on-demand therapy to less than a third of their patients. The use of icatibant and C1-inhibitors illustrated in figure 5.1.2.6.2 as the most prescribed on-demand therapies was in line with the guidelines and the efficacy data described in section 5.4.10.
However, the guidelines discussed in section 6.3.1 were more stringent as they suggest that every patient with HAE should always have on-demand therapy in case of an attack. From the survey, it appeared that only one-quarter of the participating physicians followed the guideline, spread between prescribing icatibant or C1-inhibitors. Possibly alarming is that 40% of the physicians prescribed on-demand therapy to less than a third of their patients. The possible reasons for this could be that their patients were asymptomatic or that they had full confidence in their prophylaxis treatments - although it has been reported that such treatments do not offer complete freedom from attacks as described in section 5.4.11.

6.3.3 Prophylaxis treatment

6.3.3.1 Progress in treatment options

In section 5.4.11.1 the thesis reported that, based on the available studies, 56% of HAE patients take prophylactic drugs with the aim of preventing attacks from happening. The older and cheaper androgens, which are taken orally but have a long list of side-effects which limited their use, were taken by 37% of the HAE patient population (see section 5.4.11.3). The more modern C1-inhibitors which have better efficacy and safety profiles, but have to be taken either intravenously or subcutaneously and are significantly more expensive, were taken by 25% of the HAE patients (see section 5.4.11.3). The latest generation prophylactic drug (Takhzyro®, see section 5.4.11.5) was taken by a small percentage of HAE patients as it had just been launched during the time of this research. There is long-term prophylaxis (LTP) and short-term prophylaxis (STP). With LTP the patient takes the medication continuously to prevent all attacks, while with STP patients that medication before possible triggers.

6.3.3.2 QoL, the rationale behind prophylaxis treatment

From a QoL perspective, prophylactic treatment can help mitigate the anxiety about future attacks caused by the significant uncertainty regarding the onset and pattern of acute attacks, and improve the ability to attend work or school, to plan future life events and travel, and to conduct activities of daily living. Prophylaxis may reduce the restrictions on participating in sports, hobbies, or social activities, and improve productivity at work and in school, which subsequently improves the perspectives on career advancement and educational attainment. Lastly, caregivers may also be less burdened timewise, financially or emotionally. From a clinical viewpoint, the switch should take place if there is insufficient benefit from on-demand therapy, measured for example in number of days per year impacted. Longhurst (2010) for example reported of a program in Denmark, which considered moving patients from on-demand to prophylaxis treatment if they had more than one moderate or severe attack every month. However, Nzeako (2002) reported that 84% of patients who had succumbed due to a laryngeal attack, had previously experienced no more than three attacks per year. The available data could suggest that prophylaxis treatment might have prevented the tragic results. Patients who have experienced laryngeal attacks, which can result in death, may have been extremely frightened and may, therefore, want prophylactic therapy to reduce their chances of another future event of this kind. As Riedl (2015) noted, from a patient perspective cost and insurance coverage are also important factors for decision making, followed by convenience.

6.3.3.3 Adaptations of prophylaxis treatments to specific patient situations

Riedl (2017) reported that of patients who took STP, 65% did so before they needed to do dental work (see also section 6.2.1.9 on HAE attack triggers), 59% before undergoing surgery, 30% before they embarked on travel, 11% in anticipation of stressful events, 11% before physical exercise, and 8% before other unspecified special events. LTP may or may not need to be lifelong: the condition can change its clinical course over the patient's lifetime, requiring that the patient's clinical need for prophylaxis can and should be periodically reviewed (ICER, 2018). Similarly to the discussion in section 6.3.2 on on-demand treatment, the patient association HAEi has issued principles (HAEi, 2015), which with slight adaptations could be generalized to all rare conditions which have similar treatment methods. In particular, the following are relevant in this context: modern HAE medications should be prioritized over older outdated medications such as androgens and oral antifibrinolytics (e.g. tranexamic acid) should not be used as on-demand treatment. The suggested approach with prophylactic treatment should rest on the assessment if on-demand acute treatment is inadequate to minimize the suffering, the impact the attacks have on the patient's QoL, other health problems and patient preferences. STP should be considered especially before surgeries where the airways are manipulated, such as dental ones or procedures (e.g. endoscopy) which have a risk of causing swelling in these areas.

6.3.3.4 C1-inhibitors

The studies on C1-inhibitors identified and reported in section 5.4.11.2 showed that 24% of HAE patients were administering C1-inhibitors. The large variations could be explained by the different eligibility criteria, the different geographic locations for the studies, the different healthcare systems, or simply the availability of different drugs, respectively how established and funded they were during the time of the research. The survey conducted with HAE physicians as part of this thesis reported in section 5.1.2.7 that 36% of patients were administering C1-inhibitors. The difference to the 24% in section 5.4.11.2 might be explained by the fact that the meta-analysis contained studies that were conducted when C1-inhibitors were not yet launched, reimbursed and prescribed in the same way as during the writing of this thesis. In the past years, the industry also faced supply issues with significantly reduced access to these drugs by patients, that have now mostly been addressed. Historically there have been concerns with plasma-derived products and the transmission of diseases (e.g. HIV in the 1980s). Reassuringly, Bork (2013) reported that, irrespective of the treatment duration with C1-inhibitors, there has been no transmission of viruses and no development of antibodies. Replacement therapy with C1-inhibitors has been shown to be effective for patients receiving home therapy and STP and LTP (Bork, 2013). Bork (2005) has shown that treatment with C1-inhibitors reduced the mean duration of abdominal attacks from 92 hours when untreated, to 40 hours when treated. In the same study, patients reported a mean maximal pain score reduction from 8.6 (range 1-10) for untreated attacks compared to 4.5 when treated. These results were consistent with the study by Rasmussen (2016), who reported that when using C1-inhibitors for LTP, the mean duration of an attack could be reduced by 52%. Prophylactically treating HAE attacks with C1-inhibitors was reported to reduce the overall attack rate by 63%, life-threatening attacks in the head and neck area could be reduced by 80%, also confirmed by another study (Kreuz, 2011). Zuraw (2010) measured the attack frequency comparing the prophylactic treatment with a C1-inhibitor vs. placebo, the former significantly reducing the frequency of HAE attacks from 4.2 to 2.1 attacks per month. The study also reported a reduction of the severity, the duration of attacks and the need to use on-demand treatment in case of breakthrough attacks. More recently, Agboola (2019) reported a reduction of the mean attack rate by 71%-85% when comparing a C1-inhibitor with placebo.

6.3.3.5 Difficulty in comparing C1-inhibitors to other HAE treatments

The thesis could not find any published direct head-to-head studies between treatments. A comparison between prophylactic C1-inhibitor therapies and attenuated androgens was also problematic since the published data was accumulated using vastly different study designs separated by decades. Additional complexity stemmed from the fact that some patients required dose escalations of their treatments to achieve the desired efficacy. As Bernstein (2014) reported, HAE patients could increase their dosing of C1-inhibitors to reduce attack frequency while still well-tolerating the additional drugs taken. Lastly, when patients had access to home treatment and self-administration, sometimes this involved a significant increase in the dosing frequency, as reported by Kreuz (2011), which makes comparison more difficult. Over the years, concerns about safety have been superseded and at the time

of this thesis, IV-administered C1-inhibitors were the only approved therapy for LTP against HAE attacks in children aged 6–11 years in the EU and the US, as reported by Soteres (2019). Such broad use was made possible as this class of drugs had proven itself to be effective, safe, and well-tolerated.

6.3.3.6 Recent developments on C1-inhibitors

Since 2017 C1-inhibitors have also been made available through the subcutaneous mode of administration offering improved clinical outcomes and convenience leading to better QoL (Lumry, 2019). The most common adverse events (Measured over 18,699 injections) are injection-site reactions that were 99% mild and resolved, as reported by Li (2019). The same study reported that no thromboembolic events occurred with the subcutaneous formulation, while Tachdjian (2019) reported from a survey in the US a reduced likelihood of attacks in the real world as well. Another study reported that some patients preferred subcutaneous administrations because they were not comfortable with IV and they became able to self-administer (Wayner, 2019). All combined, the data discussed strongly suggest that C1-inhibitors in combination with home therapy improve the QoL of patients and are a patient-friendly treatment option which allows patients greater control over their lives.

6.3.3.7 Androgens and their limitations

Androgens (see section 5.4.11.3) have historically been used for other indications than HAE. They have proven to be effective for both LTP (long-term prophylaxis) and STP (short-term prophylaxis), although the mechanisms causing the beneficial effects in patients with HAE are unknown (Agostoni, 2004). Androgens are also convenient to take (administered orally) and inexpensive. On the other hand, as Banerji (2013) reported, androgens show significant side-effects and may be contraindicated for different types of patients incl. children and pregnant women. The list of side effects reported in several studies such as Bork (2001), Cicardi (2012), Dagen (2010) and Prior (2012). Bernstein (2013) reported weight gain for more than 70% of patients, mood changes for 60% of patients and sleep disturbances or agitation for 46% of patients. Dagen (2010) reported virilization in women (hirsutism, deepening of the voice, and decreased breast size), menstrual irregularities or absence, headache, depression and hypertension with subsequent increased risk of cardiac and vascular disease. Bork (2001) observed the induction of liver cell adenoma or carcinoma in patients who took androgens for more than ten years. Lastly, Lumry (2010) reported decreased attention span, acne, muscle cramps, myalgia, fatigue, hemorrhagic cystitis, hepatic necrosis or cholestasis, sexual dysfunction, reduced libido, increased cholesterol, blood clots, stunted growth and anxiety. In the same study, he reported that only 6.2% of patients taking androgens did not suffer any side effects. Bork (2001) concluded that despite the attenuated androgens had shown efficacy in preventing HAE attacks, because of the side effects, they could not be recommended routinely to all patients. Later Bork (2008) reported that adverse effects occurred in 79% of patients and 25% of patients had to discontinue the therapy with androgens because of them. Specifically, for the following patient groups a treatment with androgens was contraindicated: pregnant or lactating women, children and adolescents, women with breast cancer, men with prostate carcinoma, patients with

nephrotic syndrome or significant alteration of hepatic function (Prior, 2012). In addition, Gower (2011) published data showing that androgens lost their effect in some patients after four to six years of treatment. The patient association also recommends that androgens should be avoided when contraindicated, for example when patients are at for adverse events, and when prescribed, patients should be routinely monitored for adverse events (HAEi, 2015). A survey conducted by Riedl (2015) showed results indicating that the share of physicians who preferred androgens as LTP had declined from 56% to 23% in the years prior to 2015. At the same time, C1-inhibitors increased as preferred treatment from 20% to 57%.

6.3.3.8 Modern use of androgens

The survey with HAE-treating physicians described in section 5.1.2.7 found a relatively high usage of androgens. The reason why androgens appeared to be prescribed closely as often as C1-inhibitors (weighted average of 34% vs. 37% of patients) might be explained by their much lower treatment costs, their improved convenience from being administered orally instead of through infusion or subcutaneously, the ability of physicians to titrate the dosing in such a way to minimize side effects, and lastly by the possibility to still be able to control the condition with on-demand treatment always available as per the guideline.

6.3.3.9 Tranexamic acid

Data on tranexamic acid was shown in section 5.4.11.4 with 18% of patients taking this medication for HAE prophylaxis. Prior (2012) reported that for patients suffering nausea, vomit, headache, diarrhea, orthostatic regulation disturbances, myositis, muscle necrosis, or with increased in the risk of thrombosis, treatment with tranexamic acid is contraindicated. With new and more effective prophylaxis drugs available, the use of tranexamic acid could be expected to decline.

6.3.3.10 Lanadelumab

Lanadelumab (Takhzyro®), discussed in section 5.4.11.5 has shown strong efficacy data which could lead to a paradigm change in the treatment for HAE. Treatment with this novel class of drugs could allow HAE patients for the first time realistically to aim for zero attacks, and virtually forget to have the condition. As the treatment had just been launched during the writing of this thesis, there was not a lot of patient usage data available.

6.3.3.11 Clinical trials challenges and trends

Section 3.7.15 discussed RCT (randomized clinical trials for the development of new drugs, section 3.7.17 the challenges when performing them for rare conditions, and section 3.7.18 the transition to RWE (real-world evidence). The research on social media conducted for this thesis reported in section 5.3.1.7 that about 2% of the posts on Facebook were invitations to patients, and sometimes caregivers, to participate in clinical trials, survey or registries, that had as an objective to gain new knowledge on the condition, possible treatments and other ways to improve the situation. Pharmaceutical companies, contract research organizations, or academic institutions were observed utilizing the online platforms

attempting to overcome the difficulties in recruiting a sufficient number of patients affected by rare conditions to fulfil the requirements for their studies. All activity with patients after the invitation was received and followed up upon, is confidential and protected by privacy laws, hence it was impossible to assess the success rate of such approaches. On Twitter, only about 1% of postings were of this type as reported in section 5.3.2.9. The relatively few mentions on Twitter of clinical trials were mainly for sharing results and not for recruitment purposes. This is also in line with the setup of clinical trials discussed in section 3.2.1, which requires strict adherence to a protocol and the fulfilment of eligibility criteria. Normally the recruitment for RCTs is performed through selected physicians – investigators. With the rarity of the discussed genetic condition combined with the broad implications (QoL, financial impact) on patients, caregivers (reported in sections 5.4.13 and 5.4.14) more data from patients and caregivers could enable better treatment and funding decisions. Survey and registries could provide broader and more comprehensive data for treatment decisions leading to better outcomes, as well as for health economic decisions (by integrating all cost factors), leading to more efficient use of healthcare and financial resources.

6.3.3.12 Home treatment vs. hospital treatment

Home therapy has been available for hemophilia patients since the 1980s and since then has been considered to be a routine approach, as reported by Longhurst (2007). HAE patients had to wait longer. HAE attacks are unpredictable, can happen anywhere, anytime, be highly debilitating, extremely painful and potentially fatal. They make HAE very stressful for patients and their families. Normal life during an attack is not possible, a visit to an ER and/or a hospitalization are a normal reaction for a suffering patient. The on-demand treatment options discussed above have opened the opportunity for home treatment and its strong impact in multiple ways. Gregory (2014) reported in his study conducted in the US that the share of patients who self-administered more than doubled from 20% to 44% in the years before it was conducted, confirming that this approach to treatment was viable, feasible and well accepted by stakeholders. Craig (2013) reported that an increasing number of healthcare providers adopted the approach and are offering more patients the option of self-therapy. A few years later Riedl (2017) reported that 82% of patients where self-administering, of which 61% with no help, indicating that 39% would and could get assistance by a relative or caregiver when required. An analysis based on a cohort of patients aged between two and 18 years old part of the IOS registry reported that for 92% of attacks icatibant was administered by a family member or caregiver (Andresen, 2019).

6.3.3.13 Hurdles, requirements and steps to establish home treatment

Similarly, Petraroli (2015) reported that self-administration of an intravenous infusion of C1-inhibitors can be taught to patients and/or caregivers within one day. How the training and support are provided can differ from one healthcare system to another. In the US home care agencies train patients and follow-up with them in their homes, while in Canada 2-3h were seen to be sufficient for training (Symons, 2013). Caballero (2013) identified three main requirements for a patient to qualify for self-administration, patient motivation, patient mental ability and clinical need. Abdel-Karim (2014) suggested that children could be

considered for self-administration as the process does not have to be either long or complicated. During such training patients are also advised to keep a log of their condition, noting the attack types, the severity, the medication taken, the time to resolution, and more, which help to reduce recall bias and the physician to adapt the treatment as necessary. Part of the training includes a sterile technique and the use of equipment for home administration, including how to manage emergencies and when to present to an ER (Rizk, 2013). Riedl (2017) reported that once taught, few patients refused self-administration. However, when patients refused it, they indicated as reasons the fear of injections, concerns about possible infections, lack of skills (specifically dexterity, interference with daily activities, and financial restraints. Tuong (2014) reported that some of the nurses involved in the training mentioned worries about safety, the risk that patients might not retain their acquired skills, and/or that might make inappropriate use of the drug. When discussing intravenous treatment such as with C1-inhibitors, a challenge arises in obtaining venous access, yet Rizk (2013) showed that less than 2% of self-administration through venipuncture resulted in technical failure. With the proper training and practice, home therapy has not caused a significant increase in the dosing, however a significant increase in dosing frequency.

6.3.3.14 Results and benefits from home treatment

All types of attacks can be treated, and in his research, Kreuz (2011) could not observe additional side effects or injection site complications. Normally nurses conduct the training and guide the patients, offering to continue ongoing support as needed, as reported by Gregory (2014). Levi (2006) assessed that all patients can be capable of self-administering, with technical failure rates of self-injection being less than 2%. Graig (2013) had already suggested that patients appear to learn the skills of self-administration quicker than expected and in fewer sessions than the guidelines recommend. Researching the results of the approach, Abdel-Karim (2014) reported that pediatric patients aged 13 had rapidly learned self-administration and subsequently benefitted from reduced frequency and severity of attacks. Despite these considerations, proper training to suitable patients should be pursued, as there is an inherent risk of long term intravenous access, corroborated by reported fatalities due to pulmonary arterial embolization due to inappropriate infusions (Tilles, 2013). Combining all factors, it appears that home treatment offers a further range of advantages.

6.3.3.15 Benefit of early intervention and shorter time to relief

Self-administration of medication contributes to early intervention, it can help to significantly reduce the time between the onset of the attack and taking the medication, which above has shown to contribute to a lower severity and shorter time to resolution – with the critical threshold being at about one hour. Petraroli (2015) reported that patients taking icatibant within one hour from onset can reduce the attack duration from an average of 16.8 hours to 6.1 hours. Craig (2013) reported in his study with C1-inhibitors for prophylactic use that treatment taken within 6 hours after the onset of the attack resulted in considerably shorter times to onset of symptom relief compared to placebo. If treatment was taken after the threshold of 6h the effect was reduced. Rusicke (2006) researched the use of

C1-inhibitors for on-demand treatment and reported that home treatment prevented more severe attacks and additionally allowed for a lesser consumption of drugs, while Tourangeau (2012) measured the attack frequency to remain approximately similar. Lastly, Longhurst (2007) reported that 58% of patients administering prophylaxis drugs themselves, enjoyed complete freedom from attacks.

6.3.3.16 Benefit of more rapid resolution of HAE attacks

Looking at dosing, Gregory (2014) measured that the treatment doses per week increased from 1.40 in infusion centers and physicians' offices to 1.85 at home, indicating a higher propensity to take medication which by itself may also have led to better clinical outcomes. Banerji (2013) suggested that home administration may have decreased dosing needs, while Rizk (2013) reported that patients who self-administer on average took treatment 1.4 hours after onset, compared to 3.4 hours for those who relied on medical professionals. Combined with the superior clinical results from treating as early as possible (see also sections on icatibant 5.4.10.3 and 6.3.2), this leads to complete resolution of symptoms 5.9 hours after self-administration, vs. the 13.8 hours with conventional treatment (Rizk, 2013). Research with a different cohort of patients has shown a reduction of the time between the onset of the attack and the initiation of relief or complete resolution of symptoms from 7.9 hours to 2.2 hours thanks to self-administration (Levi, 2006).

6.3.3.17 Benefit of reduced mortality

Ghazi (2013) suggested that the more rapid dosing of the drug in the case of laryngeal attacks led to a potentially reduced mortality, while Longhurst (2007) reported improved life expectancy with self-administration.

6.3.3.18 Benefit of healthier and more productive life

Longhurst (2010) also reported that the improved control over the symptoms enabled patients to live healthier and more productive lives, possibly allowing them to resume a normal life without restrictions caused by HAE (Bygum, 2009). These patients have been observed having a reduced need for health centers or ER visits (Blasco, 2013), less hospitalization time and less absenteeism from school or work (Rusicke, 2006) and possibly a decreased mortality (Wang, 2015). Bygum (2014) measured a reduction of acute hospital visits by 84% thanks to home therapy, Javaud (2015) measured an 11-fold lower risk of needing admission to an ER following self-injections of icatibant, and Kreuz (2011) reported a reduction of the mean annual number of days hospitalized from 3.8 during physician-based therapy to 0.11 during home therapy.

6.3.3.19 Benefit of increased independence

Patients who have learned to self-administer the medication (by infusion or subcutaneous injection) during an emergency, acquired a strong sense of independence and felt much safer. Bygum (2009) reported patients having been no longer afraid of life-threatening laryngeal attacks or painful abdominal attacks, which was discussed in section 6.2.1.14 to be a main source of the comorbidities anxiety and depression. The acquired autonomy may boost self-confidence and QoL, as HAE patients are subject to less disruption in their daily activities (work or leisure). Patients reported less pain, less vomiting, fewer circulation breakdowns, no more waiting for emergency medical personnel, no more use of drugs that would not work, because the treating physician was not trained in HAE. Rauch (2004) observed that in case of laryngeal attacks, HAE patients on self-administration of on-demand treatment had no longer a need to run to the hospital breathless and in a panic and potentially facing the risk of their orphan drug not being in stock at the hospital pharmacies (Banerji, 2013). The same results could be achieved or even reinforced when in addition to the patient, also the caregivers are taught to administer the infusion or injection to the patient (Bygum, 2015). Longhurst (2016) reported in addition that the shift from depending on health care professionals to being able to self-administer triggers a transformation from being a disabled HAE patient to being able to perform a controlled treatment and be in charge of one's QoL.

6.3.3.20 Benefit of reduced costs

Long before HAE therapy for home treatment had been developed, home therapies for hemophilia and antibody therapy were studied and reported to reduce costs by up to 20% compared with in-hospital treatment. Rodriguez (1991) reported that they were shown to improve the patients' independence, with less feeling of illness and less absenteeism. Home therapy requires a significantly lesser deployment of healthcare resources, as studies have reported a decrease in the mean annual number of hospitalizations from 17 to two and a reduction of missed work/school days from 20 to seven compared to conventional treatment. For example, Petraroli (2015) measured for HAE patients within the Italian National Healthcare System savings of 11.3% (from around USD 30,000 p.a. for hospital treatment to USD 26,600 for home treatment). The same study reported that within the Spanish National Health System, home treatment was shown to reduce the cost per attack by 7.1% from USD 1,180 to USD 1,090, mainly driven by fewer visits to the ER and from diminished use of other medical facilities. The reduction in costs could be split into 74% from savings of direct costs, and 26% from lower indirect costs. Blasco (2013) reported the combined savings from home therapy to add up to a few million dollars per year.

A limitation of these studies was that they could not measure over or underdosing of drugs. Additional inaccuracy might result from early treatment, as potentially severe attacks may have turned into mild attacks, in which case the clinical benefits and the cost savings might have been even more important than estimated. Wang (2015) summarized that for different reasons, switching to self-administration therapy was looked upon favorably from a patient's perspective and Caballero (2013) concluded the same from a clinician's perspective. Lumry (2018) identified in his research that in many countries (for example Japan, Greece and most of Eastern Europe) self-administration was not allowed by policy, and that in some (for

example Brazil or Mexico) it was available but not reimbursed. If on-demand therapy can only be obtained, if at all, in a hospital or in specialty clinics, then HAE patients may be exposed to additional risks (due to the untimely resolution of attacks as described in section 6.3.2), additional costs, and lower QoL.

6.3.3.21 Conclusion on home treatment

In conclusion, self-administration suggests significant health benefits, possible cost savings and improved QoL. Riedl (2017) reported from a survey that 71% of patients who treated themselves reported high rates of satisfaction, and 78% believed that their approach might have lowered their levels of anxiety and depression. Such encouraging results supported the recommendation by Symons (2013) that all patients who are willing and able to self-administer should be offered this treatment option, as it can also be lifesaving. Along the line of these arguments, the patient association HAEi issued principles (HAEi, 2015), which with slight adaptations could be used for all rare conditions which have similar treatment methods. The recommendation to patients was to self-treat attacks as early as possible, as all attacks could become debilitating, and airway attacks could become life-threatening. Further, all patients should always have modern therapy available to treat an acute attack, and they should be trained in self-administration. While attacks can occur in any location, all could be treated at home and all should be considered eligible for treatment. In the case of laryngeal attacks, HAE patients should seek the ER for expert medical advice, even if normally they self-treat at home. A survey conducted in the US in the years where these observations were made, reported that the percentage of attacks self-treated at home increased from 8% to 27%, which by itself led to a decrease in ER visits from 61% to 54% and a decrease in hospitalizations from 13% to 3%. In the same survey physicians perceived an increase of patients satisfied with their HAE treatment from 13% to 40% (Riedl, 2015).

6.3.3.22 HAE switching treatments

The survey conducted for this thesis asked physicians treating HAE how often patients switched their treatment and reported the results in section 5.1.2.8. 54% of patients never change their medication and the vast majority not more than once during their lifetimes. This result could be seen as unexpected for a few reasons. First, the condition manifests differently over time and patients could be in control with an acceptable QoL with on-demand treatment only, until the number and severity of attacks increased in such a way that prophylaxis could become the preferred solution. Second, over the past decade, there has been enormous progress with the development of innovative therapies which should have replaced old treatments which have less efficacy and more side effects, as described in sections 5.4.11.5, 6.3.3.4 and 6.3.3.9. A possible reason for this relative “stickiness” could have been the hesitation of physicians and patients to change a therapeutic approach that delivered acceptable results, and to experiment with a new drug, even if the clinical data suggested much better outcomes are possible. With the current introduction of Takhzyro® more switches were expected, as the drug has already shown transformational outcomes and impact on QoL in clinical trials (see section 5.4.11.5). If the survey in this thesis was

conducted in a few years' time, the results might show an important shift to at least two therapeutic changes.

6.3.3.23 Reasons for switching HAE treatments

The survey also asked the physicians to provide the reasons why they and the patients agreed to switch medication, with presented in section 5.1.2.9. The most mentioned reasons were the side effects (for 17% of patients), the lack of efficacy (for 15% of patients), and costs (for 12% of patients). Possibly, this explains switches from androgens to C1-inhibitors as the former have a long list of side effects described in section 6.3.3.7. In comparison, modern therapies showed relatively fewer and milder side effects such as injection site reactions on the skin. Clinical studies investigating the efficacy and safety profiles of HAE drugs already showed improvements. These reasons are followed in equal percentage by the strive towards improved convenience (which can be explained by a preferred mode of administration, a dosing frequency, or adverse events) and by supply issues (Different C1-inhibitors were exposed to supply issues over the past years de facto forcing patients to switch medication). The change of frequency of attacks as a reason to switch treatment was mentioned to be relevant for less than around 10% of the patients. This could be either because an increase in the number of attacks justified moving to prophylaxis therapy, or because a decrease in the number did not warrant it any longer.

The switches due to costs could have been driven by the insurance companies not funding the treatment due to HE aspects, based on the process described in sections 3.7.25 and 3.7.26. Alternatively, it could also have been because patients could not afford or didn't want to pay the copayments, which, given the costs of the drugs, could be significant depending on the healthcare system.

6.4 Costs

6.4.1 Six types of cost analysis

Referring to section 5.4.13.1 on the costs of rare conditions and HAE specifically, a structured approach to discussing costs of drugs as part of pharmaco-economic evaluations could be divided into six types with different levels of complexity. (1) Budget impact analysis, which considers only the direct costs of a treatment (e.g. drugs) and which is relatively simple. (2) Cost-minimization analysis, which assumes all treatments to have equivalent efficacy, and suggest the least expensive one to be the most cost-effective. (3) Cost-consequence analysis presents and compares all costs and outcomes associated with a treatment. (4) Cost-effectiveness analysis uses a measure of health benefit (e.g. HAE attacks avoided, life years saved) to first estimate the benefits of treatment and then calculate an incremental cost-effectiveness ratio (ICER), i.e. the incremental difference in costs and benefit between treatments. (5) Cost-utility analysis follows the same approach but using the QALY (Quality-adjusted live years, combining survival and quality of life) as a standard cost-effectiveness estimate of the intervention. QALY can also be used to compare interventions in different disease areas. (6) Cost-benefit analysis measures costs and benefits in money terms, comparing the financial value of the costs with the benefits.

6.4.1.1 Challenges in assessing true costs of rare diseases

It is difficult to quantify the total costs of a rare disease treatment when the medical management of the patients is shared across different providers such as specialist centers (tertiary care), ER providers (secondary care) and general practitioners (primary care). As discussed in sections 5.4.7 and 6.2.1.14, HAE patients were also likely to have comorbidities with some of them having to be treated by yet other specialists. A global and general discussion on costs was also made challenging as the selection of treatments, the type and quantity of funding of the therapies could differ between countries according to tradition, financial resources and health care systems, as reported by Bygum (2014). A further limitation identified by this thesis was that the cost of labor and the prices of the drugs could significantly differ across countries. For this reason, strategies and policies that help patients prevent ER- and hospital visits were meaningful both from a QoL and from an economic perspective. Newer drugs with improved effectiveness and lower risk profile were costlier but might have been justified in selected patients when incorporating all factors. Manson (2013) analyzed several healthcare systems and found that some payers were using the concept of Integrated Care Pathways (ICP) to map how patient interacted with different health professionals and types of care over time. ICP as recorded as documents part of the clinical record of the patients and can be utilized as a tool to ensure standard practices, following of guidelines and systematic controls that the treatments with the best combination of efficacy and efficiency are met.

6.4.1.2 Direct vs. indirect costs

Section 5.4.13.2 identified from the data that the costs of health conditions can be divided into direct vs. indirect costs. Kavalec (2013) reported that direct costs were difficult to quantify due to lack of data, lack of comparability between treatment options, differences in prices and costs of procedures. To estimate indirect costs of a condition, like when a patient suffers HAE attacks, the human capital approach could be used. When patients or caregivers are experiencing lost productivity because of the attacks, the treatment, or the hospitalization, then the productivity loss can be estimated by multiplying the time required with the average hourly wage based on the Bureau of Statistics of the respective healthcare system. The gap in using all types of costs for reimbursement and treatment funding considerations occurs when payers, (such as for example the Spanish National Health System) consider in their decision making only direct costs (Blasco, 2013). This chose approach could be partially explained by the rapidly escalating healthcare costs which create tension with the need to provide adequate patient care. Rare diseases and HAE could be examples to showcase how prevention could reduce the need for expensive ER treatments and hospitalizations. Value and cost analysis need to be holistic with the aim to reduce patients' exposure to the healthcare systems, for example through visits to ERs and hospitalizations, discussed in sections 5.4.8.3 and 5.4.13.3.

6.4.1.3 Death and the differences across healthcare systems

Section 5.4.8 reported on patients succumbing due to HAE, which could be seen as the ultimate burden of the condition resulting in significant hardship both socially and economically to the patient's family and society. A review of all US death certificates from 1999 to 2010 conducted by Kim (2014), reported HAE having been a contributing factor or cause of death in 600 people. These figures need to be taken within the context of the specific healthcare system, as there are large differences between countries in terms of healthcare infrastructure, reimbursement schemes, treatment modalities, income, affordability and willingness to treat certain conditions. For example, in some emerging countries treatment of rare diseases might be de-prioritized if more urgent unmet medical like child mortality or communicable diseases needs need to be addressed. Longhurst (2016) reported that not all patients could benefit from medical progress and treatment improvements enjoyed by the most fortunate.

6.4.1.4 Specific cost challenges for HAE

The clinical impact of HAE is highly variable as discussed in sections 5.4.1, 5.4.2, 5.4.3 and 5.4.4. Federici (2018) reported that facial attacks generated 22%, laryngeal attacks 16%, and abdominal attacks 11% higher costs than cutaneous attacks. The same study also reported that severe attacks generated 30% more costs than mild attacks, with moderate one in between. Patients had theoretically a wide selection of treatments at their disposal, and their consumption of medication could depend, besides on the clinical impact, on their propensity to treat, or which drug they get refunded. In addition, patients may have needed supportive care in the form of ER, hospitalizations or nursing care for at home. Longhurst (2016) concluded as a result that the costs for patients, payers and society were highly variable. In

sections 5.1.2.11 and 5.4.7 the thesis studied the co-morbidities to which HAE patients were frequently subject to. They demanded separate consultations and treatments that vary across patients and over time for the same patients depending on numerous factors.
HAE treatments could be taken through different modes of administration. Prophylaxis treatment could be administered orally, subcutaneously and intravenously (see section 5.4.11). Wilson (2010) reported that intravenous administrations were at higher risk of generating complications causing a higher share of hospitalizations compared to subcutaneous medications (20.2% versus 5.9%), which led to higher resource utilization and costs. While modern treatments such as C1-inhibitors contributed to a reduction of the health and societal burden HAE, their increased cost compared to traditional medicine with lesser efficacy had impacted payers and raised concerns, as reported by Federici (2018).

6.4.1.5 Challenges in obtaining comprehensive cost data

Longhurst (2016) noted that few healthcare systems had the process and the infrastructure to be able to collect and consolidate all costs by the patient's primary condition. Obtaining this type of data was as of the time to research very difficult and assumptions had to be made. As for other rare conditions, the costs for HAE therapies were high. The condition is severely debilitating during attacks and additional direct costs from providing medical care plus the indirect costs of the disease on patients, their families, and on society had to be added. When HAE patients had attacks, they and their caregivers may have missed a significant amount of time from work and school. Also, between attacks, they could be less productive at work or in their education. Studies have reported that many are unable to achieve their educational and career goals, or even maintain employment as a result of their disease. This comes in addition to a higher utilization for health care resources, which in for example Helbert (2013) estimated for the UK to be 160% higher for primary care and 447% higher for secondary care (even when excluding specialist care and medications. The cost considerations studied in section 5.4.13 were caused or impacted by activities or events. In the case of HAE costs could also arise from lack of action, for example by not treating an attack. Longhurst (2007) reported that untreated attacks can be costly in social, pharmacoeconomic and QoL terms as well. The discussion on attack triggers in section 5.4.6 had highlighted emotional stress, minor infections or estrogens amongst others as possible precipitating factors. Consequently, adolescents and young adults in their education or early career stage may live with an increased risk in the stage of their life with the longest potential impact. The lifetime economic costs of a disrupted education or employment can be considerable. For this patient population, this adds up to the impact on the families of the young adults resulting from absenteeism from work or from lost opportunities. Looking beyond, the wider society also carries additional costs as a consequence of HAE through the employers and more in general as a result of the productivity loss, the burden of care and the economic costs of expensive orphan drugs and additional treatments that are necessary but cannot be afforded by the individuals without collective support (Longhurst, 2016).

6.4.1.6 Impact from advent of modern HAE treatments on costs

Before modern treatment was introduced and home and self-administration became available, most if not all HAE attacks had to be treated by physicians, and ER visits and hospitalizations were the norm. When self-administration for treatment, on-demand or for prophylaxis, became and was perceived as safe and effective, patients could treat and resolve symptoms earlier, reducing significantly ER visits and hospitalizations, improving QoL and reducing direct and indirect healthcare expenses for the payers and for society (Lumry, 2018). Since 2008 new modern treatments have been discovered, developed and made available to HAE patients. Clinical trials and RWE suggested unprecedented levels of efficacy, safety, and convenience as described in sections 5.4.11.2, 5.4.11.5 and 6.3.3. Combined they appeared to have the potential to further transform the patient experience. Modern drugs may change and innovate treatment paradigms and therefore lower the costs and the burden of disease. Petraroli (2015) reported self-administering patients to have lowered their mean annual number of hospitalizations from 16.8 to 2.1, their time to administration of treatment from 3.2 hours to 1.9 hours, their time to beginning of symptom improvement from 84 minutes to 54 minutes, and their time to completely resolve their symptoms from 12.8 hours to 10.8 hours, while decreasing the number of missed days of work or school from 23.3 to 7.1 days compared to hospital administered therapy. However, Longhurst (2016) noted that new and improved products are normally commercialized at higher prices which subsequently implies additional pharmaco-economic challenges.

6.4.1.7 Impact from increased drug development costs

Over the last years, time-consuming and expensive drug research and development activities have significantly appreciated, reaching for a new prescription drug an average cost up to winning market approval of about USD 2.6 billion (Di Masi, 2016). This was valid also for orphan drugs which are no exception as they have far fewer patients to treat, and therefore the cost per patient must be higher to recover the initial expensed. The publication EvaluatePharma (2015) quantified for the top 100 drugs, that orphan drugs cost USD 140,443 per US patient per year, compared to USD 27,756 for non-orphan ones. Lumry (2016) reported that HAE patients and payers were counting on market forces and competitive pricing to push the costs of therapies down.

6.4.1.8 Challenges in estimating costs of co-morbidities

HAE is often accompanied by co-morbidities (see sections 5.4.7, 6.2.1.14, 6.2.1.15 and 6.2.1.16) and a survey conducted by the patient association HAEi in 2018 indicated significant medication use for these conditions as well. For example, around 90% of HAE patients who reported asthma as a comorbidity were taking medication to treat it. For heart disease, the percentage was 84%, for hypertension 71%, stroke 60%. Anxiety, the most frequently mentioned co-morbidity, appeared to be treated with drugs by only 26% of the HAE patients, depression by 17% of the patients and high cholesterol by 13% of the patients. A comprehensive review of available studies for the purpose of this thesis has highlighted the difficulty or impossibility in performing comparisons or calculating averages. Different studies utilized and reported different units to measure resource use (e.g. patients,

occurrences, duration, frequency), did not incorporate or report the cost drivers in the same way, or had cost factors in different relations to each other (e.g. labor costs vs. drug costs). With these limitations, the thesis aimed to provide an overview of the costs to develop answers to the RQs.

6.4.1.9 HAE treatment costs dependence on severity of the disease

The large differences in costs reported in section 5.4.13.3 across healthcare systems may be explained by the difference in healthcare costs per capita, rather than patients in the US requiring multiple times more hospitalizations. The shift from healthcare professional administration of drugs to home and self-administration of drugs could have driven, in addition to improved clinical outcomes and QoL, lower overall costs. Table 5.3.13.4.2. appears to illustrate a link between yearly HAE therapy costs and the severity of the condition, but one must consider the caveat that the distribution might be skewed due to the diversity of patients. Their choice of medication, the consumption, the propensity to treat and which drug is getting reimbursed, and therefore was accessible, might have depended on the severity of the condition and not have been equal across all grades.
The figures presented in section 5.4.13.2 might have to be interpreted only directionally, due to the paucity of other studies and the lack of standards in defining severity. Additionally, they described purely the direct costs of clinical treatment and intervention. In section 6.4.1.9 it was discussed that the HAE condition, in the same way as for other rare or chronic diseases, also triggers indirect costs. The figures on indirect costs were only directional as they not only aggregated all degrees of severity, but also, they did not differentiate across personal job situations, or the family and wealth conditions of the HAE patients incurring them.

6.4.1.10 HAE life-time costs and key drivers

As reported in section 5.4.13.3, the lifetime costs of an HAE patient averaged at between USD 8-10 million per patient, if they took modern prophylaxis treatment. Riedl (2015) conducted and reported on a US survey that described therapeutic decision making depending on a number of factors in line with the concepts of EBM (presented in sections 3.1.6, 3.1.15, 3.6.5, and 3.6.7). In reality, the study found cost and/or insurance coverage was to be the most important factor, in line with the survey conducted as part of this thesis and presented in section 5.1.2.5.

6.4.1.11 Payers perspectives on costs

The discussion in section 6.4.1.9 and the magnitude of the costs of treating HAE strongly suggest that payers pay a crucial role in funding treatments, in line with section 3.5.5 and 5.4.13.5. Few patients and their families can shoulder yearly treatment costs that can become hundreds of thousands of dollars. Research has forecasted an average of new five orphan drug approvals per year with annual per-patient costs between a few thousand dollars to more than half a million dollars (Schey, 2011). Payers need also to factor in that most rare conditions are genetic, chronic and patients need treatment for life. In the case of orphan drugs costing several hundreds of thousands of dollars per year, copayments for patients can become tens of thousands of dollars per year. Most payers define a maximum copayment amount for patients, which means the payer is left to pay virtually the whole bill. For this reason, some payers require that the prescribing physician obtains approval from the payer before prescribing the treatment (Cohen, 2014), or is ready to justify in detail later why the drug was prescribed. For example, in the UK the National Institute for Health and Clinical Excellence (NICE) plays a key role in reviewing the clinical impact and the relative prices of expensive drugs, with the objective to force manufacturers to agree to price reductions when drugs do not perform as claimed (Hughes-Wilson, 2012). Although these drugs tend to have a high per-unit price, from a strictly economic perspective, this should not imply a special kind of evaluation by payers. Payers are using criteria that are being traded off against one another to decide on reimbursement such disease severity, availability of alternative treatments, level of unmet medical need and cost-effectiveness. The same criteria could be used across all types of drugs, including the orphan ones.

6.4.1.12 Experts and processes to establish criteria for reimbursement decisions

The challenge becomes that payers are struggling to develop appropriate criteria for evaluating which medications should best be prescribed to which patients. To help with the decision-making independent entities such as the Institute for Clinical and Economic Review (ICER) assemble experts, attempt to define the best criteria using a rigorous pharmacoeconomic approach to calculate the cost-effectiveness, and the issue a report with recommendations, which payers, physicians and patients can choose to follow (Zuraw, 2019). In addition to a fundamental de novo analysis and recommendation, before payers reimburse drugs, published list prices are negotiated with pharmaceutical companies as described in section 3.5.14. While at a later stage confidential discounts are possible the effectively paid price - net price - for the drugs can be much lower, list prices are already subject to scrutiny. In order to get a proposed price approved, companies have to demonstrate that their drugs provide value, especially relative to competitors or standards of care already used in the healthcare system.

6.4.1.13 Additional pricing and reimbursement challenges for orphan drugs

Orphan drug price reviews are more complicated as there might be only very few on no alternatives available to patients, and the prices cannot always be linked to market forces, respectively need to factor in the very small number of patients suffering under the rare condition, described in sections 3.7.22 and 3.7.25. Rosenberg-Yunger (2011) reported that with few alternatives available, payers have less negotiating power, and as a result, some orphan drugs can cost payers hundreds of thousands of dollars annually per patient. For this reason, payers pursue pharmacoeconomic evaluations and price referencing. Authorities and payers reference the prices internationally in the quest to optimize their spending as described in section 3.5.18. Price referencing takes place by sharing information and pharmaceutical companies attempt to maintain consistent prices globally. If in one country the price agreement is lower, this will trigger reactions from the others and with rare diseases the impact is multiplied considering that patients tend to stay on treatment for life. On the other side, in some healthcare systems lifesaving or life-extending treatments are labelled as essential and therefore are more likely to obtain reimbursement. An additional challenge for payers when making reimbursement decisions is the perceived risk of over-medication and economic inefficiency when a self-administered drug costing several thousand dollars per dose is given to patients to decide when and how often to take. When payers analyze the clinical benefits and the cost-effectiveness of drugs to be reimbursed, RWE is used to understand the value of a drug in a real-world setting. Additionally, payers have to consider the long term in all relevant dimensions such as efficacy, safety and costs. As discussed in sections 3.5.14, 3.7.22, 3.7.25 and 3.7.28, the assessment for orphan drugs is more difficult and often less rigorous than for non-orphan drugs. Demonstrating cost-effectiveness is difficult in rare diseases using traditional methods.

6.4.1.14 Patient perspectives on payers' decisions

The reviews by the payers and results achieved could be disappointing for patients who are seeking improved treatments. A number of limitations and opportunities for improvement could be identified. For example, when reviewing the pharmacoeconomic considerations, a possible disagreement could already arise from a different understanding of the underlying clinical assumptions, the estimates on the impact on QoL, the inclusion or exclusion of indirect costs, or the consistency or not with the ethical principles of medical decision making. Zuraw (2109) raised that the (Incremental Cost Effectiveness Ratio (ICER) studies likely underestimated the percentage of attacks that would be treated with costly on-demand medications, did not fully include the need for retreatment, or assumed no difference in survival between the different treatment approaches. As indicated in section 6.4.1.4, these considerations only factor in the direct costs of treatment, and do not factor in the alternative costs of no treatment, which manifest as hospitalizations, ER visits, indirect costs and death. Additional benefits for the patients, the healthcare structures and society could be included for truly holistic review and decision making on which treatments should be paid for by payers or society. Questions to be considered are for example if the treatment would significantly reduce the patients' caregiver or family burden, if it would provide positive clinical outcomes in patients for whom other available treatments have failed (for example

thanks to a novel mechanism of action or approach), if it would positively impact the patients' world outside their families, or if it would impact the healthcare system infrastructure. Beyond benefits, contextual considerations should also be made such as if the treatment prolongs life or improves QoL in patients with a particularly debilitating condition which also causes a high lifetime burden of illness, if the treatment is novel or offers significant improvements (such as long-term benefits). ICER considerations for HAE and rare conditions are made difficult and are subject to limitations for the same reasons discussed in 3.7.15. Scientific data is based on relatively small sample sizes, few clinical trials are available, and they are of short duration. Specifically, for HAE there is also a lack of data on the natural history of attack rates over patients' lifetimes (ICER, 2018).
Section 5.2.1.4 illustrated the perception treating physicians have on how much payers pay to reimburse treatment for HAE patients, as collected through the survey. The results suggest that patients bear a higher share of costs in the lower ranges and the situation becomes inverse for higher ranges. Payers were observed as funding more than USD 100,000 per year to about 20% of the HAE patients, while less than 4% of patients incur costs of more than USD 50,000 per year.

6.4.1.15 HAE patients' perspectives on costs

The survey with physicians treating HAE patients found in section 5.2.1.1 that one-quarter of physicians treating HAE patients didn't know if their patients carried part of their treatment costs, if they suffered from missed income or if they incurred indirect costs. It found that 38% of physicians believed that less than 10% of the patients were paying any part of the treatment costs. For a condition that has such profound impact on life through debilitating and potentially fatal attacks which affect every aspect of day-to-day activities, and of which treatment costs are known to be in the tens of thousands if not hundreds of thousands of dollars per year (see section 5.4.13), these answers might be surprising. A possible explanation could be that these physicians operate in countries where all healthcare costs are unconditionally reimbursed as described in section 0. An alternative explanation could be that these doctors focus exclusively on the clinical situations and potential outcomes of their patients, leaving completely alone considerations of QoL, income- and indirect costs. The survey also reported that 38% of physicians believe that less than 10% of the patients are paying any part of the treatment costs. Such realities would be ideal from a patient perspective and correspond to full universal reimbursement of all costs as described in section 0. The answer that one-third of patients incurred zero costs seemed incongruent with the other answers to questions in the survey and indicated that more could be done to generate awareness and transparency on all direct and indirect costs. With knowledge of the true financial impact, physicians and payers could possibly make more efficient treatment decisions from both an individual and aggregate viewpoint. Having insights on all cost drivers could induce different therapeutic decisions and allow for a different perspective on treatments that are highly expensive yet life-changing.

6.4.1.16 HAE patients' contributions to the treatment costs

Section 5.2.1.2 additionally illustrated from the survey that only 19% of patients are reported to have to contribute to a copayment. This figure may seem unexpected as most healthcare systems demand some form of copayment to reduce drug wastage, improve compliance and to reduce costs. Lastly, a percentage of physicians answered that some of the patients had to carry all treatment costs out of pocket, which could be a significant outlay when looking at the figures discussed in sections 5.4.13 and 6.4.1.9. A cross-reference with the countries of origin of these specific answers indicated these physicians working in emerging countries such as India and Brazil, where healthcare coverage, ability to reimburse and pathways to access to orphan drugs were not yet fully in place.

The search on social media discussed in section 5.3.1.2, the sharing of experience among patients on how to address the challenge of covering the high costs of orphan drugs described in sections 3.7.22 and 5.4.13). In their postings on social media patients also shared how to navigate through the insurance and reimbursement process, which has become more cumbersome for reasons described in sections 3.7.25 and 3.7.26. The postings showcased from real-life cases on a public online platform the implications of the double agency theory discussed in section 3.6.4.

6.4.1.17 Cost-effectiveness considerations and additional complications

It is established that using cost-effectiveness as a key parameter for medical decision making is necessary and valid for a healthcare system with constrained resources. In the specific case of prophylaxis treatments for HAE, the high variability of the disease across patients and within patients over time, combined with the high sensitivity of the cost-effectiveness dependence on highly variable assumptions, make a general cost-effectiveness analysis for payer's decision making impossible. Any of the prophylactic drugs can fall on either side of the cost-effectiveness thresholds depending on the patients or even depending on different moments in the life of the patients. Additional considerations complicate the situation. Healthcare per se and medical decision-making by a physician, on the other hand, is intrinsically linked to ethical principles of fairness, reducing pain and beneficence. As Zuraw (2019) stated, treating physicians have to follow these principles. Patients and society expect these principles to be followed by all stakeholders, hence once more the necessity to combine the three perspectives of EBM, HE and QoL into one framework. The above discussed indirect costs resulting from missed work, reduced productivity at work, missed education, missed career and income opportunities, will be covered in the next section. They are poorly defined and quantified, also due to the high variability and the small patient population to analyze, and further not considered by payers when making pricing and reimbursement decisions. A study states that because of these reasons, it is likely that the true indirect burden of HAE is significantly higher than reported in the literature (Wilson, 2010). Research and publications sometimes refer to the role played by caregivers, who provide assistance to patients either during attacks or during the administration of intravenous medication at home. Such support may result in caregiver absenteeism and generated further indirect costs that are not captured, not considered for reimbursement and left uncovered. Focusing back on the HAE patients and comparing all different treatments

methods, it appears that the economically most efficient one is self-administered therapy, especially ‘‘on-demand’’ for HAE attacks. At least one study (Bhasin, 2014) reached a similar recommendation leading to the suggestion to physicians to encourage self-administration as a mean to maximize cost-effectiveness while enabling patients to become more independent.

6.4.1.18 Conclusion on cost considerations

The study by means of a survey to HAE physicians described in section 5.1, the study on social media described in section 5.3 and the first part of the meta-analysis described in sections 5.4.1 to 5.4.13 have covered the dimensions in which HAE impacts patients, caregivers, the healthcare system, the payers and society as a whole. The dimensions could be grouped as follows:

(1) The clinical course of the disease with its early onset, the delayed diagnosis, the cases of misdiagnosis and wrong treatments, the chronic nature and the variability of the symptoms as described in section 5.4.1.

(2) The symptoms which manifest as attacks that are unpredictable, can be prolonged, can vary in frequency, can be disfiguring, painful, debilitating and even life-threatening; Next to direct symptoms are a range of comorbidities discussed in section 5.4.7.

(3) The treatments which are currently not available to all patients globally, are expensive and can cause side effects.

(4) The costs which go beyond the treatments and include direct costs by physicians, hospitalizations and ERs, but also the indirect costs arising from lost work and school productivity for both patients and caregivers.

6.5 QoL

6.5.1 Measures of QoL

Section 5.4.14.1 identified different variables and instruments that have been used to measure QoL of HAE patients. The thesis concluded from the research that overall data was limited due to a small number of patients' studies and the lack of well-defined disease-specific QoL instruments. Different studies used many QoL instruments making it difficult to compare findings on the humanistic burden between them. While HAE symptoms were the starting point for all QoL considerations due to the attacks, the triggers and the comorbidities, partners and families of the patients were also affected. The relationships between HAE patients and their immediate social environment were impacted - for example by the ability to perform joint activities, or by the need of the family and caregivers to help administer the medicines. Day-to-day activities are affected by the ability, or not, to perform physical and cognitive tasks, for example when the mind is fixated on depression, anxiety, worry, embarrassment. Social life takes a toll when the patients are or feel constrained from traveling and engaging socially. Work-life and education are impacted by absenteeism, reduced productivity because of diminished physical and mental capacity. Vitality and energy levels are impacted by fatigue, sleeping disorders due to anxiety, or directly sleeping time lost to attacks with their pain, or impossibility and fear to perform sporting activities. Medical care is impacted as patients need to see physicians, sometimes be hospitalized or treated in ER. Measuring all the factors in a consistent and simple manner across a representative sample of patients over time seems not to have been attempted so far.

6.5.2 QoL impact from HAE attacks

In section 5.4.14.4 different studies that collected QoL data on patients during HAE attacks have been analyzed. These studies were performed on patients that were diagnosed and on treatment. The variance of the days per year missed was relatively high, which could be explained by the studies' different eligibility criteria and the different ways of treating the condition in different healthcare systems. Additionally, HAE attacks and the condition itself presents in different degrees of severity as discussed in 5.4.3 and patients suffer greater QoL impact when having more severe attacks as they are more debilitating. More severe attacks cause HAE patients to stay at home and miss work and other activities, while milder attacks can be less disruptive. The studies identified in section 5.4.14.4 seemed to show that despite following the standards of care, HAE patients still have frequent and painful attacks, continuing to experience significant impairment physically and emotionally both during and between the attacks.

As the data presented in section 5.4.10 suggested, the QoL outcome for HAE patients could be even worse when there are treatment delays. The delays not only prolong unproductive time, but increase the risk of treatment failure, the amount of time in pain and the time until attack resolution is obtained.

6.5.3 QoL impact from HAE treatment

Section 5.4.14.5 illustrated the relatively minor impact of the HAE treatment themselves on the patients, when compared to the attacks. However, section 6.3.3.12 illustrated the multiple benefits of enabling self-administration (or home treatment) of HAE medication. These included better clinical outcomes such as significant decreases in attack duration, reduced need for pain medication and lower attack severity, with no increase of serious adverse effects or tolerability issues. In addition, home treatment was shown to lead to lower costs and improved QoL, as these patients scored better psychologically and physically, including on the depression and anxiety scales. One possible identified explanation was that self-treating patients had and perceive to have had greater control over their condition and their lives. The thesis confirms the statement by Devercelli (2018) that despite the strong progress on modern treatments and home therapy, the burden of HAE on patients' daily lives still remains high and could be reduced.

6.5.4 HAE burden on education and work

Section 5.4.14.6 illustrated from a number of data sources the different dimensions of burden that HAE can cause to its patients. Such a widespread array of impacts begins already during childhood and reinforces the need for early awareness and diagnosis, as well as a meticulous medical follow-up with the youngest patients. Section 5.4.14.9 reported the impact that HAE could have on the patients' educations, which could have long term repercussions.

The survey conducted with physicians treating HAE reported in section 5.1.3.2 reported a wide range of days of school, work or other commitments missed by HAE patients due to their condition. The figures differ across physicians and across studies reported in the literature. A possible explanation could be that several published studies were based on data collected before modern treatment was widespread and that during the time of this thesis, patients were treated more effectively. This could have led to a significant reduction of the number of days lost in such a way that it is not so much of an issue any longer. An alternative explanation could be the possible disconnect between patients and physicians described in section 3.6.7 as one of the challenges of the agency theory, and/or a combination of the two explanations. If a disconnect between physicians and patients was the cause, then it would suggest a missed opportunity for better clinical outcomes and QoL, as physicians might change treatment towards drugs with higher efficacy, if they knew of the full picture (i.e. missed number of days) of their patients and the impact this has on their lives.

6.5.5 HAE impact on the personal life

The survey with HAE-treating physicians additionally reported in section 5.1.3.3 that they observed 50% of patients felt an impact on family planning. Such results could be explained by the hereditary (dominant autosomal) nature of the condition with a 50% probability that the offspring of an affected patient will also bear the disease, as described in section 3.8. This impact of the HAE condition could also help explain the depression comorbidity, when for example some patients decide not to have children under the fear of passing on the condition and its pain. The patients who decide to procreate might subsequently suffer under the anxiety comorbidity, driven by sentiments of hope, anticipation and possible despair.

The meta-analysis of the literature produced higher results (see 5.4.14.9) with 44% of patients reported suffering a hindered education, and between 50% and 60% being exposed to career consequences. Participating physicians reported also that a weighted average of 18% of patients carried no long-term consequence from their condition. This result could be explained by these patients being either asymptomatic or by having achieved a very good control through a successful therapy. Overall the survey showed better results than what was reported in the literature, which could be explained by the different cohorts and by the fact that some of the published studies were much older. Contemporary treatments have led to improved efficacy more generally (as described in sections 5.4.10.2, 5.4.10.3, 5.4.11.2 and 5.4.11.5).

6.5.5.1 Awareness by physicians on HAE burden for patients

The survey reported that depending on the long-term aspects, between 12% and 82% of the participating physicians were unable to answer, with an average of 35%. The difficulty might have been driven by HAE patients showing significant differences in how the condition manifests (frequency, location, severity of attacks) (see 5.4.2, 5.4.3, 5.4.4, 5.4.5), but also in how they let the disease influence their life, some in everything they do, others much less or not at all. The search on social media reported the experience sharing among patients in section 5.3.1.2. A significant part of postings either in this segment or the one on inspirational content had as its objective to support fellow patients in the achievement of "leading normal life", consistent with one of the key themes of HAE and debilitating rare conditions as described in sections 5.3.1.6 and 5.3.2.8. Forty per cent of the physicians participating in the survey were unaware of the working status of their patients, as reported in section 5.1.3.4. While these results could again reflect a certain disconnect as described in section 3.6.7, they might also appear as surprising when considering how impactful the condition is on the education and career of the patients as quantified in section 5.4.14. On the other hand, this result was somewhat consistent with the answers provided to the previous questions in the survey in regards to the criteria relevant to decide on the treatment to pursue: only 30% of physicians had stated that the profession and education of their patients was very important to decide on the treatment (see section 5.1.1).

6.5.5.2 Conclusion on QoL impact on HAE patients

Combining all discussed consequences, HAE can result in productivity losses and ultimately financial costs to the individuals and their families, as they cannot achieve their full potential career and earning potential. With the key dimensions education, professional career and social life burdened, the introduction of modern therapy offered after 2008 for the first time significant positive clinical outcomes. More than a decade later and during the writing of this thesis, the data collected in the three studies presented in the sections 5.1, 5.3 and 5.4 suggests that despite the availability of treatments, a large number of possibilities persist on how the life of HAE patients can still be restricted due to the condition.

The research on social media conducted for this thesis illustrated in section 5.3.1.6 how the burdens of the conditions also expressed themselves in the postings by the HAE patients on the platforms. With the hardships caused by the symptoms and the comorbidities, the

challenges of obtaining the right diagnosis and of getting the best (and costlier) treatment approved. Depression and anxiety were commonplace. Patient groups and the social media community served not only as platforms for the exchange of information, but also as instruments that provide emotional support, where patients shared with each other life advice and emotional support. On Twitter, this type of postings represented only about 2% of the total, as presented in section 5.3.2.8. It appeared that on social media offering life advice and support specifically on HAE concerned only a small minority of users.

6.5.5.3 QoL impact on caregivers of HAE patients

Caregivers of HAE patients are affected by the condition in multiple ways and section 5.4.14.10 reported on data available in the literature. The survey of physicians conducted for this thesis reported in section 5.1.2.12 that a weighted average of 38% of patients was observed to require help from family members when having an attack or when administering treatment. This figure was less than the 52% reported in the meta-analysis in section 5.4.8. As studies have shown, support by other people is required when taking a patient suffering an attack to the ER or hospital (which can happen on average three times per year as per section 5.4.8.3, or to provide help when administering intravenous medication for prophylaxis. Such support is clearly necessary for children and youths, but also provided to adult patients and a source of indirect costs and QoL reduction that affects the family in addition to the patient. The survey also illustrated that on average 41% of treating physicians didn't know if their patients were requiring support. This figure seems relatively high given the severe burden of the disease compounded by the burden of treatment. This might be another indicator that the communication necessary between physicians and patients described in section 3.6.7 is not ideal and could be deepened to achieve a better understanding of the patients' needs leading to improved clinical outcomes and reduced risks.

The true costs incurred by caregivers were difficult to quantify and may change considerably between patients and healthcare systems. In the pursuit of a holistic assessment of the cost-effectiveness of HAE treatments for reimbursement as described in section 5.2.1.1, they should be factored in. For example, when prescribing prophylaxis treatments, it should be taken into account that such therapy would reduce not only the number of attacks and the burden on the HAE patients, but also decrease the caregiver's physical and emotional burden.

6.5.5.4 Other QOL aspects affecting HAE patients

The search on social media reported in section 5.3.2.6 that about 4% of posts on Twitter were offering goods and services for patients with HAE. It appeared that these offerings were specific to HAE patients suggesting they have a value contributing to QoL improvements for the patients. Most of the postings were offering material to generate awareness, which could be seen as evidence for patients attempting to close one of the gaps of the agency model. However contrary to the agency model described in section 3.6.7, from this part of the research it appeared that the information asymmetry was in favor of the patients, who seemed to be better and more rapidly informed about progress than their

physicians and other stakeholders who also have a say on the therapy. Another type of postings in this category was offering scholarships to patients suffering from HAE. These acquired a particular meaning since people living with HAE are burdened by both additional significant financial outlays (see section 5.4.13.11) and by a negative impact on their education and career prospected due to absenteeism and other consequences of the condition (see section 5.4.14.6 and 5.4.14.7). For a youth with a debilitating chronic genetic condition which deeply affects not only his or her QoL but also the ability to attend educational programs, any form of help that could alleviate the additional burden can be transformational. Using social media for this type of offer may generate hope and success offsetting some of the depression and anxiety observed in sections 5.4.7.1 and 5.4.7.2.

Combining the results of different studies: taking on-demand treatment as soon as possible after the onset of an attack is most likely possible if the HAE patient can perform home administration (see section 6.3.3.12). This would reduce the duration of the attack, the severity of the attack, and therefore mitigate also the QoL impact by reducing, and possibly eliminating the time wasted through absenteeism from the job, education or from social life.

7 CHAPTER SEVEN - CONCLUSION

7.1 Connection between thesis results, RQs and emerging themes from the literature search

The literature search identified recurring themes which in section 3.10 were connected to the problem statements and RQs:

RQ 1.1: How do different stakeholders and decision-makers have an impact on patients with rare diseases?

RQ 1.2 Are diagnosis and treatment decisions made with EBM, QoL, HE and RWE considerations in mind?

RQ 2: How can the decision-making process and the available and potentially available data be combined to allow the stakeholders to make economically more efficient therapeutic decisions with better health and QoL outcomes?

Pursuing the research design and methodology described in section 4, the results described in sections 5.1, 5.3 and 5.4 were attained and discussed in section 6. All combined they can be mapped to the themes and RQs as illustrated in Table 7.1.1.

Theme	Sections linking to themes	Related RQ	Section where presented results	Section where discussed results
Physicians treat patients based on a combination of scientific evidence and personal experience.	3.1.1	RQ 1.1	5.1.2.5, 5.1.2.13, 5.1.3	6.2.2.1, 6.2.2.2, 6.2.2.10, 6.2.2.11
Healthcare is mostly funded by payers who face tradeoffs and constraints.	3.5.5, 3.5.6	RQ 1.1	5.1.2.5, 5.2.1.1, 5.2.1.2, 5.4.13.5, 5.4.13.8, 5.4.13.9	6.4.1.11, 6.4.1.12, 6.4.1.13, 6.4.1.17
Pharmaceutical companies pursue market access activities to enable and influence the prescription of drugs and treatments by the physicians for the patients.	3.5.9, 3.5.10, 3.5.11	RQ 1.1	3.5.9, 3.5.10, 3.5.11	6.3.3.11

Theme	Sections linking to themes	Related RQ	Section where presented results	Section where discussed results
Agency theory describes the dynamics between the stakeholders, the resulting potential challenges and approaches to overcome them.	3.5.7, 3.6.1, 3.6.2, 3.6.3, 3.6.4	RQ 1.1	5.1.1, 5.1.2.5, 5.2.1.2, 5.3.1.2, 5.3.1.5, 5.3.2.3, 5.3.2.5, 5.3.2.5	6.1, 6.2.2.3, 6.2.2.12, 6.5.5.1
Established instruments to support Evidence-Based Medicine (EBM) such as Randomized Clinical Trials (RCT) are available, have been introduced and studied.	3.1.2, 3.1.3, 3.1.4, 3.1.5, 3.1.6, 3.1.7, 3.1.8, 3.1.9	RQ 1.1, RQ 1.2	5.1.2.5, 5.3.1.7, 5.3.2.9, 5.4.10, 5.4.11	6.3.1.7,
RCTs have limitations especially for rare conditions. Other innovative approaches are being used-	3.2.1, 3.2.2, 3.7.13, 3.7.15, 3.7.16, 3.7.17	RQ 1.2	5.3.1.7, 5.3.2.9, 5.4.13.8	6.3.3.11
Clinical guidelines support the execution of EBM by ensuring high quality medical practice from a clinical perspective.	3.1.10, 3.1.11, 3.1.12	RQ 1.2	5.1.2.5, 5.1.2.6, 5.1.2.7, 5.1.2.13 5.4.10, 5.4.11	6.3.1.1, 6.3.1.2, 6.3.1.3, 6.3.1.4
Treatment guidelines have limitations due to information gaps, their strict focus on medical parameters (vs. incorporating also QoL and HE considerations) and the incomplete involvement of all stakeholders.	3.1.13, 3.1.14, 3.1.15, 3.1.16	RQ 1.2, RQ 2	5.1.2.2, 5.1.2.5, 5.1.2.6, 5.1.2.7,, 5.1.3.4, 5.2.1.1, 5.3.1.2, 5.3.1.5, 5.3.2.3, 5.3.2.5, 5.4.1.3,	6.3.1.2, 6.3.1.4
QoL is a key factor which describes the patient's point of view. For rare conditions the families of the patients also play a prominent role and QoL acquires more importance due to the severely debilitating manifestations of the conditions.	3.4.1, 3.4.2, 3.4.3, 3.4.5, 3.4.6, 3.7.12, 3.7.19l	RQ 1.1, RQ 1.2	5.1.2.5, 5.1.2.8, 5.1.2.9, 5.1.2.13, 5.1.3, 5.4.14	6.3.1.7, 6.3.3.2, 6.3.3.18, 6.3.3.19, 6.5

Theme	Sections linking to themes	Related RQ	Section where presented results	Section where discussed results
Health Economics (HE) and the need to contain healthcare costs influence the decisions on treatments	3.5.1, 3.5.2, 3.5.3, 3.5.4, 3.5.8	RQ 1.1, RQ 1.2	5.1.2.5, 5.1.2.8, 5.1.2.9, 5.2, 5.4.13	6.2.1.18, 6.2.2.4, 6.3.1.7, 6.3.3.20, 6.4
The significant QoL implications of rare conditions generate additional costs.	3.7.20, 3.7.21	RQ 1.2	5.1.3, 5.2, 5.4.7, 5.4.14	6.3.3.2, 6.3.3.14, 6.3.3.18, 6.3.3.19, 6.3.3.20, 6.4.1.2, 6.5
Rare diseases face additional challenges on clinical evidence, QoL and HE, which pose additional hurdles and complexities for all stakeholders, caused by data paucity, low awareness, high treatment costs, and in most cases no definitive cure.	3.4.4, 3.5.19, 3.7.1, 3.7.2, 3.7.3, 3.7.4, 3.7.5, 3.7.6, 3.7.7, 3.7.8, 3.7.9, 3.7.10	RQ 1.2	5.1.2.11, 5.1.2.12, 5.1.3, 5.2, 5.3.1.3, 5.3.1.7, 5.3.2.4, 5.3.2.7, 5.3.2.9, 5.4.7, 5.4.13, 5.4.14	6.2.1.6, 6.2.1.14, 6.2.1.17, 6.2.1.18, 6.2.2, 6.3.3.2, 6.3.3.11, 6.3.3.13, 6.4.1.1, 6.4.1.2, 6.4.1.4, 6.4.1.5, 6.4.1.8, 6.4.1.10, 6.5
Orphan drugs treating rare conditions are subject to similar costs compared to other drugs, but command significantly higher prices for different reasons, adding pressure on reimbursement decisions for the payers.	3.7.22, 3.7.23, 3.7.24, 3.7.25, 3.7.26, 3.7.27, 3.7.28	RQ 1.2	5.2, 5.4.13	6.4.1.1, 6.4.1.7, 6.4.1.11, 6.4.1.12, 6.4.1.13

Theme	Sections linking to themes	Related RQ	Section where presented results	Section where discussed results
Physicians could face dilemmas between the clinical guidelines and the need to meet the expectations as described by the agency theory. The compensation and the incentives for the physicians effectively drive the decision-making process and are essential to successfully achieve the desired outcomes.	3.6.9, 3.6.10, 3.6.11, 3.6.12, 3.6.13, 3.6.14, 3.6.15	RQ 1.2	5.1.2.5, 5.1.2.9, 5.1.2.13	6.3.1.1, 6.3.1.2, 6.3.1.3, 6.3.1.4, 6.3.1.5, 6.3.1.6, 6.3.1.7
Additional considerations (such as risk management) and governance mechanisms (such as trust-based governance) need to be factored into the decision-making process and the integration of the perspectives.	3.6.15, 3.6.16, 3.6.17	RQ 1.2	5.3.1.5, 5.3.1.6, 5.3.2.3, 5.3.2.4, 5.3.2.5, 5.4.1.3,	6.2.2.1, 6.2.2.2, 6.2.2.3, 6.2.2.10, 6.2.2.11, 6.2.2.12, 6.5.5.1
Real World Evidence (RWE) complements RCTs to enable more comprehensive treatment decisions based on clinical evidence.	3.3.1, **Error! Reference source not found.**, 3.3.2, 3.3.3, 3.3.4, 3.3.6,	RQ 1.2	5.1.2.13, 5.1.3, 5.2, 5.3.1.7, 5.3.2.9, 5.4.14	6.4.1.1, 6.4.1.2, 6.5.4, 6.5.5
HE discussions between payers and pharmaceutical companies are shifting from volume- to value-based payment models which build on RWE	3.5.12, 3.5.13, 3.5.14, 3.5.15	RQ 1.2	5.2.1.2, 5.4.13.5, 5.4.13.6, 5.4.13.7, 5.4.13.8, 5.4.13.9	6.4.1.1, 6.4.1.2, 6.4.1.4, 6.4.1.11
When deciding on the reimbursement of orphan drugs, payers need to look at innovative approaches	3.7.14	RQ 1.2	5.4.13.6, 5.4.13.7, 5.4.13.8, 5.4.13.9, 5.4.14.6	6.4.1.1, 6.4.1.4, 6.4.1.5, 6.4.1.8, 6.4.1.11, 6.4.1.12, 6.4.1.13

Theme	Sections linking to themes	Related RQ	Section where presented results	Section where discussed results
RWE is required to understand and include QoL and HE into therapeutic decision making and funding. For rare diseases the importance of RWE is higher to compensate for the limitations of RCT.	3.3.5, 3.3.7, 3.3.8, 3.3.9, 3.7.18	RQ 2	5.1.2.5, 5.1.3, 5.2.1.3, 5.2.1.4, 5.4.13.2, 5.4.13.3	6.2.2.3, 6.2.2.5, 6.3.1.4, 6.3.3.11
Therapeutic decision making has evolved over time paving the way for a more holistic approach that combines all perspectives and builds on the double-agency model	3.6.5, 3.6.6, 3.6.7, 3.6.8	RQ 2	5.1.2.5, 5.1.2.13, 5.1.3, 5.4.14	6.3.1.7, 6.3.3.3, 6.3.3.14, 6.3.3.18, 6.3.3.19, 6.3.3.20, 6.5
Price differences for same treatments across healthcare systems and different levels of payment coverage suggest different levels of development and possible inequalities and inefficiencies.	3.5.18	RQ 2	5.2, 5.4.13	6.2.2.8, 6.4.1.3
Combining EBM, QoL and HE requires the intersection of different paradigms and managed care models aim to improve the health of the covered patients while reducing costs.	3.4.7, 3.5.16, 3.5.17,	RQ 2	5.1.2.13, 5.1.3, 5.2, 5.4.13.5, 5.4.13.6, 5.4.13.8, 5.4.13.9, 5.4.14	6.3.1.4, 6.3.1.7, 6.3.3.12, 6.3.3.18, 6.3.3.21, 6.4.1.2, 6.5

Table 7.1.1- Connection between emerging themes from literature search, RQs and results from the research

7.2 RQ 1.1 - Impact of different stakeholders and decision-makers on patients

7.2.1 Importance of the question and underlying theoretical framework

RQ 1.1: How do different stakeholders and decision-makers have an impact on patients with rare diseases?

This thesis aimed to measure the impact of the different stakeholders and the roles of the different perspectives in the decision making and execution of alternative therapies, with the objective to explore the combination of all in order to attain superior outcomes in a more cost-effective way. Social acceptability plays a key role, as Doll (Doll, 1974) already noted, "there is no point providing a health service that is clinically effective and economically efficient, but no-one wants". The agency model applied to healthcare and discussed in section 3.6.1 describes the most immediate way on how patients are impacted by physicians: patients are principals who depend on physicians for medical advice, and physicians are agents who are responsible for making optimal health-related decisions on behalf of the patients. When the payers, public or private insurances which ultimately fund medical treatment (see 3.5.5), and their constraints (see 3.5.6) are factored in, the theoretical framework to be used becomes the double agency model discussed in section 3.6.4 with the subsequent conclusions on the decision-making (see 3.6.5), eventual disconnects (see section 3.6.7), possible consequences and how they could be mitigated (see section 3.6.8 and following).

7.2.2 Answer contributions from the study and the meta-analysis

A survey with treating physicians has confirmed the impact both physicians (see section 5.1.1) and payers have on clinical outcomes and QoL of patients. Other stakeholders such as family members, caregivers, patient organizations, etc. can play a role, however the main and more directly affected one, and in scope of this thesis, are the patients, the physician and the payer, who encourage physicians to follow treatment guidelines, leading to outcomes with increased cost-effectiveness, utilizing the HE methodology discussed in section 3.5 and consistent with replies to the survey in section 5.1.1). The evaluation of health care depends on the criteria used by every stakeholder. Historically it has been advocated that three criteria should be used: clinical effectiveness, economic efficiency and social acceptability (Doll, 1974). EBM (see section 3.1) is defined as the explicit, judicious, and conscientious use of current best evidence from health care research in decisions about the care of individuals and populations (Brian Haynes, 2002). Once a diagnosis of the condition is confirmed, ideally patients and physicians decide together on the course of action based on the available and known evidence produced by RCTs (see section 3.1.15) and ideally also by RWE (see section 3.3). To facilitate decision-making and reduce risks, both physicians and patients can follow the guidelines discussed in sections 3.1.10, 3.1.12, and 3.1.13), which are built on evidence and experience. Payers also attempt to enforce guidelines as their recommendations are proven or more likely to produce maximized clinical outcomes and reduce the possibility of unnecessary costs generated by misdiagnosis, or inappropriate interventions. The treatment decision by the physician should not only build on research and

clinical evidence discussed in section 3.2, but also reflect the patient's values, preferences, circumstances and local context (Hoffmann, 2014). Lastly, a broader perspective developed in attempting not only to achieve the best clinical outcome, but to holistically maximize QoL, which is directly experienced by the patients on a daily basis and over the course of their lives (see 3.4 and responses by physicians to survey 5.1.3).

7.2.3 Validation of agency theory as theoretical framework

Agency theory describes the partnership between patients and clinicians (see section 3.6) and how it presumes that the treating physician facilitates patient involvement and is open to adjusting the treatment to the preference of the patient. Studies have shown that patients are unable to fully partner during the clinical encounters, and at the same time, physicians don't like their patients to engage (or interfere) in the decision-making process (Couet, 2013). Lack of time, skills, knowledge, mutual respect and effective communication processes pose barriers to effective shared decision-making (Staniszewska, 2014). A large portion of doctors believe they know how much the patient wants to be involved and even what therapy the patient would prefer, if he or she had full access to and ability to fully interpret the clinical data. This scenario may be more likely with rare conditions where the information asymmetry between physicians and patients is more significant, and where clinical data and experience are not yet translated into common language and made accessible to the layman through the normal channels. However, the survey has also highlighted that for some critical matters, a large share of physicians is not able to answer basic questions such as what the approximate financial implication or QoL impacts of the condition are for patients (see sections 5.1.3 and 5.2). Research on social media analyzing postings by HAE patients has identified instances where patients are advising one another on how to communicate with doctors, highlighting gaps, theoretically known through the agency theory, that could be closed). Nevertheless, EBM can turn into forcing evidence and measures onto a not fully engaged patient resulting in suboptimal adherence and clinical outcomes. The best working solution is best described as shared decision-making, where both clinician and patient jointly assess options with their benefits and harms, and together decide, incorporating the patient's values, preferences, and circumstances (Hoffmann, 2014). The survey with physicians has also confirmed that the patients are the most important stakeholders (besides the doctors themselves) necessary to reach a treatment decision (see 5.1.1). High-quality patient experience demands a few additional attributes from the interaction with the physician: the patient is an active participant, the physician is responsive with his or her services, he or she offers an individualized approach, provides a lived experience that includes continuous care and relationship, and lastly offers timely communication, information and support (Staniszewska, 2014), which takes commitment and time on both sides.

7.2.4 Analysis of the variables

Section 4.2.1 suggested from the literature search that patients and physicians are the key stakeholders, surrounded by other stakeholders or influencers such as payers (insurance companies), family members, caregivers, patient advocacy groups, other healthcare professionals (e.g. nurses, pharmacists), pharmaceutical companies, regulatory bodies, media). The importance and order of priority of the variables was analyzed in section 5.1 and is consistent with the outcomes of the survey and the research on social media described in section 5.3. The metanalysis performed and discussed in section 5.4 indicated especially physicians and patients to be the main stakeholders exposed to the condition and sources of data and insights on the condition and its treatment. The metanalysis also suggested the payers as key stakeholders, including the type of considerations they make to decide which treatments to fund. The criteria utilized for diagnosis, treatment decisions and for assessment of outcomes stated in section 4.2.2 were also substantiated by the survey with treating physicians in section 5.1 and found some mention in the social media as discussed in section 5.3. Epidemiology, symptoms (frequency, location, and severity) of HAE attacks, fatalities, co-morbidities, QoL impact and treatment costs have been extensively studied through numerous studies, surveys and RWE and consolidated conclusions discussed in the meta-analysis in the sections from 5.4.1 to 5.4.14). Analogously QoL variables measuring the burden of disease such as QoL scores using different types of instruments, days missed from work, school or social life due to the condition, hindered careers and reduced incomes, have been described both by the survey in 5.1, while also being measured, analyzed and discussed in the meta-analysis in section 5.4. Lastly, the economic costs of a condition, its treatment, and its impact on society comparing different alternatives, is the objective of HE and RWE as described in sections 3.3 and 3.5. The variables are the costs expressed in monetary terms as they are borne by patients, caregivers, employers, the healthcare system and society as a whole. The survey discussed in section 5.1 has shown costs and financial implications of the condition to play a role in the choice by the physician of a treatment for the patient to pursue, although a large share of physicians seems unaware or unable to quantify the full and true costs of the condition they treat. In the meta-analysis (section 5.4.13) the thesis identified a number of reports which quantified the different costs that are resulting from a patient carrying the HAE condition.

7.2.5 Assessment of methodology used

The thesis used a combination of a survey, a search of social media and a meta-analysis on a wide spectrum of publications, research reports, clinical studies, RWE, guidelines that were all peer-reviewed and cover the HAE conditions and aspects relevant to it. The different approaches provided to be consistent and complementary in their findings, while at the same time confirming the limitations described by applying the double agency theory (see section 3.6.4) to the specific situation of patients suffering from a rare condition such as HAE.

7.3 RQ 1.2 Diagnosis and treatment decisions EBM, QoL, HE and RWE considerations

7.3.1 Answer to RQ 1.2

RQ 1.2 Are diagnosis and treatment decisions made with EBM, QoL, HE and RWE considerations in mind?

The survey with physicians treating patients with HAE provided the data enabling the analysis of the criteria they use to make treatment decisions (see section 4.1 and results in section 5.1.2.5) covering all aspects with different degrees of priority. First priorities appear to be classical EBM parameters expressed in clinical terms such as patient history (symptoms and co-morbidities), the efficacy of treatment and safety. These are followed by health economics and lastly by QoL considerations. The survey highlighted that the physicians' knowledge and ability to answer decreased significantly when considering aspects that are not strictly medical in nature. This finding appears in line with the fact that QoL and HE are areas of expertise that fall outside the strict boundaries of the classical medical education which shapes and forms a clinical physician. The corollary of this observation is that gaps arise as described in the agency theory described in section 3.6, further enhanced by communication barriers between the three main stakeholders physicians, patients and payers. The analysis of the data gathered from the survey, the research on social media and the meta-analysis of the relevant scientific literature, appear to confirm how treatment decisions are made. However the analysis also suggested that the role of non-medical factors is under-represented causing potential additional challenges with patients and suboptimal outcomes from an HE perspective.

7.3.2 Confirmation of the model describing the current situation

The model proposed in section 4.1 appears to be confirmed by the utilized research instruments which include the direct observations of physicians, through a broad survey, and patients, through a search of social media postings, and the payers complemented by a meta-analysis covered in section 5.4, which aimed to include all relevant research and publications on the specific object. The influence of the payers was substantiated by their assessed importance for treatment decisions discussed in section 5.1.1 and the importance of the insurance coverage as a selection criterion for the drugs to be prescribed discussed in section 5.1.2.5. QoL parameters were assessed as relatively less significant and physicians appeared overall less knowledgeable both in quantity and in quality than what is known in the literature, as described in section 5.4.14.

7.3.3 Assessment of methodology used

To answer RQ 1.2 the same methodology and the same sources of data were used, hence the assessment of the methodology could be confirmed. The thesis was able to include a large number of diverse sources including the bulk of scientific literature on the subject, direct contribution by a large number of physicians spread across different geographies, as well as a large number of social media postings by patients themselves. With all sources, the thesis closely approached the level of data saturation without incurring into observations that could

significantly undermine the model or invalidate the theoretical framework utilized. Both model and theoretical framework appear to be validated and the thesis could apply them to the specific rare genetic conditions of HAE, allowing to reach a conclusion which can be extended to other rare conditions.

7.4 RQ 2 Combination of EBM with QOL and HE for better and more efficient outcomes

7.4.1 Importance of the RQ and method to develop an answer

RQ 2: How can the decision-making process and the available and potentially available data be combined to allow the stakeholders to make economically more efficient therapeutic decisions with better health and QoL outcomes?

The combination of the perspectives clinical outcomes (EBM), QoL and HE/RWE has to be pragmatic and consistent, allowing the stakeholders to speak the same language, align their incentives and maximize the outcome for the population. This was the core element of the thesis and the objective was the development of a framework which enables refinements of the therapeutic and funding decisions to produce better health outcomes in a more cost-effective way, leveraging new insights from the studies 1-3, the identified dependencies between EBM, QoL and HE/RWE and the integration into one framework. The framework was expected to determine optimized solutions measured as health outcomes for the patient population achieved in more cost-effective ways. The thesis aimed for the framework to be pragmatic and ready for use in the real world.

The first step was to consolidate outcomes by linking the variables through direct dependencies and co-dependencies (for example clinical decision based on EBM impacts QoL in a specific and measurable way. causing monetary costs and benefits). Subsequently the thesis estimated alternative outcomes by changing the assumptions and the decisions made to produce optimal results by integrating the three perspectives (which could be expressed in statements such as “patients with specific clinical and QoL attributes could benefit from increased prophylaxis treatments which would result in significant better clinical outcomes (reduced number and severity of attacks) which cost marginally more”).

7.4.2 Answer to RQ 2

7.4.2.1 Analysis of stakeholders, decision making process and methodology to provide answer

The stakeholders and the decision-makers who have an impact on patients suffering under a rare condition have been analyzed through different independent studies and the results have been summarized when answering RQ 1.1 in 7.2.2. Within the theoretical framework agency theory, physicians follow the EBM approach described in section 3.1.6, building on scientific research, RCTs that prove efficacy and safety profiles of drugs as discussed in section 3.2.1, with the objective of improving and maximizing the clinical outcomes for the patients. Rare conditions however present themselves with a number of additional challenges (see section 3.7) which begin with the clinical aspects such as low disease awareness, difficulty of diagnosis, recruitment challenges for RCTs (discussed in sections 3.7.16 and 3.7.17), continue with significant QoL impacts due to the frequently devastating impact of genetic conditions (see section 3.7.19) to finish with the important financial considerations that are observed both from a treatment perspective (see sections 3.7.20 and 3.7.22) and from a combination of incremental costs and reduced costs within the patients’

and their caregivers' perspective (see section 5.4.14). The motivation for the thesis explained in section 1.3 was born from the observation that most of these concepts are not considered in a holistic and fully integrated way when treatment decisions are made for and with the patients (see sections 3.6.5 and 3.6.7). The aim of the thesis was to first understand and describe in a structured way the current decision-making process (see section 1.4) confirming the proposed model. Three studies were proposed and executed: a survey with treating physicians described in section 4.3 with results in section 5.1, a study on social media postings described in section 4.4 and results in section 5.3, and a comprehensive meta-analysis which aimed to cover all relevant scientific literature on the chosen condition HAE described in section 4.5 and results in section 5.4.

7.4.2.2 Application of answer to theoretical framework

The three studies confirmed the agency theory model and have contributed to answer RQ 1.1 and RQ 1.2, and additionally, they provided data to enable proposing an answer to RQ 2. Historically already with the advent of EBM the concept of shared decision making was developed as described in sections 3.1.5 and 3.6.5, whereas treating physicians and patients jointly assess the options and decide on the best treatment to pursue. This concept helps to overcome the main challenge identified leveraging the agency theory to describe the physician-patient relationship (see section 3.6.1) with possible disconnects (see section 3.6.7). With increasing costs of medical treatments, further exacerbated within the category of rare diseases and orphan drugs (see sections 3.7.2 and 3.7.3), payers play a prominent role as a small minority of patients can afford the treatments without support by means of reimbursement as described in sections 3.7.20, 3.7.22 and 3.7.25. HE considerations become prominent (see section 3.7.26) and the payers take the role of an additional agent and the double agency theory can be applied as discussed in section 3.6.4. With three main players, patients, physicians and payers, complexity, asymmetry of information and risk of misalignment increase. The data produced with this thesis through a survey described in section 4.3, a primary search of stakeholders content on social media described in section 4.4, and through a meta-analysis of available scientific and published literature described in section 4.5, utilized the variables discussed in section 4.2 and confirmed the model underlying the thesis design described in section 4.1.

7.4.2.3 Possible improvements of clinical practice based on the findings

The findings suggest that room for improvement is possible if the three stakeholders were to share the actual values of the variables. Currently treating physicians focus on the clinical outcomes more directly linked to their fields of study, such as symptoms and clinical outcomes (see section 5.1.2) having also attained knowledge of and observed the positive impact of correct diagnosis, the positive impact of treatment (illustrated in section 5.1.2.4), the criteria for the selection of the treatment (see section 5.1.2.5), and the comorbidities (see section 5.1.2.11). However, when considering the QoL aspects, more than half of the physicians seems to know relatively little about the impact of the condition on the patients (see sections 5.1.3.1 and 5.1.3.2), while those who had the opportunity to show interest, observed a significantly positive impact of treatment also in this regard (see section 5.1.3.2).

A similar outcome was observed when studying the financial impact of the rare condition through the patient's financial exposure (see section 5.2.1.1), their reimbursement status (see section 5.2.1.2) or the yearly treatment costs to them and their payers (see sections 5.2.1.3 and 5.2.1.4). Of the three dimensions EBM, QoL and HE, most physicians are only fully informed and considering the first one, with information and consideration gaps in the latter two. The search on social media raised through the postings aimed on education, experience sharing and support (see sections 5.3.1.2, 5.3.1.4 and 5.3.1.6) that patients are putting effort in closing the information asymmetry by advancing relevant information and their agenda with the objective to obtain better and more timely treatment resulting in a superior QoL and better long term prospects.

7.4.2.4 Possible impact if improvements executed

The physicians participating in the survey for this thesis are treating slightly short of 3'000 patients suffering from HAE. If the half of them, who is not fully aware of QoL aspects and financial implication of the condition, were to close their knowledge gap and adjust their treatment approach correspondingly, then it could have a life-changing impact for their patients. Possibly more efficacious modern prophylaxis treatment with better safety profile would be prescribed as described in section 5.4.11, which would reduce the number of HAE attacks, the risk of fatalities, and the prevalence of comorbidities (with some of them being themselves also triggers of even more attacks, as discussed in section 5.4.7. Further, the estimated 1,500 patients might enjoy a better QoL and become financially better off, as the financial impacts of suffering from HAE would also be significantly reduced. These figures result from simply applying the findings to the population covered by the survey, located dominantly in advanced Western healthcare systems in Europe, North America and selected South America.

7.4.2.5 Differences across healthcare systems

A separate discussion needs to be made for other applied to other geographies and emerging markets such as in the Asia Pacific, Middle East, Eastern Europe and Africa. The same as above might produce more dramatic impact, as the vast majority of patients has not been diagnosed and still needs to close the first gap of being treated with EBM in mind, as in order of priority removal of pain and life-threatening health situation (for example through laryngeal attacks discussed in section 5.4.2) should be addressed first. On the other side, the economic situation and the state of the healthcare system in most emerging markets require other actions and progress first (discussed in section 0) such as for example first addressing and improve the general population's healthcare impacted by more basic widespread diseases (for example infectious diseases) and living conditions. An essential condition to improve diagnosis and treatment rates discussed in section 5.4.1, is having sufficiently trained and aware specialist physicians, as most rare conditions are genetic and are treated by either immunologists or allergists), a basic awareness in the population of rare diseases and a functioning referral system where doctors can advance their patients to the right specialist. The meta-analysis has shown that the time between the first onset of HAE and the actual diagnosis can easily span a decade and more across all patients who are living in

advanced healthcare systems where the studies have been performed, illustrated in sections 5.4.1.1 and 5.4.1.2. In emerging markets, these timelines can be significantly longer, and the vast majority of patients has never been diagnosed at all. There is wide disparity of most of the variables, from the frequency (see section 5.4.4), to the severity of the attacks (see section 5.4.3), from the number of hospital visits (see section 5.4.8) to the type of intervention needed, from the comorbidities to how and if they are treated by which type of HCP (see section 5.4.7), from the type of treatment to the drug selected (discussed in sections 5.4.10 and 5.4.11), from the price of the treatments to the price of the healthcare services provided across systems (see section 5.4.13), from the level of reimbursement to other financial consequences impacting patients, their caregivers and society (see section 5.2). The differences and the variability are observable across different maturity levels of healthcare systems (from advanced Western countries to emerging market), across types of healthcare systems (from universal healthcare to fully self-pay), across social segments and income groups, and lastly across individual patients.

7.4.2.6 Challenge in reconciling the differences

The data available through publications, RCTs, observations, surveys and social media appear to be not sufficient in quantity and granularity to be able to quantify every sub-segment of patients, possibly also due to the fact that the absolute number of patients themselves is relatively small, caused by the intrinsic nature of a rare condition. These factors make it difficult to develop simple quantitative models which incorporated all EBM, QoL and HE variables and which could be used to develop an overall optimized solution.

7.4.3 Application of research

7.4.3.1 Overview

Taking all into account, the development of an algorithm that incorporates all variables and which could be applied to the general population appears not possible for now. Both the variabilities of the individual variables (see tables in section 5.4) and the fact that due to multiple, not controllable and not influenceable factors they could reinforce or partially offset one another, would widely disperse the end result in such a way that no clear conclusion or call for action can be drawn. However, the thesis has shown and structured several concrete opportunities where improvements can be achieved, which will lead to better clinical outcomes, better QoL and more efficient economic effectiveness. The most significant ones could be achieved by addressing the challenges already raised by the double agency theory (described in section 3.6.4).

7.4.3.2 Prominent opportunities for application of the thesis

Prominent first opportunity would be an attempt to close or minimize the disconnects between the agents. The study has shown large shares of treating physicians not being aware or knowledgeable about key aspects affecting the lives of their patients and which should play a role in the decision of which therapy to pursue. The next important gap is when payers do not factor in all costs (not only the direct ones) into their HE considerations leading to their decisions on which treatments to fund and to what extent. Patients are consciously or

unconsciously aware that here more can be achieved and are taken matters into their own hand as proven by analyzing their voices on social media either directly or by way of the patients' advocacy groups representing their interests. This thesis could provide further and broader evidence for this mission.

7.4.3.3 Impact of the application of the thesis

Taking the study results on the individual variables analyzed in section 5.4, all of the ones linked to human behavior such as diagnosis, treatment decisions, use of healthcare services, life decisions on education, career, social activities, family planning, show individually opportunity for improvement. Nature of the studied condition and other rare diseases is, that the variables are interlinked. A patient who is diagnosed years earlier, already in his or her youth, can be treated immediately, suffers fewer attacks, is exposed to fewer setbacks in his or her education and social life, can pursue a more normal life with less pain, improved QoL and less financial burden. In aggregate, beyond the patient, also the caregivers, the community and society will benefit.

7.4.4 The possibility of a comprehensive treatment algorithm

The thesis has answered the RQs and substantiated the application of the double agency theory as an underlying theoretical framework. The variables are interrelated and theoretically it would be possible to code them into an algorithm or a formula which would allow to optimize the outcome of the treatment and the funding decisions. However, there are significant variabilities due to the intrinsic properties of the studied condition, combined with the challenge of obtaining sufficient data points which is typical of rare diseases. These constraints would probably cause such an algorithm to be cumbersome and of limited use in real life. On the other hand, the quantification of the variables as discussed in sections 5.1, 5.3 and 5.4, may be instrumental in prioritizing the efforts of physicians, patients and payers to improve the prospects of patients suffering from rare conditions, as discussed in section 7.4.3.

7.4.5 Assessment of methodology used

The methodology described in section 4, using a combination of a broad survey with treating physicians, a search through the voices of the patients expressed through social media, and the meta-analysis of scientific articles and research on the condition and ancillary relevant aspects since it was first diagnosed, seem to have proven to be a valid approach which has delivered consistent insights from different perspectives. Thanks to the methodology chosen, the thesis can possibly become a good fundament for the stakeholders exposed to HAE and other rare genetic conditions, upon which to base their comprehensive disease management.

8 CHAPTER EIGHT - CONTRIBUTIONS, LIMITATIONS AND FURTHER RESEARCH

8.1 Learnings from the thesis

The literature review in section 3 collected and structured what is known and what has been researched in the field of rare diseases, HAE, EBM, QoL and HE, confirming the motivation to conduct this thesis and supporting the development of the RQs and the methodology. The review did not find any evidence of a large scale survey covering the three dimensions, any analysis on patients' thoughts and messages expressed on social media, nor a broad meta-analysis of the available scientific literature and publications and not direct application of the double agency theory in the area of rare diseases. The pursuit of the thesis with three types of study allowed to broaden the sources, obtain different perspectives, attain confidence when there were overlaps and the findings when they were consistent, but also identify potential gaps and misalignments when they were not. The results confirmed the chosen research design and the decision to utilize a diverse range of sources, methodologies and analytical methods. The thesis obtained broader and stronger results, identified new areas for research and provided to the affected stakeholders, patients, doctors and payers, a more robust instrument to enhance the impact of their actions.

8.2 Contribution to theory

The thesis was conceived to add a more comprehensive framework as a basis to explore the network of relationships between all stakeholder patients, physicians, payers, caregivers, and society. The framework is based on currently available and potentially available data which incorporates classical EBM, QoL considerations, HE and RWE. The associations that exist within the healthcare system factor together clinical outcomes, economic considerations and ethical considerations. The challenge in these associations stems from the complication of expressing the drivers within the healthcare system from the diverse disciplines that exist (medicines, economics, business, and ethics) into variables that can be combined, compared and benchmarked. Different stakeholders have different objectives which may not be aligned as described by the double agency theory. A combined framework might generate controversy with some stakeholders and ultimately different solutions can be addressed through scholarly debate or, even better, through improved real-life health outcomes. These outcomes and potential benefits lie at the forefront foremost for people living with rare diseases and often similar conditions. This thesis has contributed to the double agency theory by extending its application to the new field of rare diseases, confirming the variables, analyzing the interdependencies and attempting to pave the way to a comprehensive framework which could be expressed as an algorithm that produces the optimal therapeutic decision. The framework and approach could subsequently be replicated, tested and improved in other fields, e.g. intersecting science, economics and ethics.

8.3 Contribution to practice

The scope of this thesis was to explore the combination of EBM, RWE, HE and QoL for rare diseases and HAE has been analyzed in detail as an example that might be generalized and applied to all rare conditions which combined affect around 8% of the population. The findings of the thesis project could have a positive impact for all stakeholders with the patient at the center of the attention, while offering a comprehensive approach that factors in not only clinical outcomes, but also socio-economic considerations. Understanding of the different levers will set the priorities and help define a roadmap for further improvements, which can be in the form of better diagnosis and treatment with a focus on effectiveness, but also a confirmation or refinement of the focus of scientific research driven by new insights on medical needs and their impact on society. The integration and consistent modeling of information, is expected to highlight the importance of monitoring, collecting and interpreting real-life data, while integrating such activities and their results into the processes for the standard of care definition, regulatory approvals and reimbursements. Change of practice and behaviors could subsequently be facilitated by refined incentive systems for different stakeholders which focus on overarching goals, and which are complemented by education and awareness programs. Each item could open up new opportunities for research, and ultimately clinical outcomes measured as a longer and less painful life with fewer disruption to work, education and social relation might be achieved.

8.4 Contribution to the industry

A more detailed, consistent and holistic understanding of all stakeholders, their drivers, and the criteria and variables for decision making covering all dimensions from clinical outcomes to economic and ethical considerations, will allow pharmaceutical companies to better position, price and promote their drugs. The prescription, frequency of use, price paid, and adherence to treatment depends on all researched factors, and not just on efficacy, safety profile and price. The pharma industry could leverage the outcome of the thesis to better and more profitably serve all stakeholders, engage closer with the patients, the payers and society as a whole. Possibly this might contribute to the effort of improving the perception that pharmaceutical company are dominantly focused on profits, while ultimately benefiting the people living with the conditions that their products treat.

8.5 Contribution to the wider society

This thesis and its resulting findings and insights could contribute to providing greater clarity and a more holistic perspective to all stakeholders, which they can use when they make decisions based on their respective needs. This includes better insights on outcomes, their costs and the compromises that need to be made, which ultimately benefits both the undiagnosed and untreated people living with a rare disease leading to accelerates treatment opportunities (Schieppati, 2008).

Access and use of a holistic and structured transparent framework which factors in all drivers and limitations, offers the opportunity of a certain peace of mind that would replace wide-spread and fragmented perceptions which can be empirically and anecdotally collected, such

as “Healthcare decisions are discretionary or mysterious in how they have been made”, “Some treatments are over-priced”, “Society is two-class where a majority has no access to needed treatment”, “Healthcare organizations are inefficient and slow”, “The pharmaceutical industry is solely profit-focused”, “Payors don’t care about the patients”, “Doctors don’t listen to patients”, or “Patients are not informed and not compliant”. More concretely, the thesis highlights the multiple ways that patients with a rare disease are affected, including all the reverberations on society as a whole. If thanks to the contribution of this thesis patients with rare diseases have better clinical outcomes, better QoL, can better fulfil their education potential, can be more productive professionally and are less hindered in their social life, then wider society benefits.

8.6 Contribution to the knowledge area

This thesis builds a bridge of connectivity between the different stakeholders. It does this by exploring the research questions and their relevant interdisciplinary relatedness. The underpinning objective of the thesis is to build and describe a comprehensive framework which can be utilized in real life to achieve better healthcare outcomes. This bridge of knowledge sharing augments the knowledge within the different disciplines as they look beyond what is immediate, but also adds new aggregate knowledge within the ontology of rare diseases and how they can be better understood (analogue to the laws of thermodynamics which cannot trivially be extracted from the laws governing the individual atoms and molecules). The different stakeholders mentioned in the thesis could build on its holistic approach to make their specific therapeutic-, funding-, or policy- decisions incorporating the broader context leading to an improved overall outcome.

8.7 Dissemination of research outcomes

The thesis generalizability extends to virtually all rare diseases, estimated at more than 8,000, which taken together affect approximately between 6% and 10% of the population. HAE has been selected as a representative condition, which shares most of the attributes of rare conditions: genetic, incurable, significant symptoms that dramatically influence the affected patients, exacerbated by such things as low awareness, low diagnosis rates, low treatment rates and expensive medication. The findings of the thesis have been formulated within concepts and terms that can be applied across the medical field. Dissemination of the information is planned across three main journal channels: (1) GP (General Practitioners) who might have the first interaction with a patient showing “inexplicable symptoms” or who follow the diagnosed patient through his life-long journey; (2) Allergists, often times the first level specialists who see the patients as the symptoms are similar or identical to allergic reactions, and (3) Immunologists, the experts in genetic conditions. As such, dissemination can be run through medical journals, allergy journals and/or immunology journals. A possible fourth option is via dissemination through mainstream media, given the epidemic significance of the conditions and the relatively low awareness leading to a large unmet medical need.

8.8 Potential issues and difficulties

Healthcare spending accounts for one of the largest shares of GDP spending in virtually every advanced economy. The stakes are significant in aggregate but also at an individual level. The selected area, rare diseases, is chronic, and in most cases cannot be cured, limits longevity and quality of life, with treatment options costing up to hundreds of thousands of dollars per year for the rest of a patient's life (Schieppati, 2008). Despite these significant stakes, there is surprisingly little research, consensus and consistency on how different treatment decisions are made and funded (Schieppati, 2008). The difficulties lie in lack of data discussed in sections 3.7.13 and 3.7.15, which is also compounded by the absence of a universally recognized coding system for most of the rare diseases. Fragmentation, lack of information exchange and education leads to suboptimal systems, processes, platforms and divergent value systems. Different drivers lead to very high costs of drugs and treatments in general, putting payers under pressure when deciding if to fund them, based on incomplete information vs. the expectation by patients, caregivers and physicians to have access to the drugs discussed in section 5.4.9. Like many others, this area is not devoid of conflicting incentives across stakeholders, territoriality and aversion to share in a world of competition and often zero-sum games, as described in the agency theory described in sections 3.6.1 and 3.6.4. A secondary aim of this thesis is to instill a sense of goodwill and foster a spirit of cooperation by building on the promise that additional insights will enable better results for all stakeholders.

8.9 Delimitation of scope

The thesis will focus on a well-defined enclosed market, spanning rare diseases and orphan drugs. This particular category of the healthcare market is particularly suitable because it is relatively new, dynamic and not yet established. The treatment of rare diseases with their lower patient and specialized healthcare professional numbers is concentrated around a few centers of excellence. The existence of fewer therapeutic options, and drugs with more differentiations, enables more data-driven and science-based decision making. Scope and depth of available data can be well captured, although due to the low prevalence of the conditions and the differing standards of care across the healthcare system, it is more difficult to find sufficient and consistent data (see 3.7.9). The selected area is of interest as the impact of drugs on both health outcomes (5.4.10 and 5.4.11) and QoL is significant (see 5.4.14). The chosen condition HAE has a devastating impact and can be fatal for any patient any time (see 5.4.1 and following). Patients' and treating physician's commitment to follow through on treatment is high, given the life-altering impact of the condition. On the other side the costs for research and development of new drugs are equally large, which poses important pricing and market access challenges (see 5.4.13). The scientific rigor of this thesis is further enhanced by these conditions not being mainstream and thus their treatment is not impacted by trends and fads which are neither scientific, ethical, nor economical in nature.

8.10 Limitations of the research

8.10.1.1 Overview

Research on rare conditions faces limitations which have multiple repercussions for all stakeholders. For example, low numbers of double-blind, placebo-controlled trials on HAE treatments made it difficult during the second Canadian Consensus discussion to assemble a sufficiently strong level of evidence to support a recommended treatment algorithm (Bowen, 2008). Overall, while reviewing the studies available for the meta-analysis performed in section 5.4, following observations could be made: study protocols are heterogeneous, the distributions of patients between the arms were seldom clearly described (possibly for the reason explained in C. below). Few efforts were made in trying to explain the high variability of the main outcomes through an analysis of the random variability in the data and the patients. In several studies there was a relatively large number of patients dropouts, but little or no explanations on the causes being the condition, the intervention selected or other factors. Similar observations could be made on the frequent lack of reporting of the probability values for the main outcomes, the lack of controls of the appropriateness of the statistical tests used to assess the main outcomes, and the lack of controls of the compliance following the treatments (for example, there seems to be no viable path to control if patients really have an attack, how they are taking the drugs inappropriately or even in the absence of a true HAE attack).

8.10.1.2 Limitations due to the low number of HAE patients

The existence of relatively few patients and the limited number of treating physicians and drugs make it challenging to derive statistically significant results from any quantitative research. Building patient databases and registries from which to collect RWE in the form of diagnoses, prescribed treatments, clinical outcomes and economic and social effects (Schieppati, 2008) is made difficult by the absence of a universally recognized coding system for most rare conditions (ICD – International Classification of Diseases). Studies on rare diseases are exposed to the fundamental limitation of being able to recruit a sufficient number of patients. Systematic recruitment has been attempted, but researchers have ultimately resorted to self-selection (Caballero, 2014). One study reported that the willingness of patients to participate in a research or a survey increases with disease severity (Aygören-Pürsün, 2014), which might lead to a bias towards more severe cases.

8.10.1.3 Limitations due to quality aspects of the studies on HAE

As clinical outcomes are retrospective and self-reported (e.g. location, frequency and severity of attacks), such recruitment method and the potential for recall bias may affect the representativeness of the study population and the generalizability of the results. When reviewing the studies available for inclusion into the meta-analysis conducted in section 5.4, the thesis observed that several of them have not done or were not clear on key aspects of high-quality RCT such as randomization, concealment of treatment allocation or ensuring the similarity of groups in terms pf prognostic factors. The vast majority of the studies in the field do not yet disclose the population from which the subjects were recruited and if the

subjects were representative of the entire population, or if the staff, places, and facilities where the patients were treated, were representative of the treatment the majority of patients receive. One research reported that randomization of subjects was also not feasible due to specific aspects of HAE (Tourangeau, 2012). For example, some patients are not comfortable with self-injections or other patients live too far from healthcare centers to ensure timely travel for treatment in case of life-threatening HAE attacks.

8.10.1.4 Limitations due to lack of head-to-head comparison studies on HAE

Treatment for HAE can vary over time, and so the clinical outcomes even when taking the same drug at the same doses (for example if the body develops antibodies or if it moves into a steady state). However, none of the available trials and cohort studies analyzed or reported if there were different lengths of treatment or periods between the interventions and the clinical outcomes. This omission might have been due to prevent further reduction in subject numbers, which were already difficult to recruit due to the rarity of the condition. To determine the clinical efficacy of one treatment vs. another, head-to-head studies are normally conducted. When the treatments are absolutely comparable and close to each other in their efficacy, larger study populations would be required to achieve sufficient statistical significance of reported results. As investigators are already struggling to recruit patients for placebo-controlled studies, it is not surprising that until now no head-to-head trials comparing treatments could be identified. The lack of head-to-head comparisons between drugs was reported as the cause for the difficulty by payers to assess which prophylactic treatments for HAE are superior in efficacy and effectiveness (ICER, 2018).

8.10.1.5 Limitations due to heterogeneity of the studies on HAE

Further different trials showed significant heterogeneity (e.g. different eligibility criteria or different endpoints) so that reliable indirect comparisons through common comparators between trials are not possible as already analyzed and reported by a study (Kavalec, 2013). For example, the research could not find consistent definitions of how the total time to onset of symptom relief is between different studies. These might be common challenges across studies on rare conditions. The methodology of this research in performing a meta-analysis was chosen to mitigate these limitations.

8.10.1.6 Limitations due to the variability of the HAE condition

Some rare conditions, especially HAE, also display a high variability of symptoms and burden of the conditions across patients and within patients across time, which make producing statistically significant results additionally difficult (see sections 5.4.2., 5.4.3, 5.4.40, 5.4.5 and 5.4.65.4.6). The lack of significant clinical results poses a challenge in writing guidelines for treatments as described in sections 3.1.10, 3.1.12 and 3.1.13. The next best alternative would be for experts to reach a consensus as an interim guide for practitioners in the therapeutic area. Ideally, such a guide should be replaced as soon as feasible with guidelines based on the whole package comprised of large phase III and IV clinical trials, meta-analyses, patient registries, QoL and cost-benefit analyses for the management of HAE (Bowen, 2010). The variability of the condition is further compounded

by the variability in the way patients report attacks, QoL impact depending on severity, attack frequency, or cultural background or age amongst other factors. Studies on the efficacy of prophylactic treatment are additionally limited by the absence of an active control, as there is no evidence that the number of reported or prevented attacks corresponds to the attacks that actually occurred or might have occurred (and where they were prevented).

8.10.1.7 Limitations due to the severity of the condition

As rare conditions are often devastating for the patients, once a treatment becomes the gold standard, it is ethically not warranted to explore in real life the alternatives on patients, especially if the resulting outcomes would result in significant pain, life-altering events and potentially fatalities. Research built on clinical trials reported that double-blind treatment of randomized patients was not justifiable because of the life-threatening nature of the condition (Bork, 2001).

8.10.1.8 Limitations due to costs

Significant costs for research, development and manufacturing limit the readiness to conduct sensitivity experiments on alternative courses of action, unless explicitly required for titration purposes (adaptation of dosing based on individually required efficacy and safety requirements). Significant pricing and market access challenges discussed in section 5.4.13.80 drive the affected stakeholders to become reticent to share anything in regard to their positions, their cost structures, and their alternative options, as these are key bargaining tools during the ongoing negotiations and worth major amounts of money. From another perspective, possibly pressure on cost was the cause for virtually none of the studies reporting high-quality consistent data on QoL.

8.10.1.9 Limitations due to privacy

In some markets increasingly stringent privacy laws make it impossible for the non-involved healthcare professional to gain access to patient-level data, even if anonymized. This can be partially overcome by gaining access to primary and syndicated reports which then flow into meta-analysis.

8.10.1.10 Limitations due to bias

Several studies utilized for this research are retrospective nature which is therefore exposed to potential biases. Bias can be introduced by most studies available including patients only from a specific country or healthcare system. Given the low prevalence of the conditions and the need for sufficient subject to reach statistical significance, it is not always possible to recruit a representative sample of the population (Bouillet, 2013) and for some studies, the subjects were chosen at the discretion of the investigators instead of random (Anderson, 2019). Several studies have reported significant numbers of people suffering from HAE to be underdiagnosed, possibly because their attacks are mild, or because the physicians may not be aware of the disease and thus fail to diagnose it correctly.

Another form of bias may arise because not all patients are treated in the same way. Patients domiciled or having access to centers of excellence in close proximity to universities, may have access to the most expert physicians and most modern treatments, while other patients have not, with resulting large differences in clinical outcomes and QoL. Patients with a milder form of the disease might be underdiagnosed and or not being treated with the most impactful medicine, albeit still showing good QoL scores. Additionally, patients may not remember all the attacks they had or only report only the most severe ones, even as many keep a log or diary on their disease. To remove some of the bias, attempts could have been too blind study subjects to the intervention they were going to receive, and/or to blind those measuring the main outcomes of the intervention. However, such attempts are not mentioned in the studies.

8.10.1.11 Limitations through types of collection and cohorts

As indicated above, due to the rarity of the conditions, few patients are available for recruitment for either studies or surveys. The Icatibant Outcome Survey (IOS) is probably the largest and longest-running, international, prospective observational study monitoring long terms safety and effectiveness of icatibant in a real-world setting (Andresen, 2019). Since 2009 it has been collecting including baseline demographics, attack characteristics, and treatment outcomes. However, as this registry is observational and covering only a cohort of patients treated with icatibant, despite its wealth of data, all results can only be considered exploratory.

Other surveys have generated results that might be exposed to other interpretations or refinements as critical information such as dosing was not collected, or as figures were based exclusively on patient's self-reporting (see limitation from memory and recall bias above), e.g. (Tachdjian, 2019).

8.10.1.12 Limitations of the survey

The survey with HAE physicians was performed using convenience sampling for the reasons listed in section 4.3. While it allowed maximizing the number of respondents, it also introduced a bias towards more advanced healthcare systems, physicians that are involved academically, physicians that follow the latest guidelines, and physicians or patients that have access to the most modern (and expensive) treatments. Any data and insights on patients also carry the bias towards the more severe cases discussed in section 5.4.3 as these are more likely to be treated and remembered (see also recall bias). Until an established, validated and the global patient registry is in existence, research in this area might have to compromise with these limitations.

8.10.1.13 Limitations of social media search

The social media search was conducted to include the patients' perspective into the findings. Facebook and Twitter were selected as the two sources as they have a broad diffusion in the population while being easily accessible and searchable as discussed in section 4.6.2. For ethical reasons no access to closed groups was attempted, where the conditions of admission could not be met (e.g. being a patient suffering of HAE). Existence of data on these platforms

presumes a number of conditions that need to be met and hence introduce bias into the findings. The patients need to be aware of their condition, have access to a device, internet and an account that enables postings. In addition, they need to be willing to share with the whole world about their symptoms, treatments, feelings, results etc. that are a consequence of their condition. Self-reports by patients are subject to a number of biases such as recollection bias or the tendency to share only about the most dramatic events. It cannot be excluded and verified that some posts are fake or made by users who aim to propagate a certain narrative or who have an agenda.

8.10.1.14 Other limitations

In the cost analysis of the different options to determine the effectiveness of treatments, several aspects were not included, for example, the costs of training patients to self-administer the treatments (see section 6.3.3.13), or the vast majority of indirect costs, or non-medical costs (see section 6.4.1.2). The research noted a general lack of data on costs of living, costs of (missed or slowed) education, missed or reduced career opportunities, reduced productivity (Federici, 2018), transportation, infrastructure). More indirect impacts, such as due to the influence of HAE on other members of society than patients or social perspectives, are not considered in clinical studies and mostly not mentioned or quantified in QoL or HE studies. The same can be said for the relatively long list of co-morbidities (for example depression, anxiety) and all may cause further impacts on their own, as discussed in section 6.4.1.8.

Studies that are based on insurance claims are limited by coding errors, incomplete claims information, misclassifications of patients and other possible inaccuracies (Tachdjian, 2017). Not all are identified, and it is not reported how significant they are in affecting the overall results either in value or in the magnitude of the confidence intervals.

8.11 Further research

For this research a survey, a search on social media and a meta-analysis the publicly available body of research was performed. Sources searched include Medline, Embase, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, conference proceedings and presentations, regulatory documents, scientific meeting abstracts and publications on the topic. These sources were supplemented by information provided by manufacturers and other grey literature.

Within HAE, confirmation or strengthening of results could be achieved with head-to-head clinical trials, access to patient registries that still have to be established, access to studies that use a consistent methodology of protocol and outcome/parameter definitions, and more in general, research that mitigates or eliminates the sources of bias mentioned in 8.10).

To strengthen the findings and their applications to other rare conditions, similar studies could be conducted on other genetic conditions such as Fabry's disease, Gaucher's disease, being able to tap into a selection of the more than 7,000 existing. An approach could be to validate key assumptions and variables from this research and subsequently confirm the generalizability of this thesis to other rare conditions.

Big data, AI and machine learning have been attracting significant attention and funding by both pharmaceutical and technology companies during the writing of the thesis. However, as the time of the research these approaches were not widespread or established in their day-to-day application, resulting in relatively little data or academic work from which significant new insights could be gained. A summary search suggest that progress could be rapid, and further research to include them is warranted to verify or build and possible new insights that will be gained.

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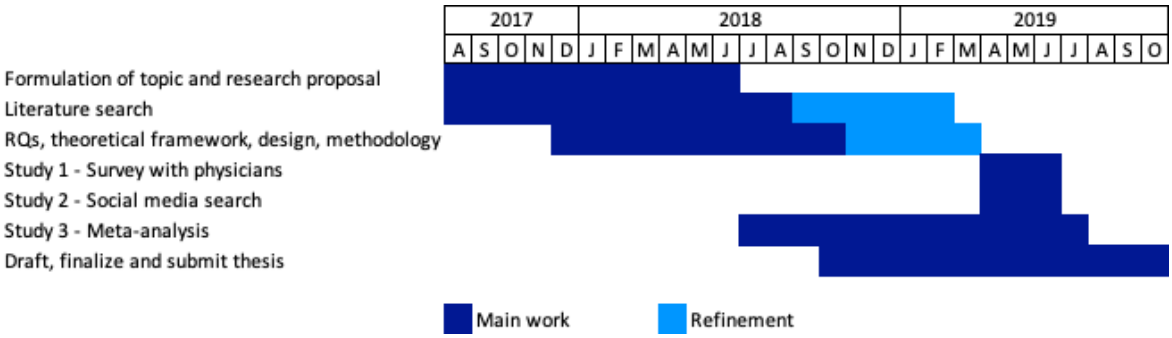
10 APPENDIX

10.1 Research Timeline



10.2 Survey with physicians

10.2.1 Participation sheet

University of Southern Queensland

Participant Information for USQ Research Project Questionnaire

Project Details	
Title of Project:	Exploring the integration of Evidence-Based Medicine, Quality of Life considerations and Health Economics for Rare Diseases
Human Research Ethics Approval Number:	HXXREAXXX TBC

Research Team Contact Details

Principal Investigator Details
Mr Andreas Amrein
Email: andreas.amrein@usq.edu.au
Mobile: +41 79 272 33 44

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Professor Jeffrey Soar
Email: Jeffrey.Soar@usq.edu.au
Telephone: +61 400 746 657

Description

This project is being undertaken as part of a PhD thesis exploring the integration of evidence-based medicine, quality of life considerations and health economics for rare diseases.

This short survey aims to help better understand your therapeutic decision-making and how, besides clinical considerations, you factor in quality-of-life and economic factors. For this survey please consider your treatment of patients living with Hereditary Angioedema (HAE).

Participation

Your participation will involve completion of an online questionnaire that will take approximately 10-15 minutes of your time.

This research is expected to contribute to the practice of treatment of rare diseases by integrating the three perspectives Evidence Based Medicine (EBM), Quality of Life (QoL) and Health Economics (HE) considerations into a comprehensive framework. It focuses on the rare disease Hereditary Angioedema (HAE) as a proxy for rare diseases. The aim is to combine and integrate different perspectives and their dependencies into a framework to allow for more holistic therapeutic decisions, treatments and their funding. Such integration is expected to generate better clinical results, better quality of life for patients, and be more cost-effective overall.

Your participation in this project is entirely voluntary. If you do not wish to take part, you are not obliged to. If you decide to take part and later change your mind, you are free to withdraw from the project at any stage. If you do wish to withdraw from this project please contact the Research Team (contact details at the top of this form).

Your decision whether you take part, do not take part, or to take part and then withdraw, will in no way impact your current or future relationship with the University of Southern Queensland.

Expected Benefits

Whilst there are no immediate benefits for those people participating in the project, it is hoped that this work will have a beneficial impact on how HAE and other rare diseases will be treated. Results will be shared with participants in order to inform their professional work.

Risks

In participating in the questionnaire, there are no anticipated risks beyond normal day-to-day living. While participation in this study is unlikely to cause distress, should you become distressed as a result of your participation please seek appropriate health services for assistance.

Privacy and Confidentiality

All comments and responses will be treated confidentially unless required by law, and your answers cannot be connected to you. The names of individual persons are not required in any of the responses.

You will not be able to be identified or identifiable in any reports or publications. Your institution will also not be identified or identifiable. Any data collected from you in the online questionnaire will be stored online in a form protected by passwords and other relevant security processes and technologies. Data collected may be shared in an anonymized form to allow reuse by the research team and other third parties. These anonymized data will not allow any individuals or their institutions to be identified or identifiable.

Any data collected as a part of this project will be stored securely as per University of Southern Queensland's Research Data Management policy.

Consent to Participate

Clicking on the 'Submit' button at the conclusion of the questionnaire is accepted as an indication of your consent to participate in this project.

Questions or Further Information about the Project

Please refer to the Research Team Contact Details at the top of the form to have any questions answered or to request further information about this project.

Concerns or Complaints Regarding the Conduct of the Project

If you have any concerns or complaints about the ethical conduct of the project, you may contact the University of Southern Queensland Manager of Research Integrity and Ethics on +61 7 4631 1839 or email researchintegrity@usq.edu.au. The Manager of Research Integrity and Ethics is not connected with the research project and can facilitate a resolution to your concern in an unbiased manner.

Thank you for taking the time to help with this research project. Please keep this sheet for your information.

10.3 Survey recruitment letter

Andreas Amrein
University of Southern Queensland
West Street
Toowoomba. 4350
Queensland
Australia

RARE DISEASE SURVEY

Dear Dr. xx

I am currently a PhD student with the University of Southern Queensland with the research topic "The integration of evidence-based medicine, quality of life considerations and health economics for rare diseases". The attached survey has been approved under the Universities research ethics application number H19REA061.

This short and survey aims to better understand your therapeutic decision-making as a medical provider. Aside from clinical considerations, it also seeks to ascertain how you factor in the quality-of-life and economic factors. For the purposes of the research topic, please consider your treatment of patients living with *Hereditary Angioedema (HAE).*

While your participation is entirely voluntary, it is extremely important to collect a strong and realistic sample of responses in order to test the hypotheses generated and the research questions posed. Accordingly, I would value your input very much as an expert in this area. In designing this survey, every effort has been made to avoid the identification of any participating individual. Indeed, all collected data will be further screened to eliminate any information that may have the potential to identify individuals. Please note that you can withdraw your participation at any time in this survey and your name will be removed from the list of medical experts. All data will be stored and disposed of securely in compliance with university and statutory regulations and guidelines.

Your answers will be collected anonymously. The data will be utilized purely for research purposes and will have no commercial objective. The results will only be published or shared in an aggregated way. Please access the following link if you would like to proceed with the survey.

I will be most happy to share with you the results of this survey. Please briefly reply to this email if you are interested.

I do very much appreciate your help and time! For any questions related to this survey, please do not hesitate to contact me at andreas.amrein@usq.edu.au or +41 79 272 33 44.

Kind regards

Andreas Amrein

10.3.1 Survey

Survey for treating HAE physicians

Description
This short survey aims to help better understand your therapeutic decision-making in regard to **HAE (Hereditary Angioedema)** patients and how, besides clinical considerations, you factor in quality-of-life and economic considerations.

Objective
This research is expected to contribute to the practice of treatment of rare diseases by integrating the three perspectives Evidence Based Medicine (EBM), Quality of Life (QoL) and Health Economics (HE) considerations into a comprehensive framework for more holistic therapeutic decisions, treatments and their funding.

Your participation
Your participation will involve completion of an online questionnaire that will take approximately 8-12 minutes of your time and is entirely voluntary. Your help would be greatly appreciated, If you decide to take part and later change your mind, you are free to withdraw from the project at any stage.

Expected benefits
It is hoped that this work will have a beneficial impact on how HAE and other rare diseases will be treated.

Privacy and confidentiality
All comments and responses will be treated confidentially unless required by law, and your answers cannot be connected to you. The names of individual persons are not required in any of the responses. You will not be able to be identified in any reports or publications. Any data collected will be stored in a form protected by security processes and technologies as per University of Southern Queensland's Research Data Management policy. Data collected may be shared in an anonymized form to allow reuse by the research team and other third parties.

Risks
There are no anticipated risks beyond normal day-to-day living in participating in this survey. While participation in this study is unlikely to cause distress, should you become distressed as a result of your participation please seek appropriate assistance.

Consent to participate
Clicking on the 'Submit' buttons in the questionnaire is accepted as an indication of your consent to participate in this project.

Questions or complaints
Please refer to the Research Team contact details below for any questions or to information requests. If you have any concerns or complaints about the ethical conduct of the project, you may contact the University of Southern Queensland Manager of Research Integrity and Ethics on +61 7 4631 1839 or email researchintegrity@usq.edu.au.

Contact
Principal Investigator
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1 Stakeholders

1. **How important is the role of different stakeholders (beyond the prescribing physician) when deciding which treatment to pursue for the HAE condition?**

		low	high	
irrelevant		importance	importance	critical

Patient	□	□	□	□
Family member	□	□	□	□
Other caregiver	□	□	□	□
Patient association	□	□	□	□
Nurse	□	□	□	□
Pharmacist	□	□	□	□
Pharma company	□	□	□	□
Regulatory body	□	□	□	□
Payer, insurance	□	□	□	□
Media	□	□	□	□
Other	□	□	□	□

2 Clinical aspects

2. **How many HAE patients do you have in treatment?**

3. **What percentage of people living with HAE in your country do you estimate are...?**

% of prevalent	<10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
diagnosed	□	□	□	□	□	□	□	□	□	□
been previously misdiagnosed	□	□	□	□	□	□	□	□	□	□

4. **How many HAE attacks do UNTREATED patients typically have in a year?**

% of pts	<10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
0-1	□	□	□	□	□	□	□	□	□	□
2-3	□	□	□	□	□	□	□	□	□	□
4-6	□	□	□	□	□	□	□	□	□	□
7-10	□	□	□	□	□	□	□	□	□	□
11-16	□	□	□	□	□	□	□	□	□	□
17-24	□	□	□	□	□	□	□	□	□	□
25 and above	□	□	□	□	□	□	□	□	□	□

5. **How many attacks do TREATED patients typically have in a year?**

% of pts	<10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
0-1	□	□	□	□	□	□	□	□	□	□
2-3	□	□	□	□	□	□	□	□	□	□
4-6	□	□	□	□	□	□	□	□	□	□
7-10	□	□	□	□	□	□	□	□	□	□
11-16	□	□	□	□	□	□	□	□	□	□
17-24	□	□	□	□	□	□	□	□	□	□
25 and above	□	□	□	□	□	□	□	□	□	□

6. **How would you rank by importance the criteria for the choice of the HAE treatment to pursue?**

	low									high

	irrelevant	importance	importance	critical
History of laryngeal attacks	□	□	□	□
Age of patients	□	□	□	□
Profession/education	□	□	□	□
Efficacity of drug	□	□	□	□
Safety profile of drug	□	□	□	□
Dosing frequency of drug	□	□	□	□
Mode of administration	□	□	□	□
Cost	□	□	□	□
Insurance coverage	□	□	□	□
Economic status of patient	□	□	□	□
Other	□	□	□	□

7. Which medications do you prescribe for HAE on demand treatment?

	<10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
Icatibant	□	□	□	□	□	□	□	□	□	□
Ecallantide	□	□	□	□	□	□	□	□	□	□
C1-Inhibitor	□	□	□	□	□	□	□	□	□	□
Fresh frozen plasma	□	□	□	□	□	□	□	□	□	□
Tranexamic acid	□	□	□	□	□	□	□	□	□	□
Other	□	□	□	□	□	□	□	□	□	□

8. Which medications do you prescribe for HAE prophylaxis treatment?

	<10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
C1-Inhibitor	□	□	□	□	□	□	□	□	□	□
Lanadelumab	□	□	□	□	□	□	□	□	□	□
Androgen	□	□	□	□	□	□	□	□	□	□
Other	□	□	□	□	□	□	□	□	□	□

9. How often do your patients switch medication during their life?

	<10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
Never	□	□	□	□	□	□	□	□	□	□
1 time	□	□	□	□	□	□	□	□	□	□
2 times	□	□	□	□	□	□	□	□	□	□
3 times	□	□	□	□	□	□	□	□	□	□
more often	□	□	□	□	□	□	□	□	□	□

10. Main reasons for patients switching medication?

	<10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
Side effects	□	□	□	□	□	□	□	□	□	□
Lack of efficacy	□	□	□	□	□	□	□	□	□	□
Convenience	□	□	□	□	□	□	□	□	□	□
Don’t like IV	□	□	□	□	□	□	□	□	□	□
Don’t like SC	□	□	□	□	□	□	□	□	□	□
Have less attacks	□	□	□	□	□	□	□	□	□	□
Have more attacks	□	□	□	□	□	□	□	□	□	□

Supply issues	□	□	□	□	□	□	□	□	□	□
Cost	□	□	□	□	□	□	□	□	□	□
Other reason	□	□	□	□	□	□	□	□	□	□

11. At how many attacks per year do you feel your HAE patient is in a "acceptable stable condition"?

0-1	□
2-3	□
4-6	□
6-10	□
11-and above	□
Cannot say	□

12. Do you observe and treat HAE co-morbidities, or refer the patient to another doctor (e.g. GP, other specialist)?

	Observe	I treat	I refer
Anxiety	□	□	□
Depression	□	□	□
Autoimm. disorders	□	□	□
Obesity	□	□	□
Hypertension	□	□	□
Pain	□	□	□
Anaemia	□	□	□
GI disorders	□	□	□
Other	□	□	□

13. Do your patients require help during attacks or for treatment?

	<10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
Family member	□	□	□	□	□	□	□	□	□	□
Friend	□	□	□	□	□	□	□	□	□	□
Nurse	□	□	□	□	□	□	□	□	□	□
Other	□	□	□	□	□	□	□	□	□	□
Don't know	□	□	□	□	□	□	□	□	□	□

14. What is the most important desired outcome for treatment?

	irrelevant	low importance	high importance	critical
Reduction in frequency and severity of HAE attacks	□	□	□	□
Disease control (stable state)	□	□	□	□
Improvement in overall QoL	□	□	□	□
Patient enabled to fully participate in society (work, education, social life)	□	□	□	□
Improve mental health	□	□	□	□

Other	□	□	□	□

15. Comments, clarifications

3 QoL aspects

16. How many days in a year do HAE patients remember having missed out from their commitments (School, work, etc.) BEFORE diagnosis?

	<10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
0	□	□	□	□	□	□	□	□	□	□
1-5	□	□	□	□	□	□	□	□	□	□
6-10	□	□	□	□	□	□	□	□	□	□
11-20	□	□	□	□	□	□	□	□	□	□
21-30	□	□	□	□	□	□	□	□	□	□
31-40	□	□	□	□	□	□	□	□	□	□
more	□	□	□	□	□	□	□	□	□	□

17. How many days in a year do HAE patients miss out from their commitments (School, work, etc.) when treated?

	<10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
0	□	□	□	□	□	□	□	□	□	□
1-5	□	□	□	□	□	□	□	□	□	□
6-10	□	□	□	□	□	□	□	□	□	□
11-20	□	□	□	□	□	□	□	□	□	□
21-30	□	□	□	□	□	□	□	□	□	□
31-40	□	□	□	□	□	□	□	□	□	□
more	□	□	□	□	□	□	□	□	□	□

18. Which long term consequences do you feel HAE patients face?

	<10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
Education	□	□	□	□	□	□	□	□	□	□
Career	□	□	□	□	□	□	□	□	□	□
Family planning	□	□	□	□	□	□	□	□	□	□
Social relations	□	□	□	□	□	□	□	□	□	□
Stigma	□	□	□	□	□	□	□	□	□	□
Reduced income	□	□	□	□	□	□	□	□	□	□
Reduce life expect.	□	□	□	□	□	□	□	□	□	□
Other	□	□	□	□	□	□	□	□	□	□
None	□	□	□	□	□	□	□	□	□	□
Don’t know	□	□	□	□	□	□	□	□	□	□

19. What is the working status of your HAE patients?

<10%	20%	30%	40%	50%	60%	70%	80%	90%	100%

Working full time	□	□	□	□	□	□	□	□	□	□
Working part time	□	□	□	□	□	□	□	□	□	□
Retired	□	□	□	□	□	□	□	□	□	□
Student	□	□	□	□	□	□	□	□	□	□
Homemaker	□	□	□	□	□	□	□	□	□	□
Unemployed	□	□	□	□	□	□	□	□	□	□
Disabled	□	□	□	□	□	□	□	□	□	□
Other	□	□	□	□	□	□	□	□	□	□
Don't know	□	□	□	□	□	□	□	□	□	□

20. Comments, clarifications

4 Economic aspects

21. Does HAE have a financial impact on the life of your HAE patients

	<10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
Treatment cost	□	□	□	□	□	□	□	□	□	□
Missed income	□	□	□	□	□	□	□	□	□	□
None	□	□	□	□	□	□	□	□	□	□
Other	□	□	□	□	□	□	□	□	□	□

22. Is HAE treatment for your patient fully reimbursed or is there a copayment?

	<10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
Fully reimbursed	□	□	□	□	□	□	□	□	□	□
Copayment	□	□	□	□	□	□	□	□	□	□
Fully out of pocket	□	□	□	□	□	□	□	□	□	□
Don't know	□	□	□	□	□	□	□	□	□	□

23. What costs do you believe your patients have to bear

	<10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
<$100	□	□	□	□	□	□	□	□	□	□
> $100 and <$500	□	□	□	□	□	□	□	□	□	□
> $500 and <$1,000	□	□	□	□	□	□	□	□	□	□
> $1,000 and <$5k	□	□	□	□	□	□	□	□	□	□
> $5k and <$20k	□	□	□	□	□	□	□	□	□	□
> $20k and <$50k	□	□	□	□	□	□	□	□	□	□
> $50k	□	□	□	□	□	□	□	□	□	□
> don't know	□	□	□	□	□	□	□	□	□	□

24. What costs do you believe the payers (e.g. insurance) are covering per HAE patient per year?

	<10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
<$100	□	□	□	□	□	□	□	□	□	□
> $100 and <$500	□	□	□	□	□	□	□	□	□	□
> $500 and <$1,000	□	□	□	□	□	□	□	□	□	□
> $1,000 and <$5k	□	□	□	□	□	□	□	□	□	□
> $5k and <$20k	□	□	□	□	□	□	□	□	□	□
> $20k and <$50k	□	□	□	□	□	□	□	□	□	□
> $50k and <$100k	□	□	□	□	□	□	□	□	□	□
> $100k and <$200k	□	□	□	□	□	□	□	□	□	□
> $200k and <$300k	□	□	□	□	□	□	□	□	□	□
> $300k	□	□	□	□	□	□	□	□	□	□
> don't know	□	□	□	□	□	□	□	□	□	□

25. Comments, clarifications

5 Identifier

26. Which country are you from?

10.4 Reflections of the researcher

The researcher's academic career covers both scientific and business angles. His background in Physics enabled him to contribute with methodology, conceptual and quantitative modeling tools combined with the rigor to test and validate the variables, models and the correlations, causalities, or independence of different parameters leading to replicable outcomes. After a short stint in research, the researcher moved into business, attained an MBA which was followed by an 20-year career in healthcare covering Pharmaceuticals, Medical Devices and Services, which exposed him to a large and diverse population of stakeholders in the healthcare space. Operating at different levels of large organizations, in different functions and across multiple market models, he worked with and learned to understand the different stakeholders, what drives them and how they influence one another to generate positive or negative impact on the patient, the ultimate center of all healthcare efforts. The healthcare sector is a complex setting with different (and sometimes independent and even misaligned) processes and incentive systems. Ultimately different levels of education, asymmetry of information and the differing stakes (level of commitment) may cause outcomes that are not linearly dependent and yet affect society as a whole. All of these are drivers to for the proposed research, having the objective to better grasp complexity, leverage the newly available quantity and quality of information, utilize innovative analytical and interpretative methods and yet deliver pragmatic recommendations to improve healthcare in an economically optimized way. Previous and current work done on the topic was performed while engaged with Novartis, Abbott and Shire (now part of Takeda), with Shire being a leading pharmaceutical player in HAE.

10.5 Publication plan

Three articles are planned to be submitted for publication where the research gaps discussed in section 3.11 based on the literature review could possibly be addressed in part with the findings of the thesis. The draft titles, the content and the type of journals to be addressed for a potential publication are described as follows:

- **"Achieving economically more efficient therapeutic decisions with better health and QoL outcomes".**
  Built on sections from the literature review such as in section 3.3 on Real World Evidence (RWE) with the efficacy and effectiveness of Evidence Based Medicine (EBM), section 3.4 on Quality of Life (QoL), and section 3.5 on Health Economics (HE). These are integrated and analyzed within the Agency Theory framework discussed in section 3.6 and applied to rare diseases discussed in section 3.7.
  The article is planned to be submitted to a highly rated journal which takes a holistic view on medical treatment and where ethical considerations are prioritized, such as the Journal of Business Ethics (https://link.springer.com/journal/10551).
- **"The physicians' perspective on treating patients suffering of a rare condition – results from a survey"**
  Built on the results of a survey with physicians treating a rare condition discussed in section 5.1 and focused on the importance of the different stakeholders (see section 5.1.1), the clinical aspects considered for treatment decisions (see section 5.1.2), the QoL aspects (see section 5.1.3) and the economic aspects (see section 5.2).
  The article is planned to be submitted to medical journals addressing physicians who treat patients in general but specifically with a higher likelihood of treating patients suffering of rare conditions. This could be immunologist (as many rare conditions are genetic) or for example allergists (as the symptoms of some rare conditions manifest in similar ways as allergic reactions).
- **"The benefits of home treatment in terms of clinical results, quality of life and health economics for rare diseases"**
  A literature review of the scholar research found a limited number of publications discussing the value of self-administration or home-administration of treatments of rare conditions. Some research was discussed in section 5.4.14 on QoL. However the broader approach of the thesis supported the argumentation for physicians and payers to further encourage self-treatment for patients suffering of selected rare conditions. This approach may lead to better clinical outcomes, superior QoL and more effective health economics. This article will derive its content from sections 6.2, 6.3, 6.4 and 6.5.
  This article would be submitted to journals covering rare diseases (for example the Orphanet Journal of Rare Diseases - https://ojrd.biomedcentral.com), journals on medical treatments and guidelines (for example the Medical Letter - https://secure.medicalletter.org/archives-tgl), or journals on immunology (as rare disease dominantly genetic conditions).