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Market Entry in the German Pharmaceutical Market

A framework for business intelligence measures

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Executive Summary

Pharmaceutical companies today are under great pressure to successfully launch new specialty drugs, high-tech products for small patient populations with cost intensive R&D and complex mechanisms of effect.

At the same time, increasing privacy regulation limits the availability of data for market research in the medical markets, forcing pharmaceutical companies to find ways of creating transparency. Researchers can draw from a large, yet disperse body of literature investigating the factors that favour early adoption of a drug.

The thesis introduces Roger's Diffusion of Innovation framework to organize literature on factors that speed up new product adoption among physicians. The framework is expanded to suit the pharmaceutical markets, especially to differentiate between fixed variables and such that are subject to change during an adoption process.

Afterwards different approaches to quantitative diffusion modelling are introduced with an exemplary paper each. The different levels of modelling, from macro-level (national sales) down to micro-level (individual behaviour) are explained. Subsequently, the limitations through German privacy regulation as well as through market specific features on data availability for pharmaceutical market research are presented. A comparison between quantitative diffusion models on different levels with the current privacy regulation shows which analysis approaches might still be feasible.

Based on the prior analysis, a quantitative model for drug adoption in the German pharmaceutical market is developed, using Multiple Regression Analysis as the statistical tool. It is found that under some conditions, a very simple two-variable model using the salesforce visits' and their assessment of a doctor's adoption behaviour can explain more than 40% of the variance in sales between hospitals. Limited availability of independent data causes the model to be largely influenced through the sales force's agenda in reporting.

Although this data is naturally biased, it seems unlikely that data availability from independent sources will improve in the future. Pharmaceutical companies will need to further utilize their sales force to collaborate with physicians and adapt their incentive systems to live up to the new requirements.

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List of Abbreviations

KAP-Gap	Knowledge, Attitudes, Practices Gap
PZN	Pharmazentralnummer (Pharmaceutical Registration Number)
PI	Parallel Imports
CME	Continuing Medical Education
MS	Multiple Sclerosis
IV	Intravenous
KOL	Key Opinion Leader
ID	Identification Number
Cytostatics	Cytostatic Preparations
GIS	Geographic Intelligence Systems
IPF	Idiopathic Lung Fibrosis
CRM	Customer Relationship Management

1. Introduction

Since the accidental discovery of penicillin in the 1920s, the pharmaceutical market has undergone great changes. The biggest development in recent years is the rising number of specialty drugs. Unlike penicillin, a cheap drug available for the mass markets which nearly everyone takes at one point in their life, most drugs approved today are not aiming for huge patient populations. The big players in the pharmaceutical industry develop specialty drugs, complex molecules often extracted from living organisms, specially engineered to target rare diseases. These new agents have helped improve the lives of countless patients suffering from grave and often chronic diseases.

The development of specialty drugs is extremely research oriented and costly. As patient populations in rare diseases are small and research is intricate, the drugs are expensive. Pharmaceutical companies also have a relatively short time period in which they can reap the benefits of their successful products. Patents for new drugs usually span for twenty years after development of the molecule, but until the drug reaches market approval a company will roughly have ten to fifteen years before biosimilar or generic competition drives down profits.

Another aspect of specialty drugs is their complexity, both in mechanism of effect as in handling and using the drug. Many of them require sterile atmospheres and constant temperatures while they are being prepared for a patient. Side-effect profiles are often grave and the indications for when they are to be used are small. All that makes them complicated and difficult to use for physicians and requires a lot of training and information.

Pharmaceutical companies have a natural interest in fast diffusion of their expensive drugs. They want to reach as many patients with innovative drugs as possible to improve their patient's condition as well as their shareholder's financial circumstances. Hence they are interested in gaining knowledge about where innovative drugs will be prescribed first. This means they are interested in gathering, evaluating and interpreting data about physicians and their attitude towards new drugs.

Researchers have identified a variety of variables that may influence the spread of a pharmaceutical innovation. They linked these variables to the adoption behaviour of doctors and tried to infer which attitudes make a physician likely to be an early adopter. These

approaches require substantial data about the physician, which leads to conflict with the individual's right to privacy.

Not only since the European General Data Protection Regulation came into force in May 2018, privacy regulation has had great influence on the collection of data for pharmaceutical companies. Unlike in other industries, pharmaceutical companies have limited transparency about where, how and by whom their products are being used. This poses a lot of issues, since it makes performance measurement, key account management and general sales analysis extremely difficult.

The question this thesis sets out to answer is how transparency on the adoption and spread of new drugs can be improved, given the constraints of privacy regulation and market specific features of the German pharmaceutical market.

The thesis begins with examining the literature on medical innovation and physician adoption behaviour using the tools and frameworks of diffusion research. Using the general frameworks as a guideline, important variables relevant for the spread of a new drug identified through prior research will be discussed and organized.

After the literature review, different approaches to diffusion modelling will be elaborated on, using exemplary papers. The idea is to show how diffusion modelling works on different levels, starting from a market level down to an individual person level. In a next step, the limitations for research through privacy regulation in the medical market in Germany will be shown. From the comparison between modelling approaches and data availability it will become clear which analyses are possible in Germany today.

Following the theoretical chapter, a quantitative model is introduced using multiple regression analysis aimed to forecast sales figures for a recently launched cancer immunotherapy and a more established drug with a recent change in the formulation.

2. Theoretical Perspective

Why and how some people adopt new technologies earlier and others do not has concerned researchers for a long time. When a new product is introduced, the individual's decision to adopt is relevant not only for the researcher, but for the planning of the sales representative and the marketing team. Diffusion literature approaches the innovation process from two different angles: The individual level and the aggregate, market level.

On the individual level, it is important to understand how these individuals get from not knowing about a new idea to using it for their own good. On the market level, scholars are interested in finding out how the different individual characters' actions come together, so that an idea can diffuse over time. The present theoretical chapter aims to explain the frameworks used to categorize types of innovators and their distribution in the market with a focus on the medical market per se and especially the market for highly developed drugs in Germany. It will then transition to show how the theoretical diffusion theory has been modelled quantitatively on different levels.

2.1 Diffusion of Innovation on an Individual Level

2.1.1 The Innovation Diffusion Process

The diffusion literature as one knows it today has its origins in the 1960s in the United States. Early research investigated the introduction of hybrid corn seeds and the spread of this new technology amongst farmers in Iowa. For the first time, scholars looked at the early and late characteristics of people adopting and generalized them into categories. Thereof, several models for the individual's decision process were introduced, describing a variety of stages someone has to go through.

Although other scholars were earlier to describe stage models (Ryan & Gross 1943), the classic text is Everett Rogers' *Diffusion of Innovations* from 1962. He introduces five stages for the process of deciding about an innovation, from first learning about an innovation over adopting to re-evaluating it in hindsight (see Figure 1). His description of the full adoption process in addition to the after-adoption perspective differentiates his model from earlier approaches (Beal and Bohlen 1957). The present chapter will elaborate on each of the stages introduced by Rogers and put them into the perspective of medical markets.

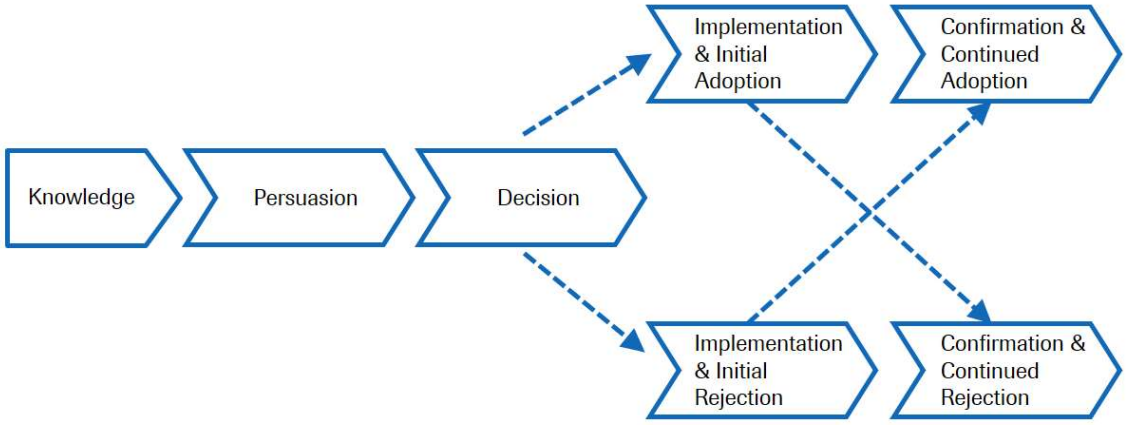

Figure 1 - Stages of the Innovation Process according to Rogers 2003

Stage 1: Knowledge (Awareness vs. Needs)

At the first stage - knowledge - an individual gets aware of the existence of an innovation. Usually, the innovation reaches a person through some form of mass media (e.g. a journal advertisement). After the individual has become aware of an innovation, he/she grows the knowledge until they fully understand it.

Rogers describes two mechanisms of creating awareness. The first one is that a possible adopter stumbles upon a new innovation by chance, recognizes that it could improve a need he/she has and seeks for more information. The other mechanism works in reverse: Someone actually has a need/problem and then goes and seeks for new solutions, thereby getting aware of the innovation (Hassinger 1959).

In one of the earliest diffusion studies on medical innovation (Sower et al. 1967), the authors found that doctors are not actively seeking for new drugs but remain passive until knowledge reaches them (e.g. through sales personnel). Only when the new knowledge of a better treatment option creates a need for the new drug, these individuals will look for information themselves. It may also be that a potential adopter could get aware of an innovation but does not perceive its existence until there is an actual problem that the innovation could fix. This bias is called *selective perception* (Rogers 2003).

If a stage of knowledge is reached, several subtypes of knowledge exist. The Rogers framework differentiates between *Awareness Knowledge*, *How-to knowledge,* and *Principles-*

knowledge. All three types describe the process of first becoming aware of an innovation, knowing how to use it and understanding the fundamental principles behind it. With the adopter´s growing knowledge, the more likely it is that the innovation is used correctly and the person continues to use it. In the pharmaceutical context, change agents (sales representatives) are heavily involved in advancing the knowledge about an innovation. As formal education only adapts slowly to new medicines (e.g. it may take years for a new treatment or procedure to receive widespread acclaim as standard of care), sales representatives spend a great deal of their time not only advertising a product but explaining effect mechanisms, study results and treatment regimes.

Stage 2: Persuasion

At the persuasion stage, an attitude about an innovation is formed. The information from the knowledge stage is now processed, categorized and labelled as positive or negative. After completing the persuasion stage, an individual has decided whether to be in favour, indifferent or negative about an innovation.

The source of an information plays a very important role in the persuasion process. Individuals will value information from peers most, rather than try and reinforce their beliefs through scientific knowledge. Hence personal networks play a crucial role in forming an opinion towards an innovation (Valente 2005) and thereby help to overcome the perceived uncertainty when evaluating how the adoption of an innovation will affect one's personal situation.

One special form of behaviour at the persuasion stage is the so-called Knowledge, Attitudes, Practices or KAP-gap. It occurs when an individual has formed a positive opinion about an innovation but still refuses its adoption (Rogers 2003).

A possible example for this is the recent introduction of a new pharmaceutical formulation for a Roche substance allowing patients to reduce the daily intake of medicine from nine capsules to just three pills. As the substance itself remains untouched, mechanisms of effect, side-effect profile and price all remain constant – seemingly a no-brainer decision. Still, eight months after the introduction, only sixty percent of patients received an updated prescription form for the new pills. One possible explanation is the existence of the KAP-gap, where doctors and their nurses are not pursuing a change of behaviour implying the change of the PZN (Pharmaceutical registration number) on their prescriptions to match the new formulation.

Stage 3: Decision

In this decision phase, an individual takes action in form of either adopting or rejecting an innovation. The individual has informed herself and built a favourable or unfavourable opinion. Now, individuals will start to move from the mental experiments of earlier stages ("What do I expect to gain from adopting") to actually testing an innovation on small scale.

Constituting a crucial point in an individuals' adoption process, a failed trial will heavily discourage further adoption. An innovation that is adopted but fails the trials will actively be rejected, while an innovation not passing the persuasion stage is passively rejected (see Figure 2). As Rogers points out, a trial by others (e.g. close peers, opinion leaders), as for instance in a shared practice, may substitute for an own trial experiment. In case of more advanced medical innovations, doctors will also often decide to conduct a trial with external help. Resident doctors could for instance send a diagnosed patient to a hospital, accompanied by a recommended (innovative) therapy.

The decision to adopt or not adopt is accompanied by common cognitive biases, which also holds true for the field of medical innovation (Bornstein and Emler 2001). Three of the most common biases applicable in the medical diffusion context are Outcome, Framing and Number of Alternatives bias (Bornstein and Emler 2001). Outcome bias refers to doctor's regretting a bad outcome more if it comes from their therapy than from disease progression: e.g. if side effects are bad, they will feel more regret than if they had waited with treatment and disease progression is grave.

The framing bias occurs when individuals alter their decision on the same statistical probabilities, if the information is provided in a different frame. In a study on lung cancer treatments, respondents (patients and physicians) preferred a more risky treatment (surgery) over conservative treatment (radiation) when framed in support of long-term survival than when framed in the context of imminent death (McNeil et al. 1982). This bias is important for pharmaceutical manufacturers as well as doctors – for instance the modern cancer immune therapies are a riskier treatment choice than usual chemotherapy. If they work for a patient, they handily beat conventional therapy, but they only do so for a certain percentage of the cases (Barlesi et al. 2016). Depending on how this information is presented (e.g. "Three quarters of your patients will die faster than if they had gotten chemo-therapy" vs. "You can significantly prolong the lives of 25% of your patients compared to chemo-therapy") doctors will value the same information differently.

Number of alternatives bias refers to doctors preferring a previously available alternative when a new option is added. The uncertainty between two therapy options may lead doctors to reconvene on a third, more certain option (possibly watch and wait) (Redelmeier and Shafir 1995).

Stage 4: Implementation

After small-scale trials have been successful, individuals may choose to alter their behaviour and adopt a new innovation altogether. In order to fully adopt an innovation, operational problems need to be solved first. In case of uncertainty about operational problems, the change agent will have to exert considerable efforts to solving these.

For example in the case of Ocrelizumab, a new MS treatment, neurologists (or their staff, respectively) in Germany had to be detailed in how to use intravenous (IV) therapy. Before the product had reached the mass markets, neurologists would only use IV therapy in case of rapid disease progression. Changing this behaviour required considerable effort from the respective pharmaceutical company, mapping out IV capacities in Germany and hiring nurses to educate neurologists.

Stage 5: Confirmation

After an individual has decided to adopt an idea, information will be sought to confirm the behaviour. In general, people tend to ignore information that disagrees with their opinion and rather seek information confirming their decision. Hereby, a state of cognitive dissonance will be avoided and adverse information might be ignored to minimize conflict (Bornstein and Emler 2001).

In the confirmation stage, sales representatives - in their function as change agents - will maintain a relationship with the doctor and continue to supply them with confirming information. They will try to convince doctors not to reject the already adopted product. Discontinuing the use of an innovation may have two reasons: Not being satisfied with the performance (Disenchantment) or having a new and better innovation (Replacement).

In the pharmaceutical context, drugs regularly replace each other. As patents for innovative drugs expire after twenty years, research pipelines continue to pump out new drugs and broaden the approvals for new indications. Replacement is therefore the usual case to expect, while disenchantment should be the exception rather than the rule. After all, scientific studies,

price negotiations with insurances, and support of opinion leaders make it unlikely that a new treatment turns out to be altogether unsuccessful in improving the current standard of therapy.

2.1.2 Adapting Diffusion of Innovation to the Medical Market

As the aforementioned concepts point out, every physician has a different timeline for the adoption process and may be at a different personal stage of adoption relative to the general product lifecycle. Research on the diffusion of new drugs often focuses on a single factor without embedding it into a larger framework. In the last ten years, two major literature reviews cover the field of medical innovation research. While both organize the researched variables into categories, any aspect of time in the adoption process is neglected.

Building on the approach of Bonair and Persson (Bonair, A. and J. Persson 1996), Chauhan and Mason (2008) sort variables into three categories: *Drug Characteristics, Actors* and *Environment.* In the review of Agnés Lubloy (Lublóy 2014), the literature is screened for quantitative work and organized in four major categories: *Prescriber characteristics, Practice Characteristics, Drug Characteristics,* and *Patient Characteristics.* Within the prescriber characteristics a lot of other aspects are subsumed, including marketing efforts from pharmaceutical firms and social network contagion, two of the presumably most influential (and most variable) factors in the adoption process.

What has not been considered in the medical innovation research before is to include the time aspect of a diffusion process and to combine the stages of adoption with variables that influence behaviour. It is beneficial to separate the variables that are independent of a new innovation and quasi-fixed (e.g. a status quo if there was no new drug) and the semi-independent variables that may change during an innovation-decision process. The status quo is usually a given, which can be measured but is hard to change from the standpoint of a pharmaceutical company. The rest of the diffusion process, e.g. network contacts, detailing visits etc. may all change in the process and can (potentially) be influenced through pharmaceutical companies.

I propose to expand the Roger's framework with a new stage called *prior status.* Within the newly proposed stage, several variables are subsumed. Variables independent of a particular innovation, but with general relevance to the likelihood of innovation, can be found here. Other variables that have been considered relevant in prior literature have been matched to the

different stages of adoption and organized around the original framework. Figure 2 shows the proposed organization of variables to complement Rogers' adoption framework.

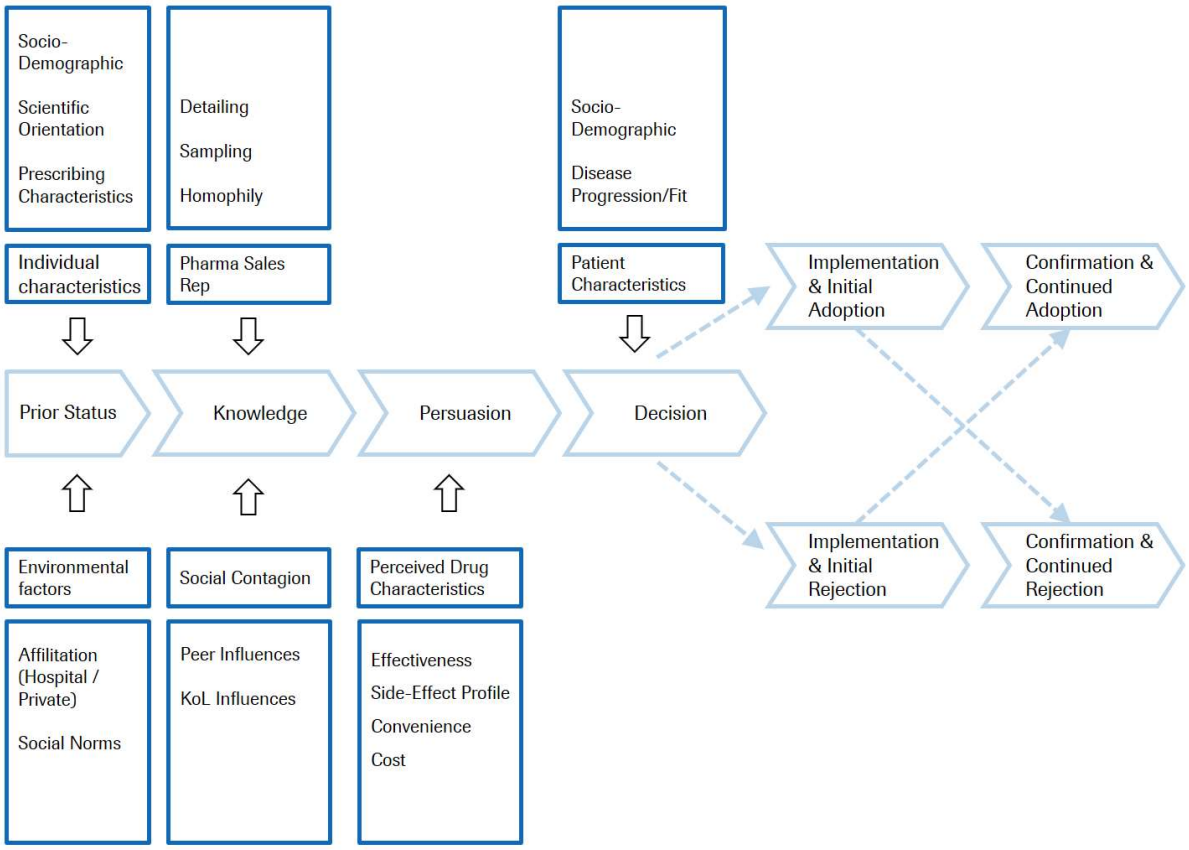

Figure 2 - Variables at different stages of the diffusion process

Prior status variables are somewhat independent of the particular innovation and are given even before an innovation comes out. They include prescriber characteristics such as socio-demographic aspects and a factor of "Expertness", constituted by variables such as years of experience, scientific orientation or prescription portfolio width. Although patients could be counted as a prerequisite for drug adoption, the choice of treating a specific patient with a certain drug comes after the general decision to adopt a drug into one's portfolio of treatments. In this regard it makes sense to assume that an expert doctor will have sufficient patients to adopt a new treatment per se, but makes it an individual decision of who to treat with it. Combining the information from this stage gives a good indication of the type of innovator we are looking at.

At the knowledge stage, two of the most influential variables for the innovation diffusion process come into play, namely the contagion through social networks and the effects of the change agent in form of the pharmaceutical sales representative.

At the persuasion stage the individual doctor looks at the perceived drug characteristics. This depends on the effects of the earlier stage. The same information (e.g. increases median life expectancy by 10%, but side effects like gastrointestinal problems may arise) can be framed and interpreted differently.

At the decision stage, the individual patients become important. As trials of a new product are conducted on a small scale, a doctor with uncertainty about a treatment could need a patient with a special condition or a strong request for a certain drug to deviate from his usual therapy scheme.

2.1.3 Literature Review Stage 1: Prior Status

With respect to individual physician characteristics, several attributes can be considered. Of the sociodemographic variables, mostly gender and (professional) age have been investigated. The current state of research delivers mixed findings: whereas some studies find that age is inversely correlated with new drug adoption (Glass and Rosenthal 2004), others find the exact opposite to be true (Kozyrskyj et al. 2007). Gender is found to be influential in some studies, e.g. Tamblyn et al. (2003) find male prescribers to be more likely early adopters of new drugs. Furthermore, specialisation of a physician is another important variable. In general, one supposes general practitioners to be less progressive in their treatment choice than specialist physicians. This intuition is supported by empirical evidence (Garjón et al. 2012).

To further distinguish scientific expertise within a specialist group, several factors can be investigated. One can look at how often a physician speaks at congresses, number of publications, affiliation with research focused institutions (e.g. university hospitals) or taking part in educational measures such as congresses or newsletters (e.g. “Fortbildungsmaßnahmen der Bundesärztekammer” in Germany or CME *continuing medical education* in the US).
Beginning with professional education, a study by Davis and Thomson (1995) revealed that relatively passive, but common measures such as participating in conferences and academic detailing have little influence on changing physician performance. Those results are confirmed by further research (Davis et al. 1999). The influence of conferences is not to be mixed with those of social contagion through networks; contact to influencers is another component that has to be considered (Davis and Taylor-Vaisey 1997).

Moreover, measures of scientific orientation could be affiliation with teaching hospitals, which seems to be a clear indicator for early adoption; a study found teaching hospitals to be

~40% faster to adopt new treatments than normal ones (D'Sa et al. 1994).
As most doctors will not be working in research, only a selected few publish in professional journals. Nonetheless, a practising physician will naturally gather information from peer reviewed and promotional journals. Measuring a physician's exposure to scientific journals can be done via self-reported data; in an early study focusing on contagion (Coe 1968), the researchers found a positive influence of the number of journals read on adoption behaviour. However, several later studies show scientific journals to have comparably small/ negligible influence on prescription behaviour (Greving et al. 2006; McGettigan et al. 2001).

A physician's experience with a certain disease, as opposed to his general scientific expertise, refers to hands-on knowledge of treating patients. There is general consensus in the literature that patient count and/or prescription volume in an indication or therapy class are strongly linked to early adoption. Iyengar et al. (2011) found that besides opinion leadership, the own expertise measured as volume of product usage plays a large role in contagion and subsequently the adoption of new products. Of several key physician level characteristics, the prescription volume of existing drugs in the therapeutic area has the largest influence on the adoption of a new drug (Groves et al. 2010). Other studies confirm those results (Liu and Gupta 2012).

The combination of scientific expertise and personal experience in a therapeutic area can be found in clinical trial investigators. These specialists not only assume knowledge leadership through scientific distinction, but also gain valuable experience with drugs before the actual market approval. In his research, H. Glass touched upon this matter several times (Glass and Rosenthal 2004; Glass and Dalton 2011) and found a positive correlation between being a clinical trial investigator and prescription volume. Additionally, investigators often play a role as key opinion leaders, thereby becoming important for the decision process of other adopters.

The prior conditions can be used to profile an adopter within the characteristic adopter classes. The sociodemographic criteria do not seem to play a huge role for adoption; gender and age are not influencing prescription behaviour significantly. Personal experience with a certain disease and/ or the therapeutic class of drugs favours adoption of innovative drugs. Generally, the more scientific expertise a physician can boast, the more he or she is prone to adoption. Simply attending congresses and reading journals delivers marginal effects only, whereas teaching hospital affiliation and speaking at congresses are strong indicators of early

innovation. The combination of all those can be found in clinical trial investigators; the opposite would be someone with small patient count and little contact to the scientific world.

2.1.4 Literature Review Stage 2: Knowledge

At the knowledge stage, there are two main sources of influence on a physician that may affect adoption behaviour: First, the pharmaceutical sales representative or detailer who functions as the change agent trying to spread an innovation. Second, there are social network effects or contagion, which may happen through either key opinion leaders or through local opinion leaders and peers.

The sales representative as the company's agent is one of the most important factors in explaining prescription variance. Broad consensus in the literature confirms that detailing has a positive effect on innovation (Kremer et al. 2008). Detailing is also found to have significant effects in a repeat purchase environment where the effects are tracked over a time series (Lilien et al. 1981). However, detailing is not the "holy grail" for product adoption. (Manchanda and Chintagunta 2004)) point out that the effects of detailing are positive, but come with diminishing marginal returns. At one point, physicians are just fed up with information or visits and further detailing efforts may even be harmful. As a supportive measure, sampling can help to spread an innovation (Gönül et al. 2001). However, the instrument is typically used for conventional finished medicinal products and not highly innovative cytostatic drugs.

The well known paper *Medical Innovation, a Diffusion Study* (Coleman and Columbia University. 1966) was the first to mark the positive effect of peer contagion on product adoption in the medical world. Ten years later, Pam Williamson was still early to prove that drug adoption happened faster within shared or group practices than for practitioners working alone (Williamson 1975).

Modern research seems to confirm that peers are the most consulted resource of information, ahead even of detailing efforts (McGettigan et al. 2001). Research on information seeking behaviour is also in line with Roger's characteristics of innovators, as individuals in social networks tend to appear either as information seekers (e.g. late adopters) or information providers (e.g. early adopters/innovators) (Peay and Peay 1994).

As Rogers points out, the effect of social influence, be it through peers or sales representatives (detailing) is moderated through homophily, the preference for similarity between a change

agent and the innovator. This effect is prominent within social groups and utilized through communication techniques by pharmaceutical companies (Lyon and Mirivel 2011).

This leads to another aspect of social networks: detailers may visit both, network peers as well as the observed adopter. Therefore, social contagion and medical detailing could be confounded. A more recent analysis of the original "Medical Innovation" dataset (van den Bulte and Lilien 2001) revealed that the effects of social contagion vanished when controlled for marketing efforts. In other studies however, the authors did find significant effects of network contagion even when controlling for detailing (Iyengar et al. 2011).

Although all members of a group may be detailed, the influence of detailing multiplies in the network. This is consistent with the knowledge from social network theory that innovation happens faster within network pockets than in inter-group relations (Valente 2005). Naturally, within a group the knowledge spreads fastest.

From Roger's Diffusion of Innovation framework stems the notion that key opinion leaders from the innovator segment will help spread the information, but have less influence in persuading the majority (Rogers 2003). This is empirically confirmed in the quantitative model of Liu and Gupta (Liu and Gupta 2012). They find that conferences and targeted meetings have an influence, mostly on early prescribers, but that the majority is convinced through peer-to-peer networks. and detailing.

Summing up: Both detailer and social network are important sources of information. Mostly, early adopters and innovators rely heavily on detailers, while later adopters tend to consult their network more strongly. Although both effects naturally confound each other, they can be empirically controlled for and stay significant.

2.1.5 Literature Review Stage 3 & 4: Persuasion and Decision

At the persuasion stage, physicians have a fairly comprehensive understanding of the innovation, started to discuss it with peers and are contemplating to bring it into action. In order for them to move from learning to trial they consider what they perceive to be the characteristics of the new innovation. They are still uncertain, but have to find a positive trade-off between efficiency, safety profile and possible side effects. If there is a current standard of care, this trade-off needs to beat that as well.

Once the physician is convinced of the advantages of an innovation and moves to deciding if she actually wants to use it, the prerequisites need to be met. The most important condition is the availability of a suitable patient.

Perceived Drug Characteristics (Persuasion Level):
Measuring the efficacy of a drug is a science in itself. Double blind or double randomized studies are the necessary standard to receive drug approval. Supposedly, it should be relatively easy to infer from that information how efficient and how safe a drug is however, that is not the case. All the biases and influential factors mentioned before come into play, changing the seemingly rational picture that was drawn up by the approval study and turning it into a notion of perceived effectiveness. As the "perceived effectiveness" can hardly be measured quantitatively, a look at qualitative studies (Prosser and Walley 2006) shows that doctors prescribe what they understand offers the best trade-off between safety and efficacy. Obviously, a breakthrough drug will always diffuse faster than one offering a marginal increment, but in a competitive environment with several similar drugs, marketing or peer influence may alter perception significantly.

Furthermore, cost is a variable playing an important role, however should not be heavily influential in a single-payer health system. As prices for new drugs are negotiated with insurances for their efficacy, doctors do not need to worry about prices too much. This holds as long as drugs are patent-protected; after that, generics or biosimilars will rapidly conquer market share.

Patient Characteristics (Decision Level):
The decision to use a drug because its perceived characteristics are positive goes hand in hand with the availability or the treatment needs of a suitable patient. Some studies point out that because innovative treatments have larger uncertainty with respect to side-effects, these will be prescribed to patients of younger age (e.g. Tamblyn et al. 2003). The intuition is that they are not as fragile as elderly patients and will be more resilient to side-effects.

The general disease progression also plays a role in the decision making. New drugs are often prescribed to patients in more advanced stages of a disease (Mark et al. 2002), when standard of care has either been tried out already or the expected patient benefits seem very small.

So, a new drug with higher uncertainty is more likely to be tried if there is a young patient with rapid disease progression; the more stable a patient is, the less likely his/her therapy is to be changed and the more elderly, the worse negative side effects will affect him/her.

2.2 Diffusion of Innovation on the Market Level

The previous chapter introduced and explained a variety of different variables that explain a difference in the variance of adoption timing. Typically, people sharing the same characteristics adopt at a specific point of the diffusion timeline. Roger's categorizes these different types of adopters in order to explain the diffusion process on the market level. Based on a normal distribution, he indicates how big he believes the population groups to be and infers their contribution to market shares. Figure 3 shows the normal distribution and the shares of different innovator types assumed within. In the following paragraphs, the innovator types according to Roger's are explained first and then related to the pharmaceutical market setting of this thesis.

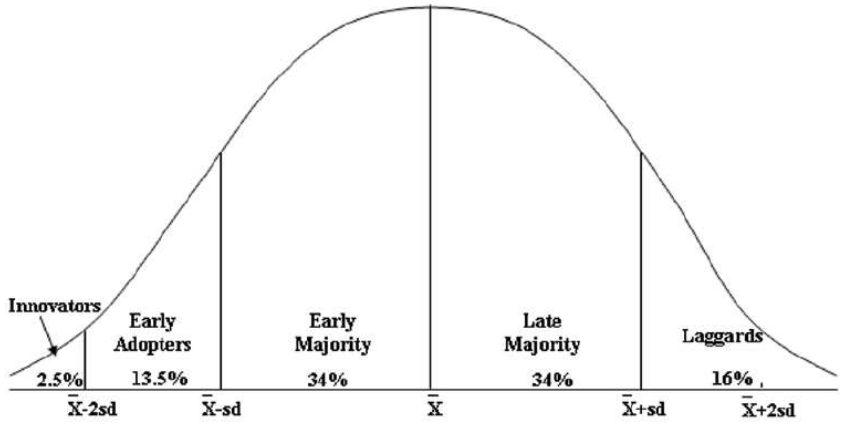

Figure 3 - Adoption Curve Rogers

Type 1 - Innovators

According to this model, innovators are assumed to make up about 2.5% of a population. They must be able to manage the high degree of uncertainty that usually comes with new innovation. The innovator's role in the diffusion process is to launch a new idea into a social system. In a pharmaceutical setting, innovators are the physicians participating in clinical trials or those affiliated with large teaching hospitals. They will be referred to as KOLs (Key Opinion Leaders), having a reputation and voice that reaches far out. Popular strategies for the

treatment of rare diseases would be “hit hard and early”, using experimental drugs or new substances in a number of scenarios.

Type 2 – Early Adopters

The early adopters make up about 13.5% of a population. Their role in a social system is the one of a respected authority to consult before making a decision. Rather than being global (or national) voices, they are opinion leaders in a local setting. Early adopters are conveying evaluations of an innovation within a close pear-to-peer or near-peer network. They will also be found in teaching hospitals and larger established practices, functioning as a local authority and expert. While they would receive the occasional invitation to speak at a congress, their main focus is not research but treatment.

Type 3 – Early Majority

The early majority constitutes just over a third (34%) of a population. They will wait for a well-established degree of certainty about an innovation before they choose to follow. They adopt just before the average and are usually still well connected with their peers. In terms of the physician setting it is reasonable to assume the early majority comprises itself of resident physicians eager to do what is best for their patients – adopting well-tested and suitable innovations without taking big risks.

Type 4 – Late Majority

The late majority, roughly another third of the population (34%) are sceptical and cautious about adoption. Even a well-established utility of an innovation will require peer pressure to convince the late majority to safely adopt. A doctor who is part of the late majority will wait until almost all risks associated with an innovation are known ensuring minimal possible uncertainty before deciding to adopt.

Type 5 – Laggards

These traditionalists are the last ones in a social system to innovate (16%). Being largely isolated and backwards rather than forwards oriented, laggards are suspicious of innovations and change agents. Although they will be aware of an innovation and know about it, they cannot be motivated to adopt themselves. In the medicinal context, laggards would be adept followers of the “watch and wait” strategy profile, reluctant to change treatment or therapy regime if there is no major sudden disease progression.

Generally, those five types of generalized innovators naturally are not fixed for everyone in every context. Depending on the field of expertise or general preferences, one can be an innovator in the one area, but will usually be part of the majority in the other. Rogers assumes that the adopter groups follow a normal distribution.

Interestingly, the arbitrary values for the distribution of innovators were tested quantitatively and help up quite well. Using the Bass forecasting model, Mahajan et al. 1990 analysed Bass' original dataset for consumer goods.

Mahajan et. al start with the cumulative market share curve of the Bass-Model (more in chapter 2.3.1). They look at necessary and sufficient conditions of the curve sketching to see where a new group of adopters comes into play. For instance, the first inflection point, from concave to convex, indicates where the early majority joins the market. The distribution of adopter groups inferred by this method is almost identical with Rogers original prediction. While this does not necessarily have to hold for any innovation, it confirms the relative importance of each group for market shares.

Overall, it is crucial to remember, that while Innovators and Early Adopters do not make up the bulk of the sales between them, they take on an important function with respect to distributing the innovation. If those two groups are not convinced, the innovation will most likely not spread to the majority – which in turn is responsible for the market share.

2.3 Quantitative Approaches to Diffusion Modeling

2.3.1 Macro-level modelling

The first and most general level of diffusion modelling is the macro-level. It describes the diffusion of a product as sales growth on a national level. The usual quantitative model based on Roger's diffusion of innovation is the Bass model (Bass 1969). It can be used to forecast product adoption over time. Without assuming any underlying population structure, its basic premise is a split of consumers into innovators and imitators. The first are influenced by media and other non-adopter sources, the latter by innovators who have already adopted an innovation. An individual in the Bass model can only choose between adopting and not adopting. The Bass model, using estimates of the rates of innovation and imitation, calculates the speed of diffusion.

The variables that are used to compute the Bass model are as follows:

(1) F(T) = Fraction of people who have adopted an innovation
(2) p = rate of external influence adoptions (innovation)
    q = rate of internal influence adoptions (imitation)

Depending on this information, the following equation gives the speed of diffusion depending on the fraction of people who already have adopted[1]:

$$f(T) = [p + q\,F(T)][1 - F(T)]$$

The first part of the equation is the rate of innovative adoption *p* plus the rate of imitation, the second part is the fraction of people who have not yet adopted. At the beginning, when F(T) is close to zero, the imitation term (q*F(T)) remains almost zero as well. The slope of the curve or the growth of adoption stems from the innovative adoption coefficient *p* only. Eventually, the adoption through imitation growth (q * F(T)) will become larger than growth through innovators (p). This is when growth is at its fastest. In the end, when F(T) is almost 1, the growth slows down again because the latter term converges to zero.

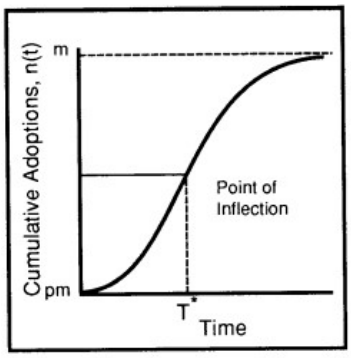

Figure 4 – Cumulative Adoption in the Bass Model (Mahajan et al. 1991)

[1] Expanding the formula for speed of diffusion gives the fraction of people adopting at a specific moment in time: $F(T) = \frac{1-e^{-(p+q)t}}{(1+\frac{q}{p}e^{-(p+q)t})}$

The mechanism of imitation growth taking over has also been depicted cumulatively:

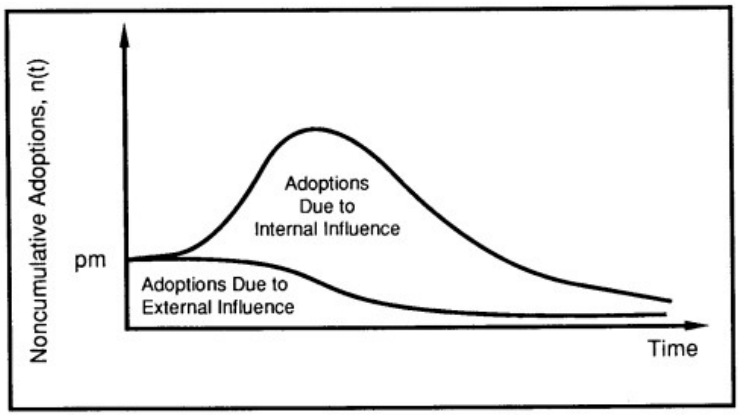

Figure 5 – Adoptions due to external and internal influence (Mahajan et al. 1991)

In the Bass Model, the spontaneous innovations or "external innovations" are especially important in the beginning of a diffusion process. Adoptions due to social contagion soon become more relevant for market share and make up the bigger part of the sales. It is noteworthy that in the Bass Model innovators are not only the first to innovate, but the ones that are convinced by external influence and that this occurs over the entire timeline.

Bass proves in his original paper (Bass 1969) that he can forecast the diffusion of consumer products fairly accurately using ordinary least square regression to estimate the parameters q and p. Later papers have either extended the model (Easingwood et al. 1983) or used different estimation approaches for the parameters, e.g. Bayesian maximum likelihood estimations (Schmittlein and Mahajan 1982) rather than frequentist statistics approaches. The model has also been used in a variety of different scenarios and industries, for instance in cross-country applications (Bass 2004). One of the biggest shortcomings of the model is that it does not take into account any population specific factors. Assuming a single "social contagion coefficient" equals assuming uniformity over geographic areas. As the adoption parameters p and q are relatively easy to estimate, the model is useful to estimate a figure displaying total sales, approximate diffusion targets or serving as a visual validation indicating whether a target sales peak seems realistic, given the current sales development.

2.3.2 Meso-Level Modelling

In between the macro and micro level modelling it is possible to measure the geographic spread of an innovation on a smaller unit than the entire market. Statistic techniques like spatial autocorrelation are being used to determine the degree of similarity between neighbouring areas. Spatial autocorrelation indicates to what degree observations in geographic locations share the same expression of a variable, e.g. market shares in federal states (Legendre 1993). While it is often used in biology or an ecological context, it may be beneficial for diffusion research as well. In diffusion research geographic clustering can be very interesting, as it seems likely that geographic proximity correlates with network effects.

A possible measure of spatial autocorrelation is Moran's I. It tests if whether geographic clusters are distributed randomly by calculating a correlation coefficient between neighbouring observation means and the general mean within a population. After obtaining Moran's I, Z-Scores and P-Values need to be checked for hypothesis testing; p-values show if the compared means are statistically different (Valente 2005). The sign of the Z-Score indicates the direction of autocorrelation. Strong negative autocorrelation resembles a chess-board where similar colours are never adjacent; the strongest positive autocorrelation would be a blank and a white side of the chess board.

In a study on innovation activity in Europe, Moreno et. al 2005 show how Moran's I can be used to statistically confirm the clustering of innovative regions.

Figure 6 shows a graphic representation of the European regions where shaded regions indicate patents per capita. The visual impression of innovative clusters in Middle Europe and Finland is confirmed by high positive Z-Scores of Moran's I (Table 1) while the low p-values prove the statistical significance of the findings. Instead of measuring patents per capita, the method can be adopted to pharmaceutical sales regions in Germany.

As explained above, positive scores indicate neighbours behave similarly, for example when large teaching hospitals influence rural areas. Negative scores show that unlike neighbours group together, e.g. when large teaching hospitals "drain" rural areas. Spatial Autocorrelation therefor introduces a way of quantitatively measuring geographic effects, but does not depict

the individual doctor / patient level. Effects remain measurable only on geographic units or via geographic proximity.

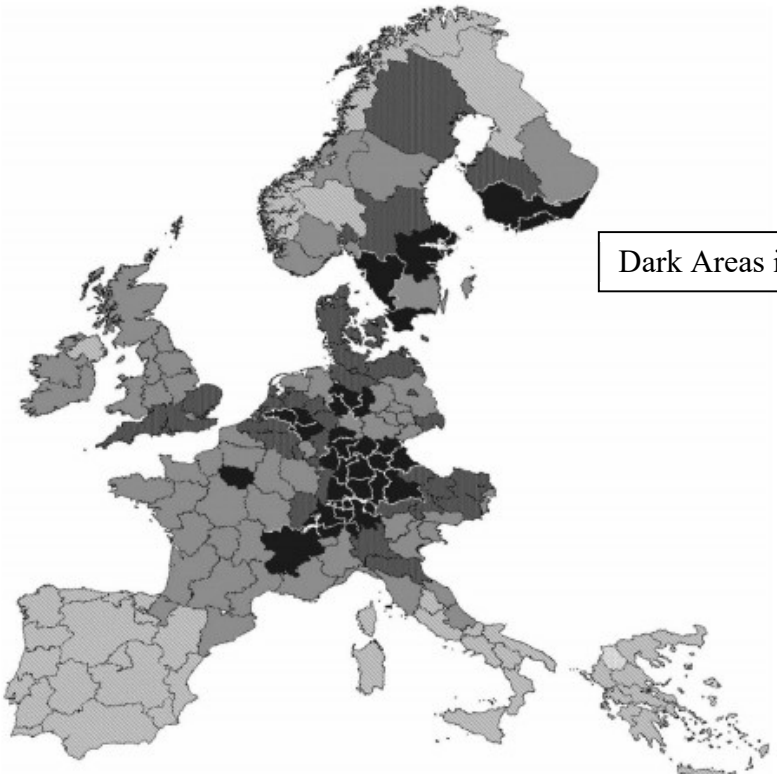

Figure 6 - Patents per 100.000 in Europe 1999-2001 (Moreno et al. 2005)

Contiguity	1981 – 83		1988 – 90		1994 – 96		1999 – 2001	
	Z-value	prob.	Z-value	prob.	Z-value	prob.	Z-value	prob.
1st-order	3.4	0.0	4.1	0.0	4.3	0.0	4.5	0.0
2nd-order	2.8	0.0	3.6	0.0	4.2	0.0	4.3	0.0
3rd-order	3.4	0.0	3.4	0.0	3.7	0.0	3.5	0.0

prob. probability.

Table 1 - Z Values and Probabilities for Moran's I (Moreno et al. 2005)

2.3.3 Micro-Level Modelling

The finest and most challenging level of modelling is the individual person level. When diffusion modelling looks at the spread of an innovation on a personal level, multi-attribute models are used for an individuals decision making process.

One very comprehensive model is by Liu and Gupta 2012, who model adoption behaviour as a function of different variables. The mathematical model that they use is a probit-model. This

means they observe a binary choice, adoption or no adoption, and infer from that a critical value of an underlying variable has been exceeded. If the physician adopts, the critical value of the latent variable was reached.

Their model explained in detail:
According to the model, a physician decides every month to adopt (1) or to not adopt (0) based on the value of the underlying function. This function incorporates several coefficients associated with innovation diffusion. The general model looks as follows:
A physician adopts if the utility of adopting is larger than the utility of not adopting.

$$(1)\ P_{it}(y_{it} = 1) = P\ (U_{it}^{*} > 0)$$

The outcome of the binary variable y (adopt/ not adopt) depends on a continuous variable *U**. *U** is defined as the individual doctor's utility of adopting vs. not adopting.

$$(2)\ U_{it}^{*} = V_{it} + \ \varepsilon_{it}\ ;\ \varepsilon_{it} \sim N(0,1)$$

So *U** equals the doctor's individual *V*, defined as a factor of multiple variables, plus a normally distributed error term.
The question the model could answer is when does *P* (y =1) become 1 (e.g. the doctor adopts the drug). That depends on *U** being larger than 0, so the question is what is the probability for *U** > 0 given *V*?

By having data on the actual date of adoption, and the status of the variables that *V* is composed of, the authors can infer the coefficients of those variables. Through the observation of the actual adoption behaviour, one can obtain the values of the variables within *V* and then being able to compute the coefficients of the variables.

V is modelled as a function of variables empirically proven to alter physician behaviour and collected on physician level.

Variable Category 1: Intercept

The authors start off with a variable for the "intrinsic property to adopt", characterized as a potential for specialization and previous prescription volume (a concept comparable to the prior status added to the Rogers model in 2.1.1). In order to compute a potential score figure *Z,* the following aspects are selected: number of category prescriptions, type of practice of the physician as well as socio-demographic criteria like median population age in the community,

percentage of ethnic whites, annual household income and insurance index on the patient. The higher *Z*, the higher a physician's likeliness to adopt.

Variable Category 2: Marketing

Marketing activities of the company are approximated by taking into account the number of detailing visits, events and meetings on an individual level. On the market level, the spending for journal advertising is tracked. Exposure for the individual physician is not measured, but one value is assumed for every physician in the month the journal is published. Furthermore, the authors include a time-effect for the variables. Naturally, the impact of a visit deteriorates over time. When a detailer visits a physician, the visit is tracked and a part of its impact then carried over to the next period. This carry-over factor can take any numerical factor between 0 and 1 (here it is 0.63). The remaining value is called "stock" and may well include multiple visits. The detailing stock of a single visit two months ago would be $1 * 0.63^2 = 0.39$.

Variable Category 3: Social Contagion

In order to describe the modelling approach for social contagion, some background information on this type of research is needed. Social contagion models are based on the hypothesis that contact with a non-random distribution of adopters will influence behaviour of an individual (Iyengar et al. 2011). The measurement of such exposure is undertaken in two different ways.

One way is to measure the degree of personal exposure to an idea within the personal social network. The more people in one's personal network have already adopted an innovation, the higher the degree of exposure (Manchanda et al. 2008).
The second method is to measure exposure in geographic proximity. The more people in a geographic area have adopted an idea, the higher the exposure (Manchanda et al. 2008). The underlying rationale is that proximity leads to social mixing and thus measurable effects of contagion.

Social network models require information about the person's personal network and its ties, the strength of the relationship and so forth. While this is very precise, data is difficult to obtain. Easier to obtain, but still difficult is to measure centrality in the network position or analysing behaviour differences between people in similar network positions (Valente 2005). Geographic proximity on the contrary only requires precise location data.

Liu and Gupta used the geographic approach. The authors decided to measure social network contagion through the percentage of physicians that already adopted in a 20-mile radius. This approach was also used in the medical diffusion modelling by Manchanda et. al 2008, where the authors demonstrated significant effects of proximity on adoption behaviour. In their paper, doctors in the same city within a 20-mile radius who adopted a drug influenced others within that same radius.

Liu and Gupta apply the same method. They look at a 20-mile radius around a physician and how many doctors already adopted a drug. One advantage of using the proximity approach is that effects of endogenous group formation and homophily are minimized to some extent. Doctors with different backgrounds working in neighbouring areas influence each other rather than the old friends from college living hundreds of miles apart. Nonetheless, with 2000 physicians in a study covering the US, the data is bound to be noisy as physicians are spread out far over the US and exposure rarely exceed one or two physicians.

Variable Category 4: Patients

The last variable the model takes into account is the number of patient requests for the specific drug. This can be considered to be easily and straightforwardly measurable, with the only pitfall being bad quality of reporting through the physicians.

Afterwards, variables (exact date of adoption for every physician, patient requests, number of days visited etc.) from a survey report of >2000 physicians are entered into the model. Thereby all the required information in order to compute Z is available. As the actual day of adoption is known, the model is used to determine the influence of the variables. The goal is to learn if meetings are more influential than patient requests or vice versa. One example: Physician 1 adopts the drug in month 4, physician 2 in month 6. They had both been visited xy times, read the journals and had a patient request for the drug. The model now tries to infer their responsiveness to the variables, e.g. if a journal advertisement is more effective than a detailing visit et cetera.

To do so, the researchers simulate the entire sample in a Markov-Chain Monte Carlo Simulation 30.000 times. Thereby they obtain the median response coefficients for the variables, or in other words, how much of the variance in individual adoption behaviour is attributed to every variable. Table 2 shows the results of the simulation; the largest influencing factor in the model are the patient requests. Journal advertisement has little significance on individual level. The remainder of detailing stock can be used to infer the long-term effect of one detailing visit, which is found to be 0.73 (Liu and Gupta 2012). Meetings and events are influential, but only a small number of physicians in the present sample were invited or actually at the event.

Parameter	Posterior Mean	95% interval
α—Intercept	–2.43	(–2.70, –2.26)
β_1—Detailing stock	.27	(.24, .31)
β_2—Contagion	.26	(.12, .40)
γ_1—Meetings and events stock	.27	(.08, .45)
γ_2—Journal advertising stock	5e–4	(4e–5, 1e–3)
γ_3—Patient requests	1.12	(.90, 1.35)
γ_4—Linear time effect	.07	(.03, .09)
λ—Stock retention rate	.63	(.54, .72)

Table 2 - Parameter Estimates of the Adoption Model

The physician specific characteristics are subsumed in α. Within alpha, the findings revealed that specialists are more likely to adopt than general practitioners and that prescription volume in the drug class is the most influential variable.

After the parameters are inferred, the model is applied to forecast the diffusion for a new drug in a similar drug class using the specifications obtained from the model described earlier. Furthermore, the authors ran a standard Bass-Model on the parameters inferred from the survey product, the results of which can be seen in Figure 7.

While both predictions on the macro level slightly overestimate the adoption, the Bass-Model prediction, which requires just two parameters, holds up well compared to the much more complex micro-level model.

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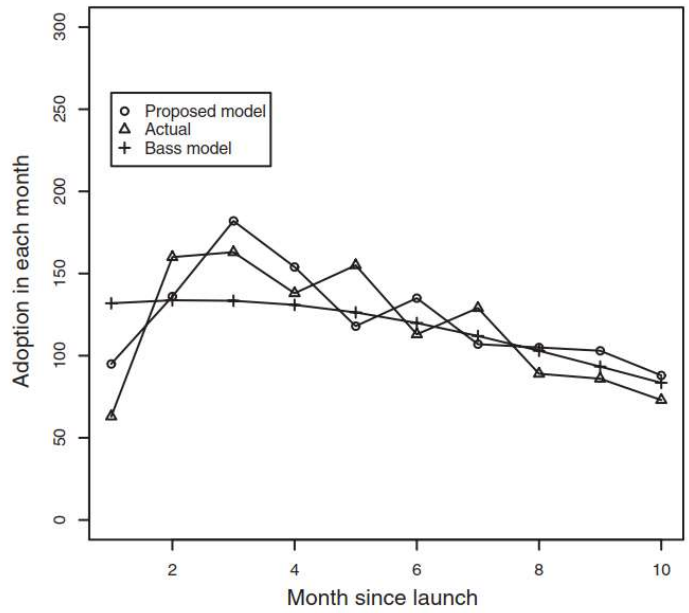

Figure 7 - Proposed vs Actuals of Model 2

On the micro-level, the authors conduct a ranking of physicians by their likelihood to adopt based on their intrinsic property to adopt, their responses to detailing and contagion drawn from an estimated distribution, and the posterior mean of the other covariates as common to all physicians. Afterwards, the mean of the adoption probability from a 100 draws for an individual is applied to compute a monthly top ranking of physicians and their likelihood to adopt.

This computation of every physician's chance to adopt in a certain month is used to model an optimal targeting approach. Unfortunately, the authors only compare the efficiency of their model against a random targeting approach and not against the company's usual targeting method. Usually, the a priori characteristics of a physician will be the basis for a targeting approach and the model proposed could prove its value for forecasting by determining how important the individual's response to detailing and contagion are in improving targeting. For instance, the model could be used to determine which physicians are most receptive for detailing and those who are more receptive for social contagion and set up a targeting approach to maximize contagion values. By comparing to random targeting the authors are, to remain in the medical language, testing against placebo and not standard of care. The efficacy of their mathematically satisfying and complex approach cannot be properly assessed in that fashion.

The present and previous chapters explained different methods of modeling. Furthermore, they each elaborated more specifically on a typical tool applied on that level. The next chapter will

point out how privacy regulations constrain the efforts to collect data and which of the different models are still applicable in the context of the German pharmaceutical market taking these regulatory restrictions into account.

3. Privacy Regulation in the German Pharmaceutical Market

The individual's right to privacy is one of the cornerstones of Western legislation. Laws are in place to protect sensible personal data. Naturally, this leads to conflict with the interests of (pharmaceutical) companies that are dependent on assessing prescription origin in order to understand where and how their treatments are used. Their reasons for this are twofold: rapid diffusion of a pharmaceutical innovation is expected to benefit patients while simultaneously increasing sales figures. Hence, the more transparency a company has over its customers and the markets it serves, the more efficiently it can distribute its products and utilize its sales force.

In addition to the influence of privacy regulation, market specific features make pharmaceutical sales tracking challenging. Prescription medicines are not marketed to patients; instead, a doctor makes the decision for a certain treatment. The doctor however does not buy the product himself. Rather, the patient decides to which pharmacy to go to for the respective drugs. This implies that a patient may get a prescription for a treatment in city x, take the car back home to city y and pick up the medicine there. The pharmaceutical company is usually interested in knowing where the prescription originated from – to know their customers but also to incentivise sales representatives.

Pharmaceutical companies have to use two different systems of sales tracking. They differentiate between *sell-out* and *sell-in* data. *Sell-Out* data refers to the "consumption" of a product, *sell-in* to the delivery.

Sell-Out data sources try to measure the origin of prescription as close as possible. The point where the physician decides to give a certain treatment to a patient is of relevance, because it marks the "real" point of sale. It is also used to evaluate the sales force. The prescription origin is valuable information as it constitutes a measure of unbiased, behavioural data. Because of its high importance and value, an individual doctor's prescription behaviour is a sensitive matter, strictly protected by privacy regulation. How exactly will be elaborated in the following chapters.

Sell- In data on the other hand shows the ways the product takes from the manufacturer to the patient. This is not necessarily identical with the prescription origin and hence not as valuable,

making it available on a smaller scale. After all, a direct sale to a hospital will always remain transparent. Even a direct sale should not be equated with prescription information, since it is not clear who in a hospital ordered the drug.

Although sell-in and sell-out data may differ, it can be useful for various analyses to deploy two sources of data: first, prescription data to measure behavioural data accurately and second, delivery data to better understand the market on a smaller regional grid.

This chapter introduces the various ways of how a treatment can reach a patient and how the two data sources interact, as well as it shows how data availability is limited through German privacy regulation in 2018. Content is mainly based on methods, procedures and products of the data science company IQVIA and the reporting system of Roche; their competitor's reports will however work in similar fashion.

3.1 Private Practices

In Germany, most patients are members of the mandatory general health insurance. As such, they receive a prescription form for most drugs. The flow of information from a patient needing a drug to how this information lands in the systems of pharmaceutical companies is depicted in Figure 8.

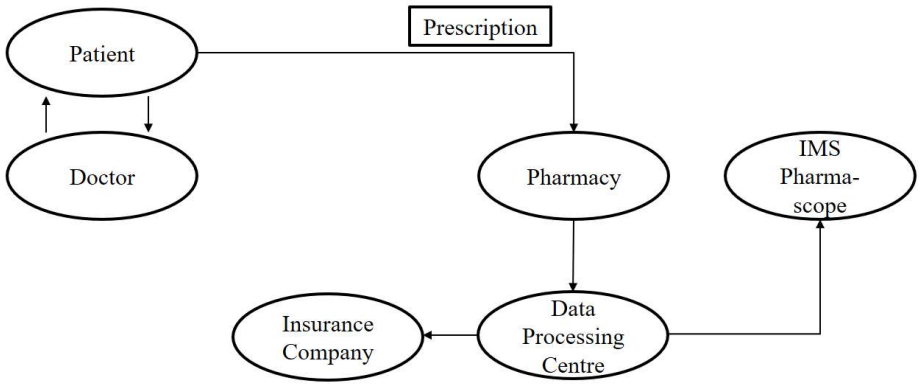

Figure 8 - Private Practice to IQVIA

Firstly, patient and doctor interact and the decision for a treatment is made. The prescription form then reaches the pharmacy. Pharmacies accept the insurance prescriptions instead of cash because they receive their money directly from the insurance companies. Pharmacies do however not go to the insurers to collect their money individually. This would leave a

pharmacy invoicing every insurer in Germany every month and vice versa. Instead, the collection and evaluation of the prescriptions is usually outsourced to data processing centres, which invoice the insurance companies collectively. In order for this system to work, the prescription form contains all necessary information for the transaction: identification (ID) of the pharmacy, the product code, the life-long physician ID and the doctor's establishment ID.

This information reaches the data processing centres when the prescription form is entered into the pharmacy's system and when the prescriptions are collected at the end of the month. After the prescription has reached a data processing centre, data science companies like IQVIA are able to buy anonymized information and the insurers are being invoiced. For market research purposes, data is anonymized by aggregating individual level prescriptions on 1868 geographical units, called *Segments.* At this point, IQVIA has almost complete transparency over every prescription written in Germany on any given day.[2]

IQVIA then sells these data to pharmaceutical companies – further anonymizing information in accordance with the state of the current privacy law. Aggregated sales data from IQVIA, or to be precise, their product called IMS Pharmascope, is the definitive standard for private practice prescriptions. Private prescriptions to self-payers/ with private insurance are not collected at the data processing centres and therefore a calculated sum is added to the general insurance prescriptions. Different companies offer various methods here, but the general idea is to have some statistical tool that incorporates demographics and data from panel pharmacies in the area and to further extrapolate from the general insurance prescriptions.

3.2 Hospitals

Hospitals are different from private practices as they usually order drugs directly at the manufacturer without involving a public pharmacy. This does not necessarily simplify things however. There are four possible ways of how a drug can reach a patient through a hospital. The two most prominent ways are depicted in Figure 9.

[2] Pharmacies have the option to opt out of the data collection. Data processing centres receive royalties for the use of their data for market research, but pharmacies are not being penalized for opting out. Basically this is a free rider problem in which most pharmacies still take part.

The first and easiest case are ward patients; their treatment way is depicted above the dotted line in Figure 9. The patient and doctor interact, the doctor decides for a treatment and then the hospital buys the drugs, cares for patients and later sends a general invoice for treating a patient to his/her insurance. In this case, the sell-out (prescription) happens at the point of sell-in (delivery). The direct sales to a hospital are not tracked by a third party. The information is not collected in a central record like Pharmascope; instead, direct sales to the hospitals can only be fully tracked by the manufacturers themselves. This also means that there is no way to directly measure competitor sales to hospitals, which can only happen if the hospital takes part in a market research panel.

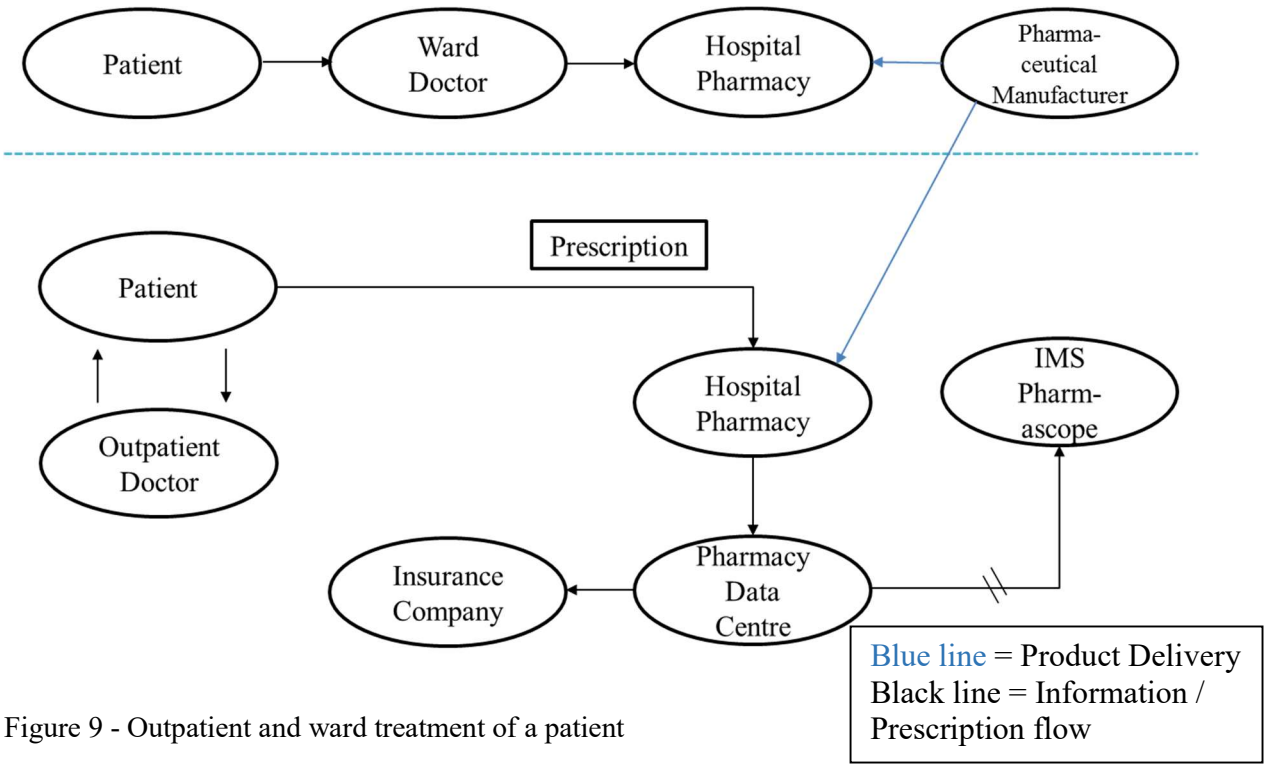

Figure 9 - Outpatient and ward treatment of a patient

The second case is outpatient treatment. Here, the hospital also orders directly from the pharmaceutical company, but the hospital does not invoice the insurers themselves. Rather, the hospital pharmacy functions like a public pharmacy, receiving a prescription and invoicing via a data collection centre. Patient and doctors interact, prescription is written etc., just as in the case of a normal public pharmacy. These prescriptions are collected at the data processing centres, but later removed from the IMS Pharmascope. There are two reasons for that: a) Pharmascope then becomes a public pharmacy only data source and b), pharmaceutical companies have their own products on direct sale basis and would not need a more inaccurate data source showing them their own sales. The downside is that outpatient prescriptions of competitor products are not visible in a comprehensive data source like Pharmascope.

Besides the two first cases described above, hospitals have a third way of using their pharmacy to supply patients, which is only applicable for the case of cytostatic preparation drugs[3]. In accordance with §11.3 of the *Apothekengesetz*, a hospital pharmacy may prepare cytostatic drugs for the use of a private pharmacy. An insurance prescription will be written and the drug will be listed as a private prescription in IMS Pharmascope. These three ways will all lead a hospital to order directly at the manufacturer, but with different customer numbers and also different prices[4] for each situation.

The fourth possible situation is that the patient is treated in outpatient care and receives a prescription physically to go and collect the drugs themselves. This might be the case for someone arriving at the emergency ward, and, after treatment, being sent home. It is the usual way for any non-cytostatic drugs, as the reimbursement system only allows hospitals to give out a single dose. In that case the prescription follows the usual way of a private practice prescription, e.g. the product is sent to a local public pharmacy where the patient collects it. The drug never enters the hospital.

3.3 Exceptions

As with any rule, there are some exceptions to the "normal" cases mentioned above. They may lead to ambiguity or errors when analysing sales.

Public pharmacies: Any public pharmacy has the possibility to disallow use of their prescriptions for market research purposes. If a public pharmacy chooses to opt out of the data collection from IQVIA, all the prescriptions handed in there will not appear in Pharmascope. In that case, pharmaceutical companies have to assign direct sales to a geographic cell instead.

Manufacturers of cytostatic preparations: Another special case are companies like *Zytoservice,* a manufacturer of cytostatic infusion preparations. They are in a hybrid position between a wholesaler and a licensed pharmacy – as such, they operate a delivery service of cytostatic

[3] Cytostatic preparations are drugs that need to be dissolved into an infusion under strict conditions (e.g. sterile environment, a constant temperature etc.). Most pharmacies cannot do so themselves and therefore rely on others to supply them. The majority of Roche's 2018 oncology portfolio are cytostatic preparations. The terms "cytostatic preparations" and "cytostatic drugs" are used simultaneously throughout the thesis

[4] Drug pricing is marked by complex legislation and pricing schemes making it difficult to disentangle the information in net sales. Geographic sales tracking therefor assumes one identical price per unit in every form.

infusions. They can receive prescriptions and provide patients with their infusions, but do not report their data to IQVIA.

Parallel Imports: Lastly, some pharmacies and hospitals use sources abroad to acquire drugs. In case of prescription drugs in private practices this is not a big issue, as the prescriptions are registered in Pharmascope. In the case of hospitals however, these so-called parallel imports have to be specially monitored.

3.4 Data Aggregation

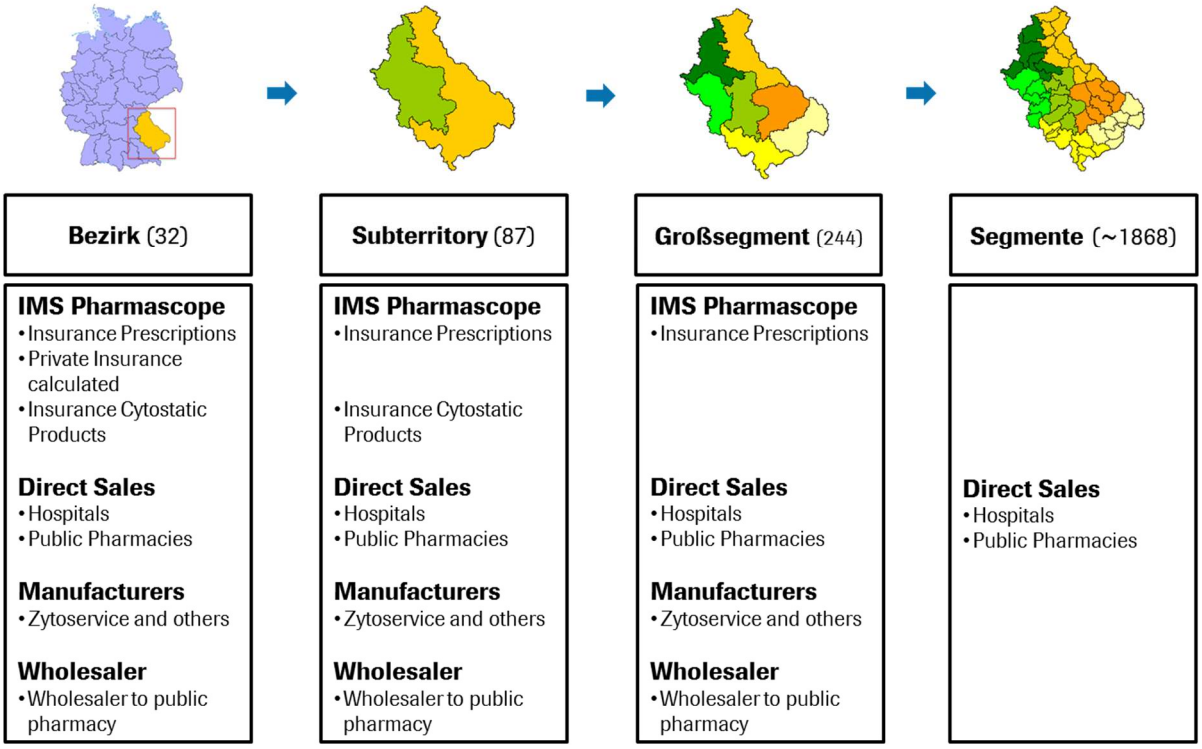

Figure 10 - Possible Data Aggregation Levels in Germany

The privacy regulations determine on which level which data may be available. The aim of the legislation is to prevent conclusions about individual prescription behaviour. To ensure anonymity, data of several prescribers are aggregated on a geographic scale. The scales are designed to protect individual behaviour data. Historically, the IMS Pharmascope started to deliver data on *Segments,* a geographic cell requiring the existence of minimum of four to five pharmacies. Starting with the smallest unit, Figure 10 will be explained from right to left.

Today, 1868 Segments exist in Germany. On this structure, IQVIA still orders the Pharmascope data from the data processing centres, but they are not allowed to provide

information to third parties like pharmaceutical companies. Depending on the company and the classification of the product, any company may choose to build their own overlaying structure by combining the *Segments* to bigger units (Figure 10).

The first level on which IQVIA may give out prescription data for a finished medicinal product are *Großsegmente*. Finished medicinal products are for example pills, ready-to-use syringes or capsules. On this level, 244 units can exist in Germany. The mandatory minimum requirement to aggregate *Segments* to a *Großsegment* are 300.000 inhabitants.

Moving up one level, the geographical unit is called *Subterritory*. 87 of those can exist on the IMS Pharmascope structure. On *Subterritory* level, prescriptions for preparation medicines such as cytostatic infusions can be disclosed. The minimum size criterion here are: three prescribing establishments in hospitals and private practices each; this does not sound much, yet, specialist oncology stations or practices are rare.

The biggest level for data disclosure via Pharmascope data are *Bezirke*. This area is typically visited by one sales representative and it is the only level in which demographic data for privately insured/ self-paying patients is calculated.

3.5 Implications for Data Analysis

As the previous chapters have shown, privacy legislation in Germany makes market analysis of behavioural data very challenging. Prescription data (Sell-Out) for cytostatic products needs to be aggregated onto the S*ubterritory* level. Data on those large geographic cells are too inaccurate to measure individual or specific group behaviour. However, delivery data (Sell-In) is available on a smaller grid. If that is the case, why not simply use that instead of the tedious collection via Pharmascope?

The reason for that is that data is not identical. In theory, if one assumes that there are no parallel imports and every prescription is handed to the data processing centres, then it should be possible to find a prescription for every shipment sent into the market. In practice, however, this turns out to be different. The complex structure of pricing gives several parties incentives to create complex delivery structures and foreign imports and exports are used in an attempt to gain price arbitrage. The following paragraphs take a closer look at the difference between sell in and sell-out data in Germany.

In order to assess the difference between sell-in and sell-out, the aggregate data for a typical cytostatic product in 2017 was compared on the national level and on the level of a single subterritory. On a national level, matching sell-in versus sell-out works quite well, with a deviation of 1.5% of private practice prescriptions in Germany. For most products, hospital vs. private practices sales are identical. Nonetheless, data accuracy may suffer from parallel imports into hospitals from another country (Table 3).While sell-in and sell-out are fairly close on national level, this is not necessarily the case on a smaller level. In the hospital area numbers are almost identical as no imports or exports seem to happen. The private practices on the other hand show a significant difference between sell-in and sell-out; precisely spoken, 28% more prescriptions than deliveries into the subterritory are recorded (Table 4).

While the imports into practices are covered in the sell-out data, exports into other countries through wholesalers are not accounted for. In the cytostatic oncology sector, products typically are not cheaper in Germany than abroad. Therefor exports only happen when a country has higher drug prices than Germany, which is unusual.

Sell-Out		Sell-In	
Private Practices (60,1% of sales)			
Pharmascope	79,87%	Compounders	41,26%
Private Insurance	9,60%	Public Pharmacies	43,93%
non-reporting Pharmacies	3,46%	Wholesaler to Pharmacy	6,21%
Zytoservice	7,07%	Zytoservice	7,07%
		GAP	1,53%
	100,00%		100,00%
Hospitals (39,9% of sales)			
Hospital Direct Sales	97,97%	Hospital Direct Sales	97,97%
Hospital Parallel Imports	2,03%		
		GAP	2,03%
	100,00%		100,00%

Table 3 - Distribution of Cytostatic Preparation on Datasources, National Level

While sell-in and sell-out are fairly close on national level, this is not necessarily the case on a smaller level. In the hospital area numbers are almost identical as no imports or exports seem to happen. The private practices on the other hand show a significant difference between sell-in and sell-out; precisely spoken, 28% more prescriptions than deliveries into the subterritory are recorded (Table 4).

Sell-Out		Sell-In	
Private Practices (52,3% of sales)			
Pharmascope	58%	Compounders	11%
Private Insurance	6%	Public Pharmacies	55%
non-reporting Pharmacies	36%	Wholesaler to Pharmacy	7%
Zytoservice	0%	Zytoservice	0%
		GAP	28%
	100%		100%
Hospitals (47,7% of sales)			
Hospital Direct Sales	100%	Hospital Direct Sales	100%
Hospital Parallel Imports	0%		
		GAP	0%
	100%		100%

Table 4 - Distribution of a Cytostatic Preparation on Datasources, Subterritory Level

There are several possible explanations for this: pharmacies in various subterritories could be ordering collectively to profit from scale pricing or a hospital in another subterritory could be preparing cytostatics for pharmacies within the subterritory (§11.3 regulation, see chapter 2.1.2). Other explanations are possible, and probably several of them come together. Additionally, the gap has to have a negative somewhere else in Germany to balance out nationally, so other subterritories are affected as well.

This analysis shows that the knowledge of sell-in data may give insights into how the market works. The individual detailer may gain a lot from knowing how delivery streams work or even guessing which pharmacy orders where. For research on geographic diffusion it is important not to mix between the two data sources, as they are not necessarily consistent.

To conclude the analysis of data availability, its effects at the different levels of diffusion modelling will be examined in the following:

1) Macro-Level

   Forecasting sales rate on a national level is not limited or restricted by any measure of the privacy relations. Forecasting methods like the Bass-Model can be applied.

2) Meso-Level

   On a geographic basis, spatial autocorrelation methods can be used. As data will be available on a 244 cell grid for finished medicinal products in Germany, measures of market share or adoption uptake can be drawn and processed through Geographic Intelligence Systems (GIS).

3) Micro-level

The micro-level is both the most valuable and most restricted level for data analysis. Data about an individual´s physician, practice characteristics, demographics and location are always available. If a physician is using a certain company's products, then a variety of data will be collected: Visits by detailers, congresses or events by the company, a likelihood for adoption and patient potential are assessed. The latter two are however subject to the assessment of the individual detailer, which can be marked by several biases.

Behavioural data (e.g. prescriptions) are either available on business account basis (hospital affiliation) or on 87 or 244 geographic cells. This makes tracking of network associations for individuals almost impossible, as only reported data can be used but not verified through behavioural data.

4. Empirical Model

The previous chapter has shown how diffusion modelling is limited through data availability in Germany. The aim of this chapter is to develop a model helping to link drug sales to variables identified in the literature review. Different data sources will be discussed and the model will be applied for two different drugs with different preconditions. The measurable variables identified will then be empirically tested using multiple regression analysis.

4.1 Multiple Regression Analysis

The basic idea behind regression analysis is to show how an independent variable affects a dependent variable. In the most basic case of simple linear regression, the equation for Y as a dependent variable of X looks as follows:

$$Y = \propto + b_1 * X + \varepsilon$$

α is the constant, b_1 the coefficient of the independent variable and ε the error term of any unobserved variables (Hair et al. op. 2010). Ordinary least squares regression, the mathematical technique used to estimate the coefficient b and the intercept for Y given X, mathematically fits a straight line through the observations of X which minimizes the difference between sample observations and estimated values. The equation can be read as the change in Y explained through a one-unit change in X, the magnitude of which is given by the coefficient *b.*

Multiple linear regression expands the number of variables used to explain the variance in Y. Rather than having just one variable X, multiple regression may (theoretically) contain any number of variables. While the technique of minimizing distance to a fitted line remains the same, the space is no longer two-dimensional but has i+1 dimensions (Hair et al. op. 2010).

$$Y = \propto + b_1 * X_1 + b_2 * X_2 + \ldots + b_i * X_i + \varepsilon$$

The multiple linear regression method allows explaining different influences on Y through the accommodation of several explanatory variables. The coefficients of the regression line have to be interpreted as the change in Y created by a unit change in X_i, keeping all other factors constant.

Multiple regression can also show non-linear relationships between Y and the dependent variables. The coefficients may for instance reflect a logarithmic or exponential relationship. Depending on the hypothesis tested and the relationship presumed, an appropriate transformation has to be used (Hair et al. op. 2010).

Multivariate regression analysis has several underlying assumptions. These have to be met in order to achieve reliable test results. The most important assumptions for regression are homoscedasticity, absence of autocorrelation and normality of error distribution.

Homoscedasticity means equal variance of the residuals across the range of predicted variables. For every observation of the independent variables, there is an error of estimation between the fitted and the actual model. This distance is called residual. The variance of these error terms needs to stay constant. If the variance of the residuals changes with their size, one speaks of heteroscedasticity. A typical change would be an increasing variance of residuals with larger estimates of the regression, resulting in a cone-shaped residual plot (Hair et al. op. 2010). That would imply that the regression is becoming less precise for larger estimated values and statistical significance might be overestimated. Besides the plots of the residuals, a mathematical test for heteroscedasticity in linear regression is the Breusch-Pagan test. It tests for the null hypothesis of homoscedasticity (Bartholomew et al. 2008).

Another important condition that has to be met for the residuals is that they have to follow a normal distribution. Not unlike the homoscedasticity assumption, large deviation from the normality distribution indicates a bad model fit. A skewed distribution of error terms might for instance imply a systematic overestimation of the actuals. Normality distribution should be checked for by using P-P or Q-Q Plots and statistical tests like the Kolmogorov-Smirnoff Test and Mann-Whitney-U Test (Bartholomew et al. 2008).

A typical source of error in a time-series regression is autocorrelation. That term refers to a situation in which the prediction of Y is largely dependent on the earlier time-period predictions. For instance for a stock market, a very good estimate of today's stock price is yesterday's stock price. Autocorrelation is not expected in this model, since it is one period only, but may be tested for using the Durbin-Watson test statistic (Hair et al. op. 2010).

The last issue that is common for models of multiple regression is collinearity between the explanatory variables. This phenomenon occurs when the independent variables have strong correlation among them. In that case, the inference of the explanatory power of a single

variable may be inaccurate. If variable A and B exert the same influence on Y, one of them is redundant but the model will not predict this. The Pearson correlation matrix offers a good overview of the collinearity (Hair et al. op. 2010).

4.2 General Model Specifications

In the literature review the most important variables were identified and then matched to Rogers' stages of innovation. These variables should be taken into consideration when trying to model innovation diffusion or make predictions about sales. The idea of the model is to describe prescription volume as a function of several variables favouring adoption of a new drug. While data can partially be collected on an individual level, the limitations of other data only allow looking at a more aggregate level. The variables available hence differ from drug to drug. The model should be applicable to various levels of data availability in order reflect this characteristic of the market. Thus, the model used will be a multivariate regression of available variables, which are related to the major influences in the innovation process. Firstly, the model will be applied to the drug Tecentriq, a cancer immunotherapy most prominently used in lung cancer treatment.

The independent variables introduced are mostly measured on physician level. The dependent variable of sales, cannot be measured using this scale. Hence the explanatory variables have to be aggregated onto the level of the response variable, which - in the case of Tecentriq - is the hospital level. In the following, the variables used on the different stages are introduced and discussed. In a second step, applicability of the model to a different drug in a different therapy class will subsequently be shown.

The second drug is Esbriet, a more established product with a newly introduced tablet formula. Esbriet is used to treat patients with idiopathic lung fibrosis, a chronic and incurable disease. For Esbriet, the analysis for Tecentriq will be repeated in more or less the same fashion; differences between the two drugs will be pointed out at the respective moments of the analysis.

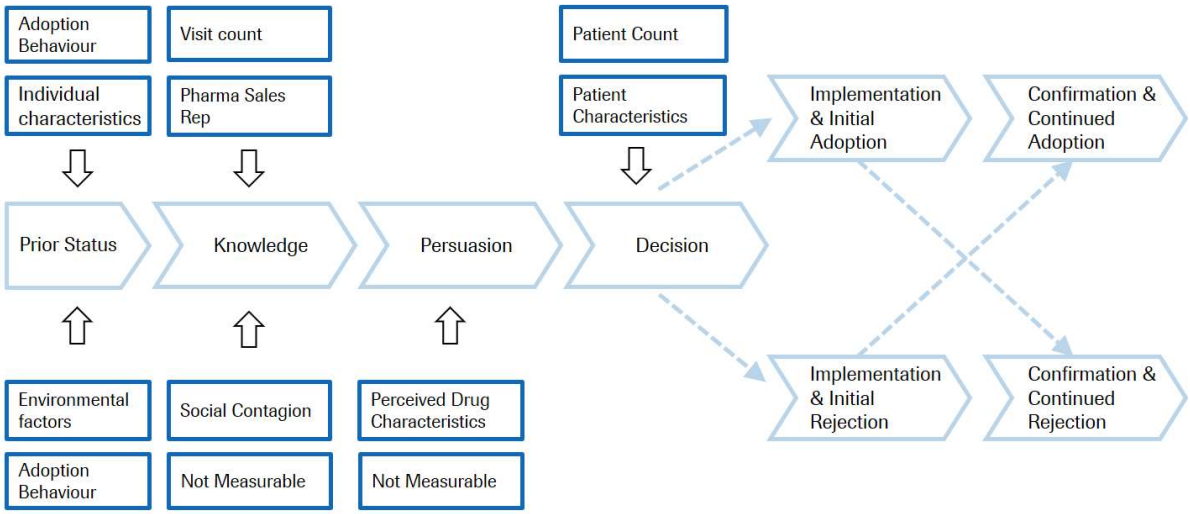

Figure 11 - Variables Tecentriq Regression

Stage 1: Prior Status (Environmental Factors and Individual Characteristics)

The prior status variables are split between environmental factors and individual characteristics. Regarding the environmental factors, affiliation and norms of the social systems are of relevance. On the individual level, socio-demographic criteria have been investigated as well as variables to measure scientific orientation and general prescribing characteristics. These variables taken together make up what has been called the "intrinsic propriety to adopt" (Liu & Gupta 2012). In a new market for a company, proxy data such as prescription levels of a related competitor product or reported survey data have to be taken into consideration. In an established market or a familiar indication, a pharmaceutical company has valuable information from their sales representatives that can be used to assess the likelihood of adoption. Norms of the social system are represented in that estimation, but hardly measurable quantitatively. Thus, the variable used is the sales representatives' assessment of the adoption behaviour of the physician, which is labelled *ScoreAdopt.*

The second variable on this level is an account level variable. A neutral estimate of patient potential on hospital level is the historic count of lung cancer diagnosis. The Statistisches Bundesamt (federal statistical office) collects historic diagnosis counts in form of quality reports. It is important to note that the selected cases of lung cancer diagnosis are not equivalent to the number of patients – a patient with lung cancer may be treated in several hospitals or different departments within a hospital and would then appear in the statistics multiple times. Unfortunately, a second limitation of this data source is the relatively vague

diagnosis. Lung cancer is differentiated in different stages. At the time of the analysis, Tecentriq is approved for use in patients in 2nd line therapy, which roughly translates to ~57% of lung cancer patients[5]. Hence the number of cases may not be an accurate measure, but the relation between actual patients and cases could be the same. The contribution of this variable is that it is independent of the sales representative's estimate of patient potential in stage 4; in the model the case numbers are labelled *Cases.*

Stage 2: Knowledge Level (Pharma Sales Representative and Social Contagion)

The knowledge level variables investigated are the influence of the sales representative, moderated by visit count and homophily with the target physician. A further variable is the influence through social contagion, be it through networks or key opinion leaders. At this point in the innovation process, the sales representatives will start visiting the doctors. While the quality of visits is hard to assess, the number of visits is easily measurable. The same applies to homophily between physician and detailer, a moderating variable that cannot be properly investigated without surveys. Homophily or lack thereof might lead to the effect that the same sales representative has a larger influence on one doctor than on the other.

Social Contagion has been measured in two distinctively different ways: either via surveys from which a network has been mapped, or via geographic proximity. Both approaches require the knowledge of when a physician within the network adopts. This information is hard to come by without the doctor reporting herself, so it is difficult to use it on a large scale regularly. In order to support important launches, surveys may be used. So far, no survey has reached enough coverage to use the variable as a predictor yet. An experiment with the most extensive survey so far is depicted in Appendix 19. It shows that even with extensive coverage it is difficult to quantify the effects of social contagion when aggregated onto larger units.

To conclude: Quality of visits, be it through sympathy between doctor and sales representative or length cannot be assessed. Social contagion is not reported for Tecentriq. The only variable left to measure detailing impact is the number of detailing visits, *VisitCount.*

[5] 2nd line therapy is usually applied to patients in stages III band IV of the lung cancer histology. For an overview of the stages, refer to Appendix 3.

Stage 3: Persuasion Level (Perceived Drug Characteristics)

The effectiveness and side-effect profile of any innovation obviously have massive influence on the diffusion speed. Nevertheless, this variable would require survey data to be quantified. The individual assessment of the study results (e.g. "prolongs median overall survival by 2 months") underlies several prior criteria from the previous stages. To model the regional diffusion of a single product in practice it may be best to just include the national forecasts from (internal) analysts as a threshold for the cumulative sales values. If individual data is not available, a possible solution is to draw the effect on the single doctor from a distribution (Liu & Gupta 2008). While this may be mathematically satisfying to do, the explanatory power is limited. Hence, the variable is excluded from this model.

Stage 4: Decision Level (Patient Characteristics)

Patient characteristics are very important for the individual adoption decision. As has been pointed out in chapter 2.1.3, patient characteristics also play a role in the prior status variables. The existence of a "patient stock" is a requirement for the doctor to gain experience with respect to indication and thus a prerequisite for adoption. On the other hand, the decision to use a drug is always made in connection with the patient.

The closest variable available to suitable patients in the indication stems from the sales representative's estimate of patient potential. The patient potential does not directly translate into Tecentriq patients. Rather, the estimate counts patients that are applicable for 2nd line lung cancer treatment, where Tecentriq is one of several therapy options. Hence, the patient count has to be interpreted as a potential – not an actual - count. The variable applied for drug one is number of patients applicable for 2nd line lung cancer treatment, labelled *PatCount.*

Optional: Additional Variables

The model is general enough to allow for additional variables to be added. The additional variables may either serve to specify the category variables introduced here or to add new information for a specific product that has not been used in this general framework. For an unfamiliar indication where physician level information is not yet available, it may make sense to look at information on a higher level.

For visit count and adoption, the relationship between explanatory and response variable is assumed to be linear. The relationship between detailing visits and sales has been proven to

be diminishing, so a log model could be appropriate. However, in the time window of this particular model, no single physician has been visited more than three times, so diminishing results seem unlikely and the linear model is used.

The final regression equation in the case of a linear relationship between dependent and independent variables in a geographic unit *a* looks as follows:

$$Sales_a = \alpha + b_1 * ScoreAdopt_a + b_2 * VisitCount_a + b_3 * PatCount_a + b_4 * Cases_a \ldots + b_i * X_{ia}$$

4.3 Data Introduction

4.3.1 Drug One – Tecentriq

Sales

The drug inquired is a cytostatic preparation. Thus, private prescriptions have to be aggregated on subterritory level. This implies there cannot be more than 87 geographic units for which prescription data is available. Delivery data would be available on 244 units, but as has been pointed out in chapter 3.5, the prescription data cannot be reliably interchanged for delivery data.

In order to be as precise as possible, the geographic unit for the model should be as small as possible. Tecentriq is an innovative cancer immunotherapy with a high percentage of usage in hospitals – close to 50% in the first quarter of 2018. Hence, the sample chosen for the model are relevant hospitals who order directly at the manufacturer. The sample contains 88 unique hospitals with 468 relevant doctors. A hospital is considered relevant if it either has ordered the drug since its launch at least once or has important physicians[6]. The sales data is available from October to April, spanning seven months. The data considered in the model are year to date sales 04/2018, so from January to the end of April. This specification is in place to ensure that early adopters with seven months of sales data do not have over proportional influence over those with only four months of data.

[6] Important physicians are the P1 physicians from the targeting matrix. Refer to Appendix 2 for more information.

PatCount, ScoreAdopt, Cases

The data on physicians collected by Roche for most of their products, including Tecentriq, looks as follows: name, location, business account (affiliation), patient count in the specific indication, adoption behaviour towards the new product, and monthly visits by detailer. Adoption behaviour and patient count are modelled in predefined ranges. The ranges for Tecentriq can be inferred from Table 5. Sales representatives typically visit a targeted physician at least once a quarter and in the present sample, 369 out of 468 had been visited in 2018 (78%). The physicians that were not visited are mostly of low or no priority. Only ten of the 99 not visited ones were considered as high priority. As almost all relevant physicians have been visited within the estimation window, it is reasonable to assume that the reported data on patient counts and adoption are fairly recent, especially as the sales force is encouraged to report development in that area.

Patient Count Ranges	Adoption Ranges
no information	
<5	Has not yet used the product
5-19	Has tried Tecentriq (1-10% Usage)
20-50	Uses it sporadically (11-25% Usage)
>50	It is the most common therapy option (>25%)

Table 5 - Ranges Tecentriq

Physicians are grouped in priority classes depending on a 4x4 Matrix (See Appendix 2) of adoption and patient count. The matrix is used to classify the physicians from high to low priority. Sales representatives for Tecentriq are requested to report the patient shares and product usage levels of their targeted physicians as closely as possible. This information should then be very closely related to the actual sales in a hospital. To compute a score for adoption, the ranges need to be transformed to numbers. Table 5 shows the patient count ranges according to the respective adoption range which has been translated as follows:
1-10% usage as 0.05, 11-25% as 0.18 and >25% as 0.25. Thus, the *ScoreAdopt* of a single physician with medium adoption is 0.18.

The patient count is treated in similar fashion. The ranges are translated as:
<5 as 0 patients, 5-19 patients as 12, 20-50 patients as 35 and more than 50 as 50. The *PatCount* of a physician with 17 patients will be counted as 12 in the model.

Data of the number of diagnosis for lung cancer are available for 84 of the 88 hospitals in the sample. Selection was made according to the ICD-10[7] classification for lung cancer. The data is available on department level for 2016 and aggregated onto hospital level, then labelled *Cases.*

VisitCount

In order to assess the detailing impact, the monthly product calls of a sales representative with a doctor are tracked. A product call may be either a personal visit in the practice/hospital or a meeting at a conference. This allows for either a percentage-wise score of frequency (e.g. 4/5 planned contacts equals 80%) or just a raw measure of contact count. The latter is used here to see the difference in absolute terms. Patient count is derived from the reported data of the sales representatives. The patients are specified as lung cancer patients scheduled for second line treatment. The ranges are translated into the model as follows: <5 = 0, 5-19 = 12, 20-50 = 35, >50 = 50.

Moreover, Tecentriq has a second indication for bladder cancer. The ranges here go from zero to larger than five, where in lung cancer five patients are rounded off to zero. Hence the influence of the bladder cancer indication in the potential ranking is negligible. Because the ranges are not compatible, the second indication is not taken into account. While this is a shortcoming of the model, the effects will be marginal for the assessment of the potential.
The descriptive statistics of the variables used in the model can be seen in the table below.

	Sales	*Adoption*	*Patients*	*Visits*	*Number of Cases*
Mean	76.497	0,329	155	15	545
Standard Error	8.184	0,042	13	2	67
Median	58.275	0,165	119	11	397
Mode	-	-	-	11	424
Standard Deviation	76.768	0,396	123	15	621
Sample Variance	5.893.371.990	0,157	15.051	212	385.799
Kurtosis	7,332	2,838	2,692	12,090	15,539
Skewness	2,233	1,717	1,402	2,734	3,497
Range	463.223	1,770	673	99	4.148
Minimum	-	-	-	-	2
Maximum	463.223	1,770	673	99	4.150
Sum	6.731.725	28,920	13.610	1.313	46.892
Count	88	88	88	88	84

Table 6 - Descriptive Statistics Tecentriq Regression

[7] The International Classification of Diseases (ICD) is the WHO's standard system of classifying diagnostic codes. ICD-10 refers to the current standard.

4.3.2 Drug Two - Esbriet

For the second drug, the data is partially different. The drug comes in form of a pill or capsule, which means it will not be ordered through the outpatient or stationary customer number of a hospital. In chapter 3.2 the subject was first touched upon: Hospitals have strict regulations where and how they can order drugs from manufacturers, as they get different prices for different patients. Patients in outpatient treatment may only get a single dose of product, anything else needs to be prescribed via a public pharmacy. The only reason warranting a direct hospital delivery in the case of Esbriet are ward patients.

Sales

Esbriet is a ready-to-use medicinal product. Patients are usually treated in private practices or in outpatient treatment – ward treatment is a rare exception. Since the condition rarely calls for ward treatment, hospital direct orders are virtually non-existent. Instead Pharmascope data has to be used to show the public pharmacy prescriptions. As it is common for ready-to-use medicinal products, data regulation allows sales tracking on the *Großsegmente* level. Sales data is available from 244 geographic units, of which 220 report prescriptions.

PatCount, ScoreAdopt, Cases

For the estimates by the sales representatives, the matrix differed somewhat from the one used for Tecentriq. A detailed version can be found in Appendix 4. Adoption behaviour is measured on physician level, on a scale from 1 - high to 3 - low. As Esbriet has one major competitor with very similar market share and product characteristics, adoption high means to treat 50% of the patients with the product, adoption medium 33% and adoption low 10%. The variable *ScoreAdopt* is the sum of the adoption scores of the individual doctors in one Großsegment.

Patient potential is measured in four ranges, from 0 to > 40. The question posed here is how many patients with IPF are treated every year? The possible levels are 40, 30, 20 or 10. Again, potential is simply aggregated from all individual physicians onto Großsegment level and the variable labelled *PatCount.*

The case report data for Esbriet is irrelevant, as the sales data evaluated mostly stems from private practices. Just looking at the case reports of hospitals would leave out the majority of patients, which is why *Cases* is not considered in the Esbriet model.

VisitCount

The detailing visits are available on physician level as before. For Tecentriq, the detailing visits were aggregated onto the smallest possible unit, hospitals. In the case of Esbriet the procedure is the same, only the level is different. Summing up visits on Großsegmente level, the absolute count of visits in a certain Großsegment are labelled *VisitCount.*

Table 7 - Descriptive Statistics of Esbriet Variablesshows the descriptive statistics of the variables used for the Esbriet model.

	Sales	*Adoption*	*Patients*	*Visits*
Mean	59.777,82	4,16	13,36	14,52
Standard Error	5.053,07	0,20	0,71	0,90
Median	39.450,88	3,50	11,00	11,00
Mode	-	1,00	4,00	-
Standard Deviation	74.607,65	2,89	10,55	13,28
Sample Variance	5.566.300.829,37	8,34	111,40	176,25
Kurtosis	15,65	1,84	4,52	4,51
Skewness	3,35	1,25	1,83	1,68
Range	530.121,20	14,47	61,00	81,00
Minimum	-	0,10	1,00	-
Maximum	530.121,20	14,57	62,00	81,00
Sum	13.031.565,06	910,93	2.925,00	3.179,00
Count	219	219	219	219

Table 7 - Descriptive Statistics of Esbriet Variables

4.4 Analysis

4.4.1 Drug One - Tecentriq

All analyses were run by using the software SPSS in version 25 on the NHH remote student desktop.

In the first run of the model four variables were used. The residual plots show that there were several outliers and the distribution of the residuals differed significantly from a normal distribution (Appendix 10). A list of the residuals differing more than the respective standard deviation from the usual error term was presented to the respective sales force analysts. A closer examination of the hospitals revealed that several of them had to be removed from the model due to participation in buying cooperatives with affiliate hospitals. Either sales were a multiple of what was expected because these hospitals where buying drugs for other hospitals, or the other way round, a hospital that was treating patients did not order any drugs. Thus,

respective clinics were removed from the model changing the number of hospitals used in the model from 84 to 68.

The model was then run again with a smaller sample of 68 clinics. The overall significance increased to an Adjusted R – Square of 0.439 (Appendix 6). Out of the four variables, two were significant and two were insignificant (Table 8). The patient potential and case numbers (Fallzahlen) had insignificant results (p = 0.448 and 0.386, respectively) and confidence intervals stretching to negative values. The two variables of visits and adoption were both significant at the 95% confidence level with p-values of 0.01 and 0.019.

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients			95% Confidence Intervall	
		B	Std. Error	Beta	t	Sig.	Lower bound	Upper Bound
	(Constant)	32299.899	6583.798		4.906	.000	19143.230	45456.569
	Visits	1493.559	564.595	.446	2.645	.010	365.305	2621.812
	Adoption	38103.738	15807.259	.283	2.411	.019	6515.453	69692.024
	Patients	50.781	66.508	.132	.764	.448	-82.124	183.686
	Fallzahlen	-8.140	9.317	-.104	-.874	.386	-26.760	10.479

Table 8 - Coefficents of 4 Variable Regression

Subsequently, the two variables concerned with patient potential were taken out of the model as both did not contribute to the explanatory power of the model. The first variable that was eliminated was *Cases* (Fallzahlen); besides the insignificance, the ambiguous confidence intervals violate the theoretical assumptions of the model. *PatCount* (Patients) was then removed for the same reasons. The results of the two-variable regression can be seen in the table below.

Model Summary[b]

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate	Durbin-Watson
1	.679[a]	.461	.444	34422.04375505072000	2.458

Table 9 - Model Summary of Two Variable Regression

As Table 9 indicates, the two variable model offers an explanation of variance of more than 40% with adjusted R-Square of .444. As could be expected in a single-time period regression, autocorrelation is not an issue with a Durbin-Watson score of 2.458.

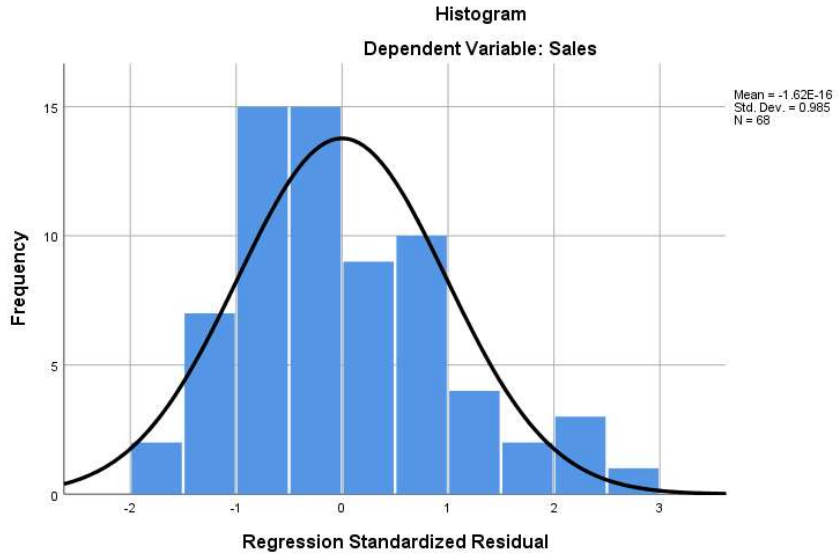

Figure 12 - Histogram of the Residuals for Two Variable Regression

The histogram of the residuals for the two variable model shows that the residuals are not normally distributed (see Figure 12). Both, the Kolmogorov-Smirnoff and the Shapiro-Wilkes test are significant enough to accept the null hypothesis that a non-normal distribution is present ($p = 0.022$ and $p = 0.015$, respectively).

The distribution of the residuals is positively skewed (0.787). This implies that positive residuals are more prone to the extreme, so if actual sales were higher than what has been predicted, the difference was large. Negative residuals, when actual sales were lower than the model prediction, were more common than would be expected in a normal distribution. The value of these residuals was smaller on average. Kurtosis is positive, with a score of 0.424 further confirming the non-normal distribution. The descriptive statistics of the residuals can be found in Appendix 13.

The final test conducted on the residuals of the two-variable regression was the Breusch-Pagan test for homoscedasticity. To include the function of the Breusch-Pagan test in SPSS, it is possible to regress the squared residuals of the original test against the independent variables of the original model. The R-Square of this regression times the number of observations gives the test value of the Breusch-Pagan Test (Baltes-Götz 2018). The test value is chi-square distributed with df = 1. The results can be seen in Appendix 13.

The Breusch-Pagan test result was calculated as $R^2 * ndf = 0.023 * 68 = 1.564$.
At df = 1, the result is not significant (see Appendix 17). This means that the null-hypothesis of homoscedasticity is not rejected. Figure 13 - Standardized Residuals Plot for 2-Variable Model shows the residual scatterplot which visually confirms the impression of homoscedasticity. Nonetheless, some residual outliers are still present.

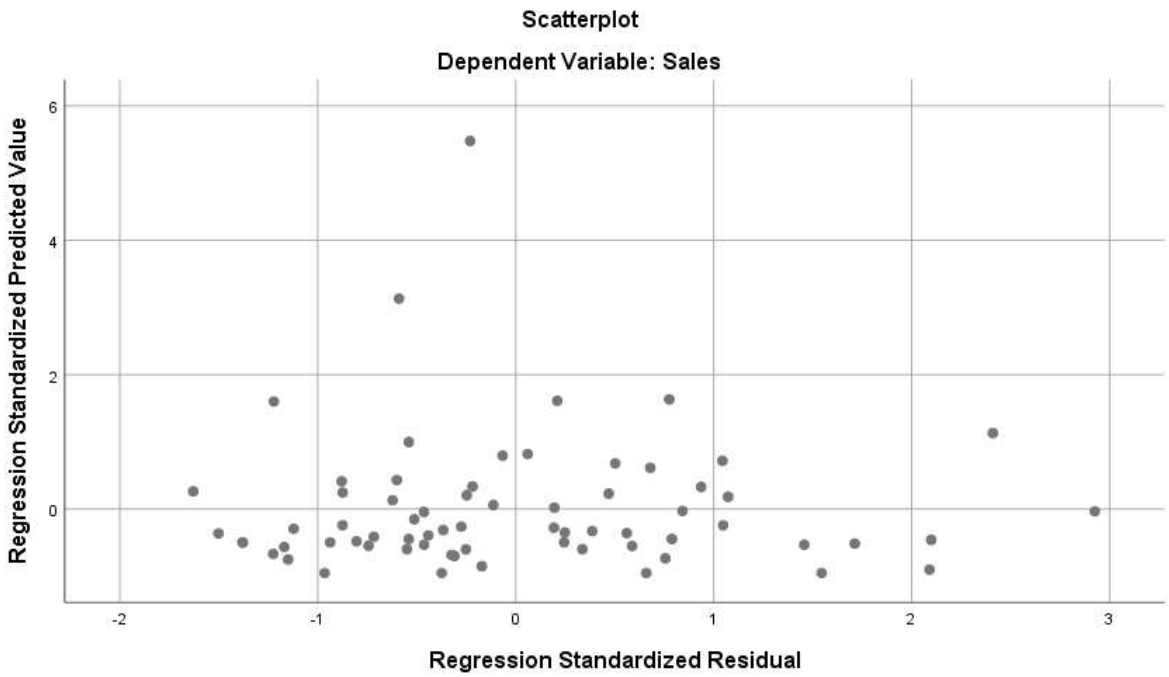

Figure 13 - Standardized Residuals Plot for 2-Variable Model

4.4.2 Drug Two - Esbriet

The second drug was analysed using three variables. *Cases* was dropped, but the rest of the Tecentriq regression variables were present. So *PatCount, ScoreAdopt* and *Visits* were available.

The residual plot shows that the error terms were not normally distributed when using ordinary least squares regression (Figure 15). To achieve normality of the residuals, the dependent variables was transformed. *Sales* were transformed using a cube root transformation, where after the residuals were closer to a normal distribution (Figure 15)

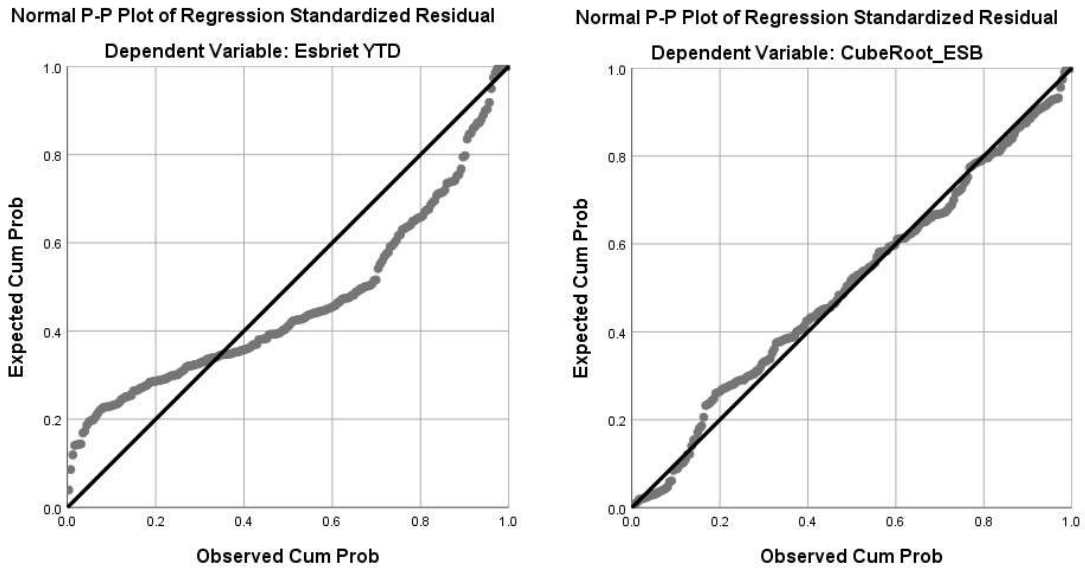

Figure 15 - P-P Plots for Esbriet

Still, the distribution of residuals is non-normal. Both the Kolmogorov-Smirnov test (p = 0.043) and the Shapiro-Wilk test (p = 0.000) have significant results and it has to be concluded that the distribution is not normal.

The model summary shows that the correlation coefficient is at .433 and the Adjusted R-Square lies at 0.176 (Table *10*). Of the three coefficients, *ScoreAdopt* is the only one with significant results at p = 0.018. The relationship is also strictly positive since lower and upper bound of the confidence intervals are positive (Appendix 9)

The other two coefficients are neither significant (p = .991 and .998, respectively) nor have a clear relationship with *Sales*, since confidence intervals range from -.513 to + .508 for *PatCount* and -.207 and +.208 for *Visits* (Appendix 9).

Model Summary[b]

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate	Durbin-Watson
1	.433[a]	.188	.176	14.08176	1.586

Table 10 - Regression Summary Esbriet

In order to check for heteroscedasticity, the residual plots were first inspected visually. The graph (Figure *16* - Esbriet Residuals Scatterplot) clearly indicates that several outliers distort the image of a homogeneous "middle" section. The lower bottom corner shows a range of residuals where Großsegmente did not have sales at all. The Breusch-Pagan test was conducted in the same fashion as for Esbriet. The test statistic at n = 218 was calculated as $0.03 * 218 = 6.54$. At df = 1, this would reject the null-hypothesis at the 10% confidence level (Appendix 17). Since the distribution shows some outliers, the presence of heteroscedasticity cannot be rejected.

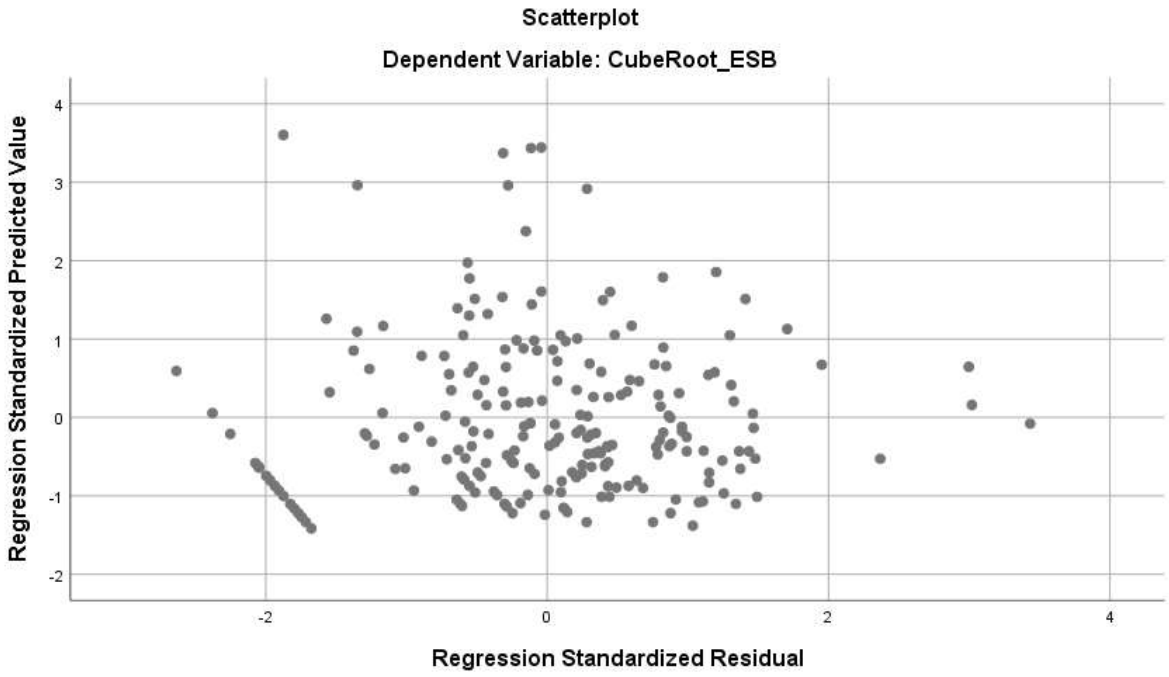

Figure 16 - Esbriet Residuals Scatterplot

4.5 Discussion

4.5.1 General Discussion

Tecentriq

The quantitative model aimed to explain differences in sales based on important variables for drug adoption for the cancer immunotherapy Tecentriq. The variables identified through theory were not always available. Still, the attempt to model sales based on the available data delivered satisfying results for Tecentriq. A very simple model with only the two variables of adoption and visits in 2nd line lung cancer can already explain a good portion of the variance (more than 40%). Due to the non-normal distribution of residuals this has to be seen with caution however. The skewness of the distribution of residuals is a warning sign that predictions of sales levels are prone to error. Positive values seem to have single errors, which are more extreme while the general tendency is to have a slight underestimation of sales. Nevertheless, statistical testing for heteroscedasticity showed that homoscedasticity is present, which increases the credibility of R-Square.

A possible explanation for the skewness lies in the nature of the scales. The extreme values are cut off at 25% usage of the drug. Thereby, single high performing doctors could be underrated and produce higher error terms than necessary. To effectively forecast sales in a hospital setting, more significant variables have to be added to the model.

Another possible explanation leading to underestimated sales are specialist doctors or centres who draw in a lot of patients. Since the model has no reliable variable indicating the quantity of patients treated, this factor could skew the distribution. The assessment of patient scores through the sales force was evidently inaccurate.

Furthermore, the quality of the case numbers of lung cancer as an explanatory variable for immunotherapy was very limited. The correlation between case numbers and innovative therapy is weak and ambiguous. While patients are a prerequisite for the use of the new drug, the case numbers are too unspecific to explain adoption variance.

The detailing visits however did clearly correlate with the adoption. A possible improvement of the model would be to build in a time-lag in order to account for the time that has to pass for a physician to alter his behaviour. Hence it might be beneficial to use the visits from one to two months earlier.

Necessarily a general shortcoming of a two variable model might be omitted variable bias (Clarke 2005). There are several variables which are missing in the model that might lead to overestimation of the coefficient effects. This effect cannot be controlled for with the data available, so again, caution is advised when interpreting the results of the present regression.

Esbriet

The regression model for Esbriet focussing on the same variables as Tecentriq does not repeat the explanatory power. Rather, it shows that just one of the three variables has a clear and unambiguous correlation with the independent variable. While a transformation of the data fixes the error distribution, the model itself remains a lot less significant. Especially the patient potential seems to have nothing to do with the actual distribution of sales. Visits too were completely irrelevant for explaining sales.

A possible explanation lies in the market concentration. Sales representatives report that many patients are treated in specialist centres rather than at a local, private pneumologist. Some outliers showed sales that where several standard deviations above the regression prediction, thereby confirming this intuition. With a single centre drawing patients in, the potential of different physicians may be of little value.

If better variable accuracy on the individual level cannot be achieved, then a possible solution for analysis is to switch the level of analysis up to a higher level. On the meso-level of geographic cells, reported data on market shares could be used to show a development and read trends on a higher level. In Appendix 18 a possible analysis on meso-level has been depicted.

The analysis on a geographic level allows to see changing patterns of diffusion over geographic cells. While this does not equate knowledge on a micro-level, it may still give valuable insights into how the market works. Currently these analyses are not yet backed up by statistical test values, since the software used for medical markets is a limiting factor. Hence it needs to be visually scanned for patterns, which is informative, but of little empirical value.

4.5.2 Issues with reported data through sales force

The regression heavily relies on two reported variables. However, reported data is never fully objective. While in this case the sales-force is instructed to report the adoption behaviour as

accurately as possible, they nevertheless have incentives to over- or underestimate certain physicians' behaviour.

An incentive to exaggerate would be to gain praise or gratification from their superiors, for "developing" a customer. On the other hand, it may be beneficial to first underrate someone's likeliness to adopt and then have higher sales data than initially anticipated. Through this mechanism, the target setting and target achievement might be turned in favour for the sales representative. Generally, one might suspect that initially adoption is underestimated and then later exaggerated to increase the impression of successful work. Any lack of sales might then be attributed to a lack of patients.

Moreover, patient count underlies similar shortcomings. Besides the incentive to underestimate patient count to counteract over exaggerated adoption, underestimating the actual patient count initially might help to reduce one's targets and thereby make it easier to achieve them. A deliberate overestimation of patient count through the sales representative seems unlikely, as it would increase expectations for sales unnecessarily. Hence, patient count is expected to be underestimated for single doctors. This behaviour applies to all sales representatives, although the magnitude of the mechanism may differ. Thereby, patient data is not completely comparable between sales representatives.

A different angle from which bias in the data may arise is a wrong report of behaviour through the doctor himself. The physician might be in a situation where the sales representative is heavily encouraging him to try the new therapy. In order to avoid conflict, it may be easiest to overstate the adoption behaviour and satisfy his conversation partner. In turn, the sales representative might then just falsely report the physician´s status of adoption and only later realize the mistake when sales do not match expectations. Besides this deliberate false reporting of adoption, it is often possible that a physician does not know the actual patient count himself. For a specialist reading case files of hundreds of patients, it may be difficult to estimate exactly how many patients with a certain disease he/she is treating.

One mechanism leading to increased patient count are doublets. Patient count questions are often posed: "How many patients with condition XY do you treat in time span Z?". If you ask several physicians within the same hospital, it seems possible that one patient is counted several times. One example: the head of the department might suggest he is involved in treating 300 patients every year – which the department might surely do. But then her

subordinates might report any number below that which will then add up to those 300 and patients are suddenly doubled.

To conclude: There are three possible mechanisms that might lead to underestimated patient counts, one that overstates them and two mechanisms leading to overestimated adoption even if the adoption-potential matrix is filled in as realistically as possible.

A different reason to have inaccurate reporting of adoption behaviour and patient count or patient potential may be that the matrix serves a different purpose. In an attempt to achieve a certain distribution of priority one, two and three customers, the ranges given for adoption may be ignored. If there are too many priority two doctors, the sales force might resolve to either over- or underestimate certain key characteristics to move them to the desired status, thereby gaining the customer distribution that was asked for.

This phenomenon of categorization is present in the case of Esbriet. Rather than reporting actual behaviour of the physicians and an accurate assessment of their situation, the sales force is distributing the physicians to some category in order to adhere to a certain distribution of physicians rather than realistically judging their behaviour. Appendix 1 shows the distribution of targeted physicians for the two different drugs. Tecentriq shows a realistic distribution for a newly launched drug, with very few high adopters and a pyramid shape of patient potential. On the other hand, for Esbriet the distribution between adoption statuses looks very evenly. There are just as many high-adopters as there are low adopters, which is unrealistic. A special case is for instance the 200 High-Adopter and D-Potential. Theoretically, these are doctors who are very open to progressive therapy but have zero patients. In practice, these will be physicians who for some reason the sales representative wants to exclude from his list of targeted physicians and sets their potential to zero.

One last source of error that shall be discussed are ill-defined ranges for the measured variables. Although unlikely to be completely off, the ranges might skew the distribution in a certain direction by being set too low or too high. It could be that some specialist or renowned doctor have significantly more patients than usual and that their role is understated in the ranges. Sales outliers as in the case of Esbriet show that single doctors may have five to six times as many patients as the highest range suggests. Reversely, the ranges could be set in a fashion that leads to constant overestimation of the actual behaviour.

4.5.3 Other Limitations

The model for Tecentriq ended up incorporating two variables only, the model for Esbriet just one. Both of the variables are reported data on the individual level, aggregated onto a meso-level of a certain unit. As the previous chapter pointed out, neither of the two variables comes without bias and may only work if sales management instructs the sales representatives to be as precise as possible.

The biggest shortfall is certainly that other variables measurable on small scale could not improve the model and explain more variance in sales. With a maximum R-Square of .42 in the best case, the quality of the model is too low to predict sales for future product launches.

The assessment of the sales representatives is a prerequisite for the model to work. That implies that any pre-launch assessments are extremely limited or need a survey-based approach with analysists assessing every single physician who might be relevant for the targeting.

The only variable investigated in the regression analysis that is independent of the sales force are the case numbers of the quality reports. However, this data source is too imprecise to improve on the sales forces' assessment of the patient count and furthermore only available for hospitals. Its scope in pre-launch activity is limited to drugs with a focus on hospital treatment and it becomes somewhat irrelevant after launch, as a more precise estimate can be obtained from the sales representatives.

Beside the prior status variables, the only other variable that could be incorporated was detailing visits. Especially network information might be extremely valuable and could be used for a more precise and targeted approach of the doctors through the sales force.

The residuals of both analysed variables have shown that the relationship between explanatory and explained variables has not necessarily been linear. Nonetheless, if the assessment of the sales force was really precise, the relationship can be expected to be linear. There could either be underlying variables influencing this relationship or the two dimensions are just reported with a larger error than expected.

5. Conclusion

5.1 Implications for Further Research

The research on medical innovation has largely been focussing on some single factors or groups of variables that influence a doctor's decision making. Papers concerned with diffusion modelling in the medical sector do not make the connection to the existing large body of diffusion literature conceptually. While Rogers is being referenced frequently, respective papers are not incorporating their work into the existing frameworks.

The introduction of the Roger's framework to organize the vast body of literature on medical drug diffusion and variables influencing adoption behaviour proved effective. Categorizing the factors that influence adoption behaviour helps in two ways: One, it is easier to get a clear picture of which variables have been investigated to what extent and to decide on relevant variables to investigate. Two, it helps to understand how certain variables play a role in the adoption behaviour and strictly differentiates between characteristics that may change and those that cannot. For anyone interest in investigate (or causing) behavioural change, this distinction becomes important. It is recommendable that further research should build on a general framework when investigating factors that influence adoption behaviour, rather than having a proliferating number of papers standing alone.

The quantitative model has shown that behavioural data is extremely hard to come by in Germany. Neutral sources either have no data on adoption favouring variables at all or are not allowed to hand them out to pharmaceutical companies. Hence, a strong focus for future research should be on obtaining, evaluating and improving reported data. One key aspect would be to improve data on regionalized patient potential.

Another promising approach is to conduct research outside the boundaries of a pharmaceutical company. This would minimize bias through the sponsoring company as well as a much improved data availability. Especially precise micro-level modelling is almost impossible in Germany from the viewpoint of a pharma company, due to the regulatory constraints. One possible angle might be from within a data science company like IQVIA, which possess finer reported data.

A future source of data comes from a company called Veeva who are currently building a key opinion leader platform for oncologists[8]. Data on publications, attended congresses, participation in studies etc. is collected and graphically presented in a social-media look. Approaches like this may make network data available for researchers and pharmaceutical companies in a broad fashion and hence open new angles for diffusion research. If platforms like this evolve from tracking key opinion leaders only down to the mass of doctors, network information may become a pillar of targeting approaches.

Veeva and their "social network" of KOLs automatically remind one of the Big Data approaches in Silicon Valley. Big Data naturally influences the pharmaceutical industry as well, just recently Roche bid 2.4 billion dollars for the final shares of Foundation One, a data science player in personalised healthcare. Nevertheless, attempts to utilize Big Data to forecast disease spreads like Google tried have proved futile so far. While it cannot be ruled out, an immediate impact of Big Data in diffusion modelling is not in sight.

Besides the micro-level modelling, data availability may force research to switch the level of observation. In view of this development, the use of geographic information systems is still in its early stages in the German medical market. The thesis shortly touched upon the topic with the introduction of diffusion maps for Esbriet, but currently the software used still has great limitations and geostatistical tools are not being applied yet. Translating the commonly used segment structure from IQVIA into files that can be processed with more advanced/ open source software might be a start.

5.2 Managerial Implications

The biggest issue the model has revealed is that as of now, there is no reliable assessment of the potential of a drug. While there might be estimates on national level, an accurate geographic distribution is nowhere to be found. An accurate potential of a clinic or a geographic cell would enable the company to precisely distribute sales targets, detect over- or underperforming regions and precisely navigate through the launch of a new product. Managers should encourage precise reporting of patient potential, focussing for instance on clinical decision making rather than treating patients. "How many patients do you treat" may

[8]The product is called Veeva Oncology Link

lead to patients being counted several times, whereas “For how many treatment decisions are you responsible” might deliver more accurate results.

The regression model has shown that some of the influential variables for doctors’ adoption decisions can already be tracked. If the sales force attempts to realistically report adoption behaviour, the model shows that the variable has significant influence on the sales of a product. However, this is not always the case today and requires some change effort from sales management.

The distribution of targeted doctors for Esbriet shows that the targeting matrix is used to create a desired image of a customer structure. While it may be satisfying to have equal parts of high, medium and low potential customers, such a distribution distorts reality and is ultimately wishful thinking. Rather than squeezing the customer landscape into a certain form, the segmentation criteria should be developed from objectively reported data.

One aspect in every diffusion model are marketing efforts. As far as those go, detailing visits are already tracked on a monthly basis. There is however no qualitative component regularly monitored; a simple two minute small-talk might appear as detailing visit the same way an extensive consultation meeting would. First steps towards measuring the quality of visits have been undertaken already. CRM systems already offer the possibility to track pre-defined messages targeted at customers. If the database is properly maintained, one could for instance select customers already convinced of a certain attribute. In regard to a long-term customer relationship, measures like this should be encouraged.

The lack of precise data for diffusion modelling shows that pharmaceutical companies need to play an active role in data creation even for market research purposes. When the launch of a new product is prepared they should already take into account which factors might be favourable for adoption and try to measure them, either via a survey or their sales force in an early stage. The Ocrevus survey (Appendix 19) is testimony of this: Network data was mapped, but on a scale that does not allow to properly use it. While better than nothing, this approach does not match the excellence standards applied to the research & development in the life science industry.

Besides all its shortcomings, the model does have a practical application even today. Regression analysis quickly points out observations that do not fit the model. While precise predictions for sales seem unlikely, a “target corridor” is quickly defined and outliers handily

spotted. Especially when the sales force has no long-term experience with a product this method may show if sales are in a normal range or lean towards the extreme.

5.3 Conclusion & Final Discussion

The general aim of the thesis was to create more transparency over the diffusion process of new drugs in the German pharmaceutical market. The introduction of a larger framework to categorize variables which are important for the diffusion process already contributes to a better understanding of how and why doctors decide to adopt a new drug.

The quantitative modelling of diffusion on an individual level is extremely limited due to a lack of precise data on a personal level if conducted from inside the industry. Nevertheless, under some conditions it is still possible to explain more than 40% of the variance in sales with simple two variable models. Since it cannot be expected that regulation will open up for market research, pharmaceutical companies need to find ways to create data themselves.

The obvious choice to collect data on doctors are the pharmaceutical sales representatives who visit the relevant doctors several times every year. Their reporting underlies several limitations and biases which need to be addressed if accurate data is to be gained. The sales force managers need to be aware of their employee's agenda in assessing doctors and need to find ways to disentangle performance measurement and reported data. Otherwise the incentives to cheat on the reported data are too great.

If the incentives for misreporting are to be changed, performance measurement needs to stop rewarding the "aim low and jump high" strategy for target setting. No longer focussing solely on sales for incentives would mean abandoning the thought that detailers are just commercial agents and entrusting them with more responsibility.

One major development in the pharmaceutical industry today is the trend towards personalized healthcare. The simple formula "Disease X is best treated with product Y" no longer holds. In oncology, diagnostics becomes increasingly important - genomic profiling of patient and tumor will become the standard. Combination therapies of different molecules and targeted immunotherapies are the vision of the industry. In this context, it seems absurd to have a commercial sales representative just selling one product.

In reality, the detailer will have to grow into the role of a consulting agent for the physician. After all, the detailer knows best about the studies, mechanism-of-effect and what other therapies or combinations thereof are currently approved. In medicinal products, detailers todays are sometimes bystanders during surgery to assist the surgeon with their knowledge. A similar role could be assigned to pharmaceutical detailers in the future.

This development would further increase the physician's dependency on the industry. Even today, it is striking how few of the variables found to be influential for the diffusion of modern drugs come from a neutral institution. Treatment guidelines from neutral sources are overshadowed by the efforts of pharmaceutical companies to educate doctors. Many physicians already seem to rely on pharmaceutical companies not only for drug development and testing, but for treatment guidelines as well. Even the personal networks between doctors are heavily influenced by pharmaceutical detailers, since one's best colleague's opinion might just have been developed in a conversation between him and his detailer.

Pharmaceutical companies evidently are in a hybrid position. They are the change agents interested in modernizing health care and bringing new treatments to patients while at the same time the actors that profit most from such change. They have to respect the individual's right to privacy while at the same they profit from collecting as much data as possible. The solution to this is not easily found – but it will most definitely involve the contact person between company and doctor. Sales representatives will be at the heart of a respectful interaction between pharmaceutical industry and the health care professionals.

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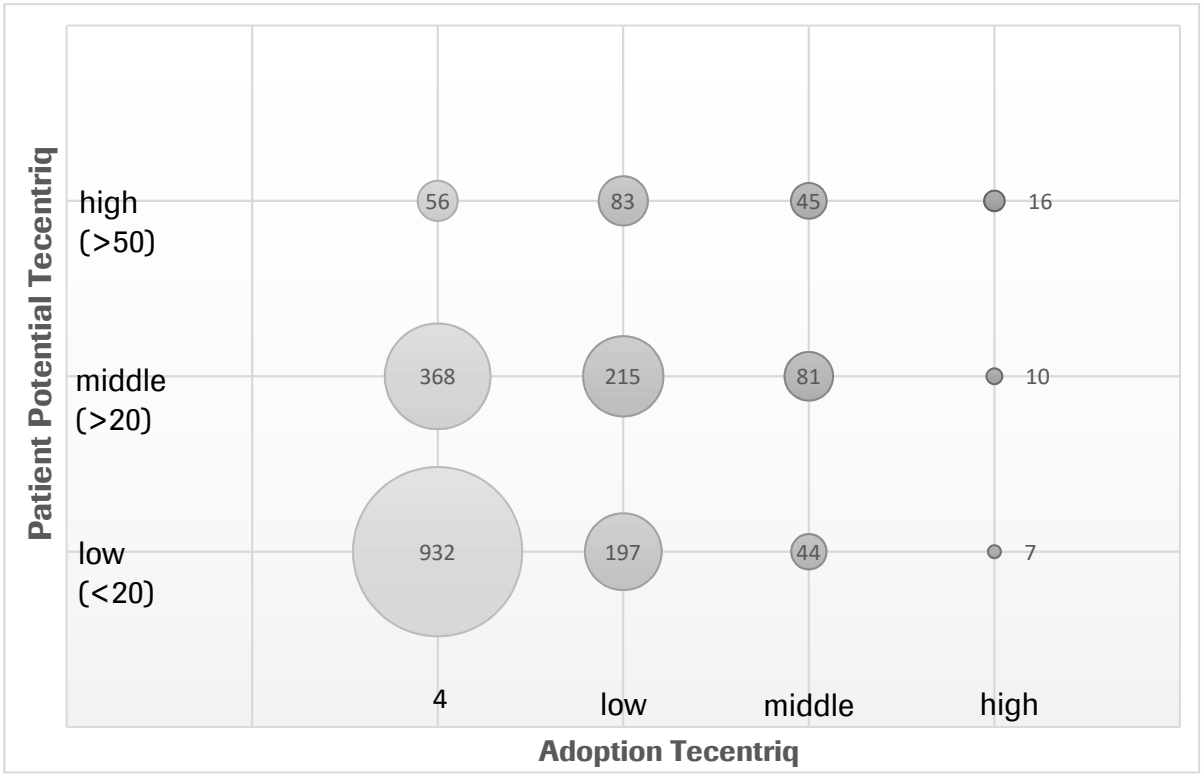
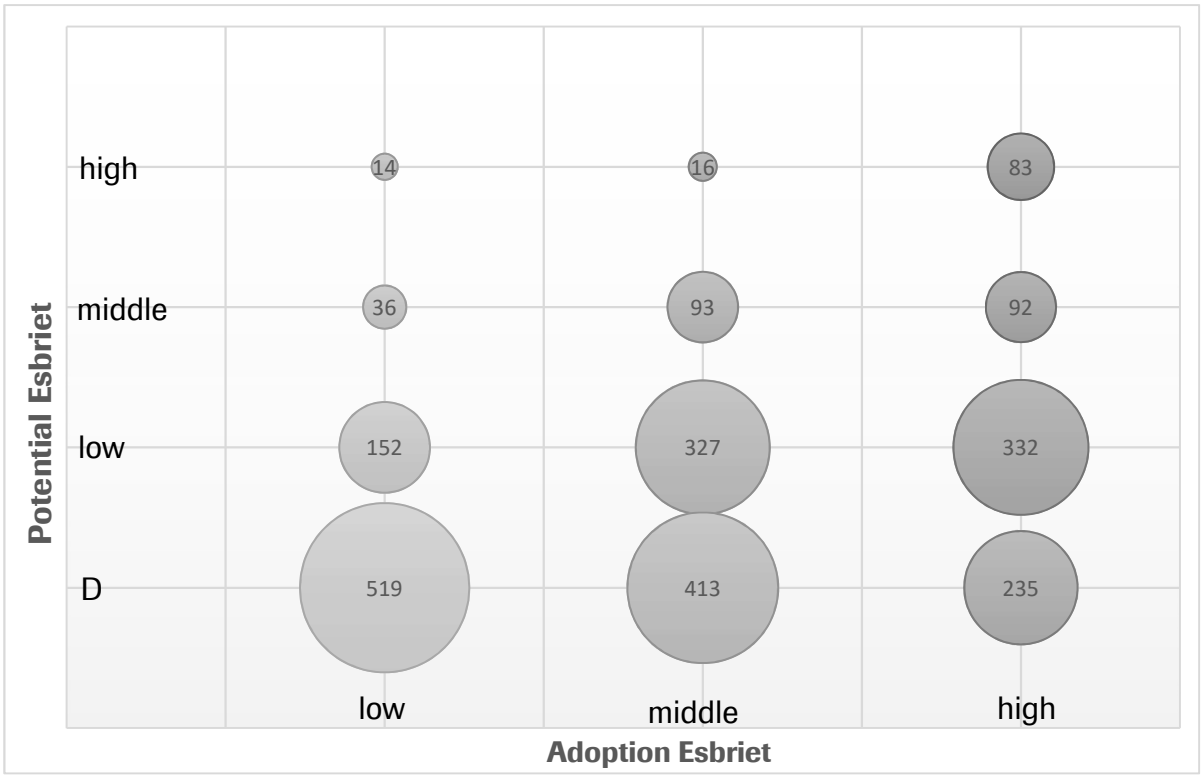
Appendix 1 - Potential Matrices Tecentriq & Esbriet





Appendix 2 - Priority Matrix Tecentriq

Adoption					
	High	D1	C1	B1	A1
	Middle	D2	C2	B2	A2
	Low	D3	C3	B3	A3
	Not Yet	D4	C4	B4	A4
		None	5-19	20-50	>50
	Potential	D	C	B	A

Colour Scheme

P1
P2
P3
PX

Appendix 3 - Lung Cancer Histology Germany 2015

Lung Cancer Histology 2015	
Stage IA	11%
Stage IB	9%
Stage IIA	8%
Stage IIB	6%
Stage IIIA	9%
Stage IIIB	7%
Stage IV	49%
Stage I-IIIA	43%
Stage IIIB-IV	57%
Total Incident Patients	**100%**

Appendix 4 - Priority Matrix Esbriet

How important is the doctor for the prescription decision?

Patient count every year			Usage:	50%	33%	10%
				1 - high	2 - middle	3 - low
40	> 40		Potential A	A1	A2	A3
30	30 - 40		Potential B	B1	B2	B3
20	10 - 29		Potential C	C1	C2	C3
10	1 - 9		Potential D	D1	D2	D3

Appendix 5 - Regression Summary Tecentriq 4 Variables, n=85

Summary

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate	Durbin-Watson
1	.468[a]	.219	.180	58729.30447534160000	1.903

Anova

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	77470222244.313	4	19367555561.078	5.615	.000[b]
	Residual	275930496332.590	80	3449131204.157		
	Total	353400718576.903	84			

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	49183.078	10446.213		4.708	.000
	Adoption	61655.996	22072.197	.368	2.793	.007
	Patients	-117.976	101.976	-.222	-1.157	.251
	Visits	2036.010	813.619	.437	2.502	.014
	Fallzahlen	-9.848	14.481	-.086	-.680	.498

Appendix 6 - Regression Summary Tecentriq 4 Variables, n=68

Summary

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate	Durbin-Watson
1	.687[a]	.472	.439	34594.80670684317000	2.459

ANOVA

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	67428255810.196	4	16857063952.549	14.085	.000[b]
	Residual	75398441018.282	63	1196800651.084		
	Total	142826696828.478	67			

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	32299.899	6583.798		4.906	.000
	Visits	1493.559	564.595	.446	2.645	.010
	Adoption	38103.738	15807.259	.283	2.411	.019
	Patients	50.781	66.508	.132	.764	.448
	Fallzahlen	-8.140	9.317	-.104	-.874	.386

Appendix 7 - Regression Summary Tecentriq 2 Variables, n=68

Summary

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate	Durbin-Watson
1	.679[a]	.461	.444	34422.04375505072000	2.458

ANOVA

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	65809685570.627	2	32904842785.314	27.771	.000[b]
	Residual	77017011257.851	65	1184877096.275		
	Total	142826696828.478	67			

Coefficients

Model		95,0% Confidence Interval for B		Correlations		
		Lower Bound	Upper Bound	Zero-order	Partial	Part
1	(Constant)	21661.550	44768.170			
	Visits 04	896.803	2278.602	.621	.495	.418
	Adoption	13961.838	69639.725	.535	.349	.273

Appendix 8 - Regression Summary Esbriet, n=218

Summary

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate	Durbin-Watson
1	.347[a]	.120	.108	70465.522635854780000	1.737

ANOVA

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	145293845580.568	3	48431281860.189	9.754	.000[b]
	Residual	1062593434393.651	214	4965389880.344		
	Total	1207887279974.218	217			

Coefficients

		Unstandardized Coefficients		Standardized Coefficients		
Model		B	Std. Error	Beta	t	Sig.
1	(Constant)	22419.991	8507.009		2.635	.009
	Adoption	8027.392	4922.198	.310	1.631	.104
	Patientenzahl	182.932	1297.809	.026	.141	.888
	Visits YTD	94.201	526.208	.017	.179	.858

Appendix 9 - Regression Summary Esbriet, Cube Root Transformation, n=218

Summary

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate	Durbin-Watson
1	.433[a]	.188	.176	14.08176	1.586

ANOVA[a]

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	9803.267	3	3267.756	16.479	.000[b]
	Residual	42435.361	214	198.296		
	Total	52238.628	217			

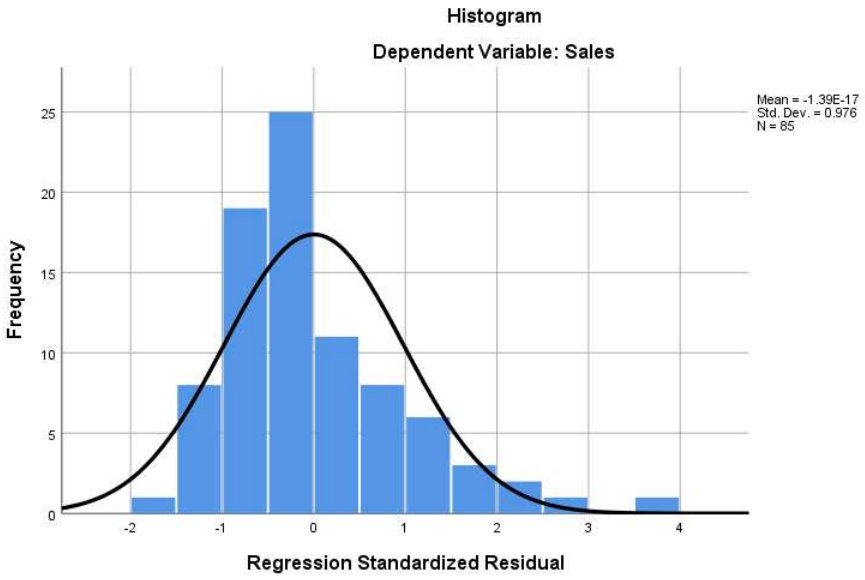
Coefficients[a]

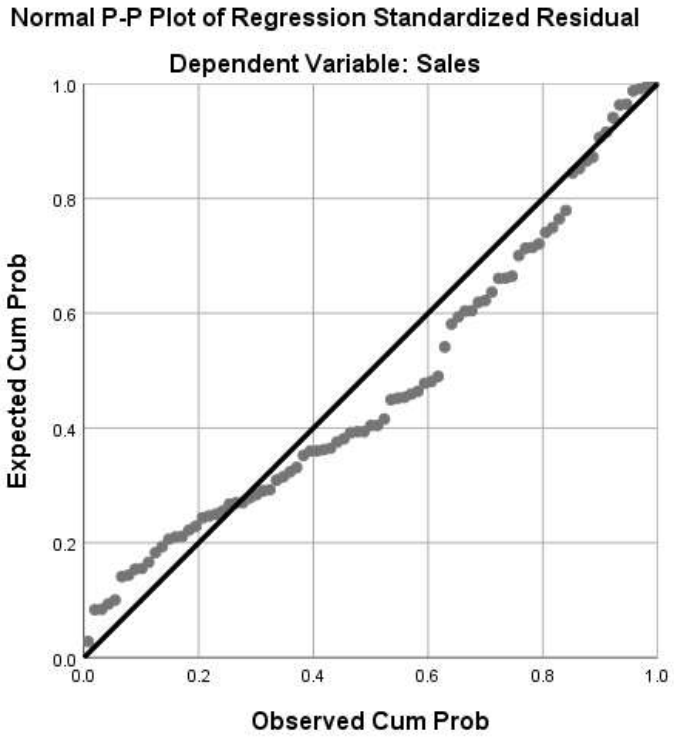
Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	23.379	1.700		13.752	.000
	Adoption	2.342	.984	.435	2.381	.018
	Patientenzahl	-.003	.259	-.002	-.012	.991
	Visits YTD	.000	.105	.000	.002	.998

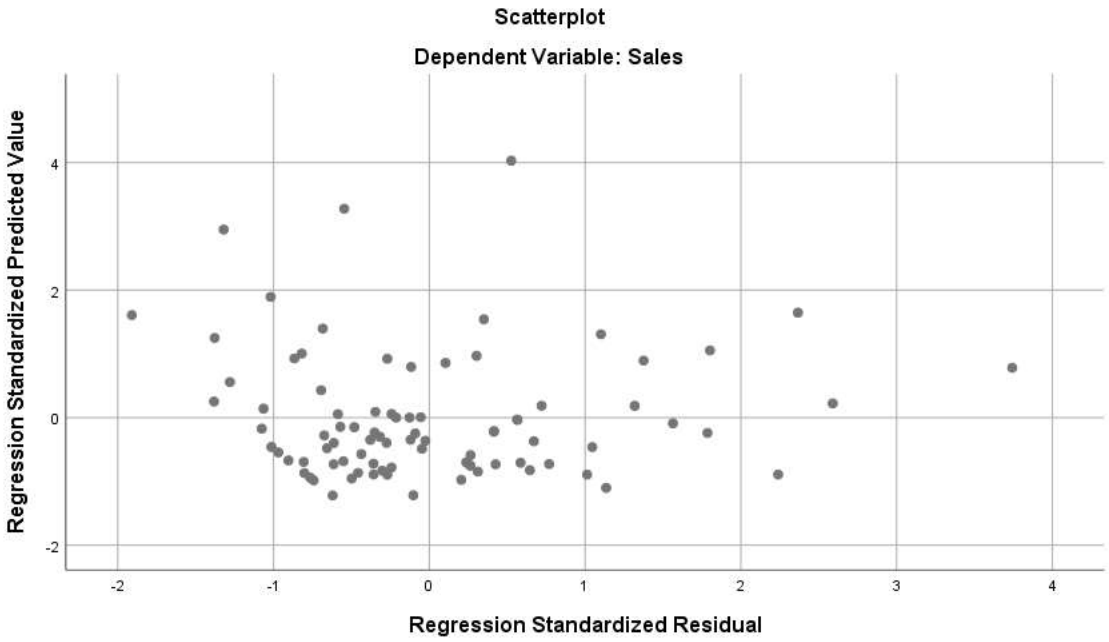
Appendix 10 - Tecentriq 4 Variables, n = 85, Tests of Normality & Plots

Tests of Normality

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
Unstandardized Residual	.134	85	.001	.924	85	.000



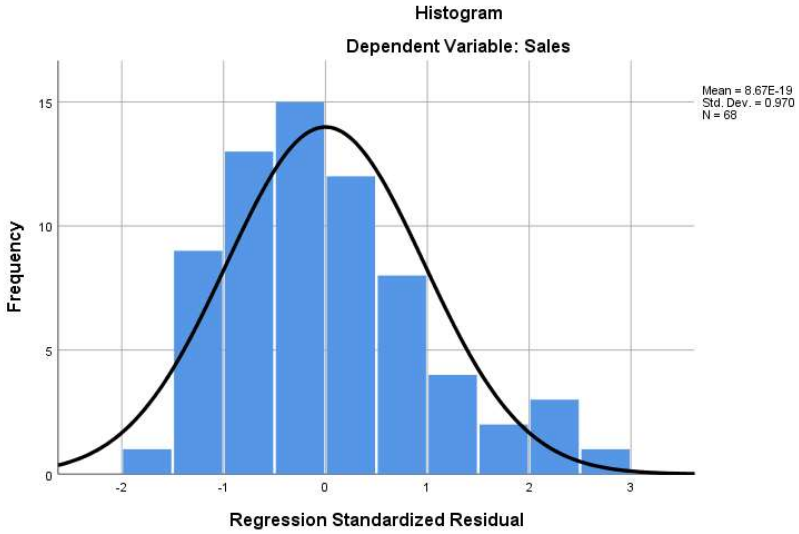


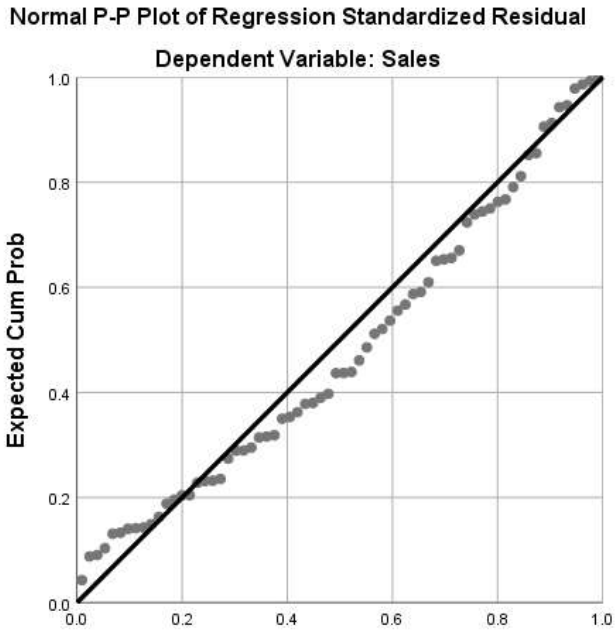

Scatterplot
Dependent Variable: Sales
Regression Standardized Predicted Value
Regression Standardized Residual
4
2
0
-2
-2
-1
0
1
2
3
4

Appendix 11 - Tecentriq 4 Variables, n = 68 Normality Tests & Plots

Tests of Normality

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
Unstandardized Residual	.092	68	.200*	.952	68	.010

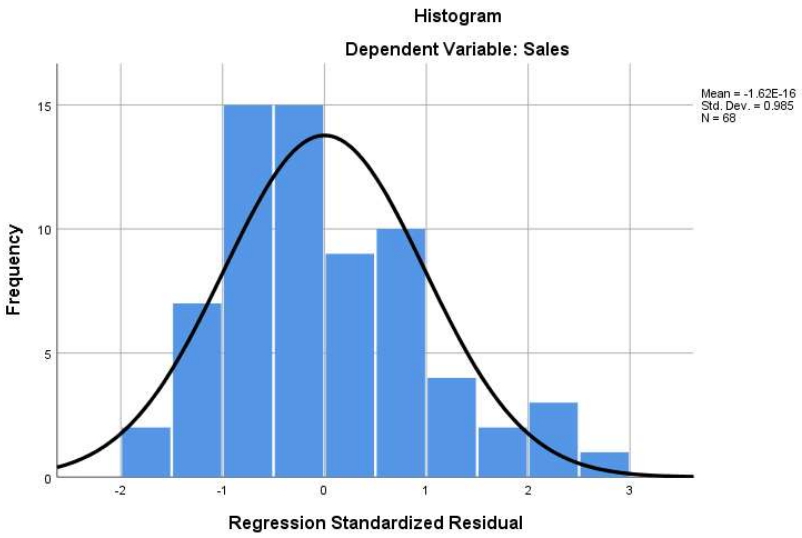


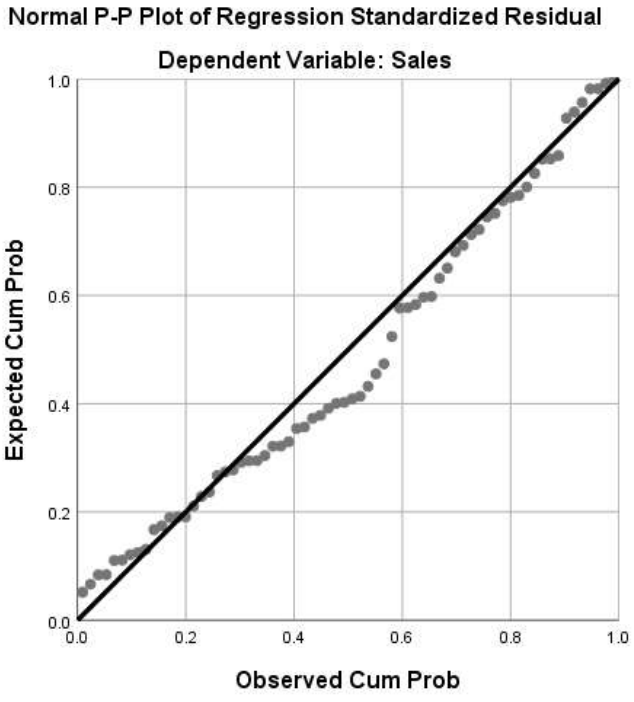


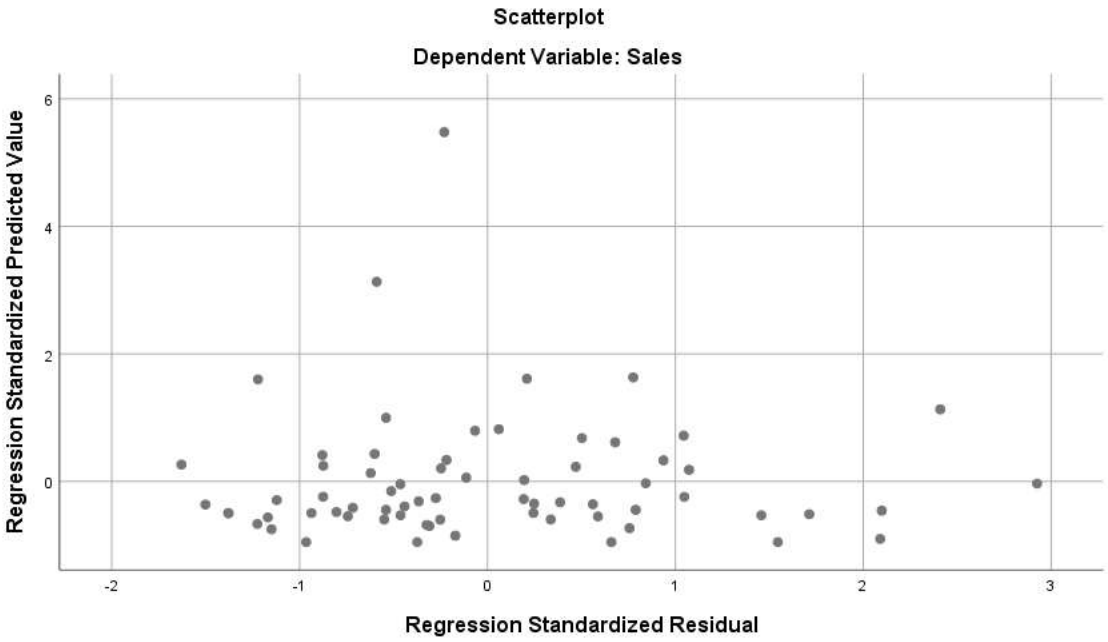
Appendix 12 - Tecentriq 2 Variables, n = 68 Normality Tests & Plots

Tests of Normality

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
Unstandardized Residual	.117	68	.022	.955	68	.015






Scatterplot
Dependent Variable: Sales
Regression Standardized Predicted Value
6
4
2
0
-2
-1
0
1
2
3
Regression Standardized Residual

Appendix 13 - Breusch-Pagan Regression and Residual Descriptives

Model Summary[b]

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate	Durbin-Watson
1	.150[a]	.023	-.007	1739318563.66888	2.282

a. Predictors: (Constant), Adoption, Visits 04

b. Dependent Variable: Squar_RES2

ANOVA[a]

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	4543269806756462600.000	2	2271634903378231300.000	.751	.476[b]
	Residual	1966398892850073400000.000	65	3025229065923189800.000		
	Total	2011831590917638000000.000	67			

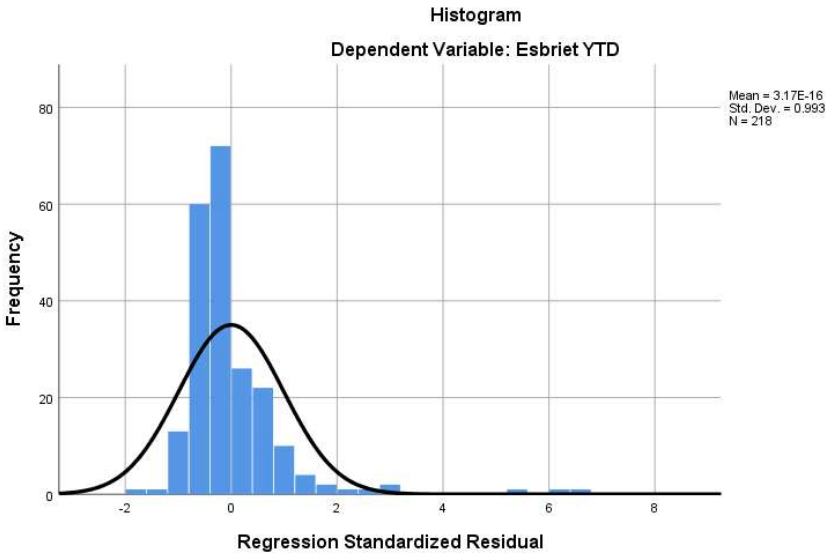
Descriptives

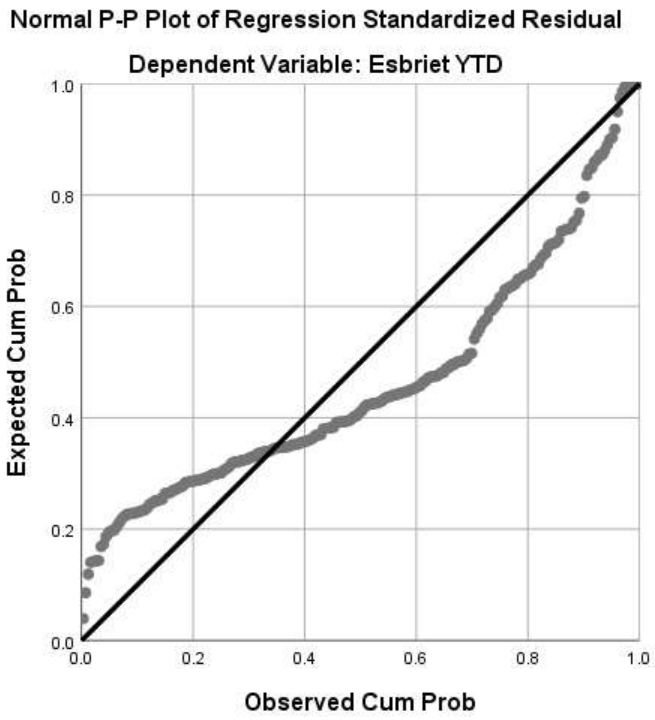
			Statistic
Unstandardized Residual	Mean		.0000000
	95% Confidence Interval for Mean	Lower Bound	-8206.6106139
		Upper Bound	8206.6106139
	5% Trimmed Mean		-1804.2447847
	Median		-8210.9920013
	Variance		1149507630.714
	Std. Deviation		33904.38954935
	Minimum		-56077.89880
	Maximum		100687.42681
	Range		156765.32560
	Interquartile Range		45945.68829
	Skewness		.787
	Kurtosis		.424

Appendix 14 - Esbriet 3 Variables Normality Tests & Plots

Tests of Normality

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
EsbrietYTD	.192	218	.003	.984	218	.000

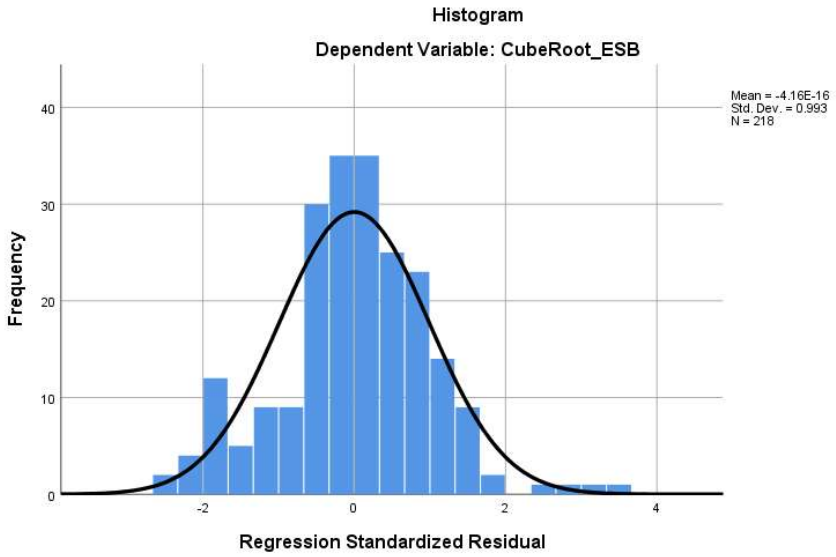


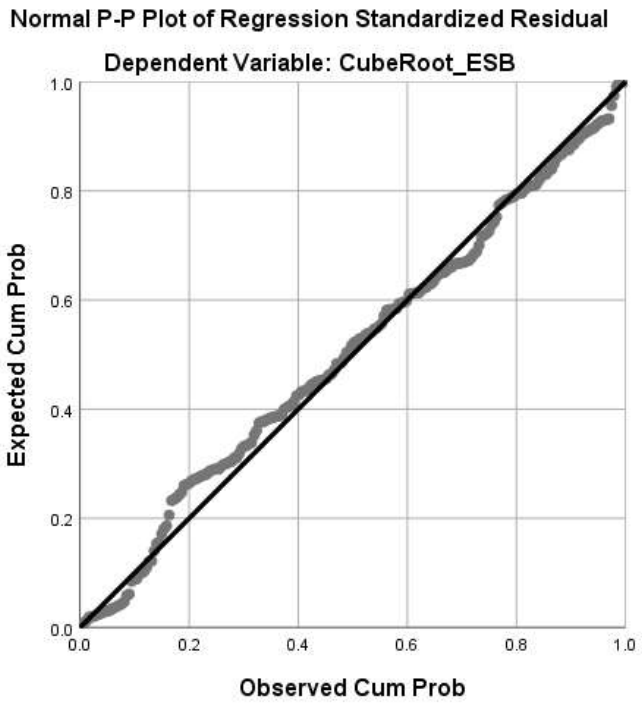


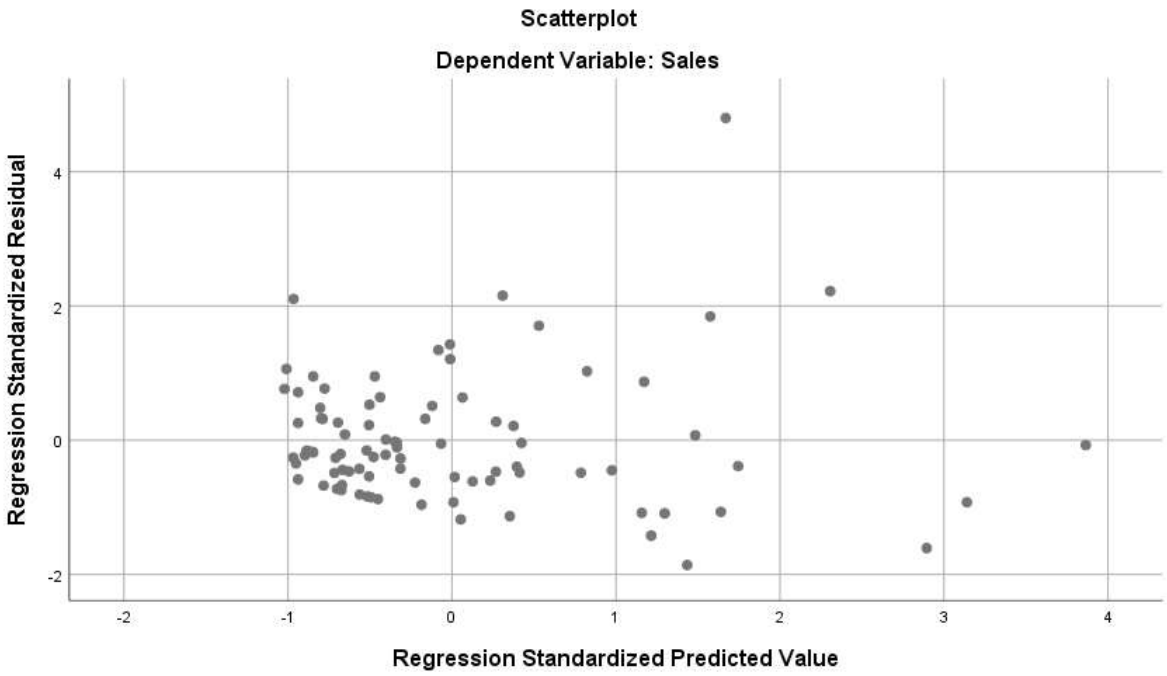
Appendix 15 - Esbriet n=218 Cube-Root Transformation Normality Tests & Plots

Tests of Normality

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
CubeRoot_ESB	.062	218	.043	.972	218	.000






Scatterplot
Dependent Variable: Sales
Regression Standardized Residual
Regression Standardized Predicted Value
4
2
0
-2
-2
-1
0
1
2
3
4

Appendix 16 - Esbriet n = 218, Breusch-Pagan Test

Model Summary[b]

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate	Durbin-Watson
1	.054[a]	.003	-.011	324.05674	1.840

a. Predictors: (Constant), Patientenzahl, Visits YTD, Adoption

b. Dependent Variable: Res_Squared

ANOVA[a]

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	65334.664	3	21778.221	.207	.891[b]
	Residual	22472732.715	214	105012.770		
	Total	22538067.379	217			

a. Dependent Variable: Res_Squared

b. Predictors: (Constant), Patientenzahl, Visits YTD, Adoption

Appendix 17 - Chi-Square Distribution Table

$\gamma \rightarrow$ $r \downarrow$	0.995	0.990	0.975	0.950	0.900	0.750	0.500	0.250	0.100	0.050	0.025	0.010	0.005
1	7.879	6.635	5.024	3.841	2.706	1.323	0.455	0.102	0.016	0.004	0.001	$1.6 \cdot 10^{-4}$	$3.9 \cdot 10^{-5}$
2	10.60	9.210	7.378	5.991	4.605	2.773	1.386	0.575	0.211	0.103	0.051	$2.0 \cdot 10^{-2}$	$1.0 \cdot 10^{-2}$
3	12.84	11.34	9.348	7.815	6.251	4.108	2.366	1.213	0.584	0.352	0.216	0.115	0.0717
4	14.86	13.28	11.14	9.488	7.779	5.385	3.357	1.923	1.064	0.711	0.484	0.297	0.207
5	16.75	15.09	12.83	11.07	9.236	6.626	4.352	2.674	1.610	1.145	0.831	0.554	0.411
6	18.55	16.81	14.45	12.59	10.64	7.841	5.348	3.455	2.204	1.635	1.237	0.872	0.676
7	20.28	18.48	16.01	14.07	12.02	9.037	6.346	4.254	2.833	2.168	1.689	1.239	0.989
8	21.95	20.09	17.53	15.51	13.36	10.22	7.344	5.071	3.490	2.733	2.180	1.646	1.344
9	23.59	21.67	19.02	16.92	14.68	11.39	8.343	5.898	4.168	3.325	2.700	2.087	1.735
10	25.19	23.21	20.48	18.31	15.99	12.55	9.342	6.737	4.865	3.940	3.247	2.558	2.156
11	26.76	24.73	21.92	19.68	17.28	13.70	10.34	7.584	5.577	4.574	3.816	3.053	2.603
12	28.30	26.22	23.34	21.03	18.55	14.85	11.34	8.438	6.304	5.226	4.404	3.571	3.074
13	29.82	27.69	24.74	22.36	19.81	15.98	12.34	9.299	7.041	5.891	5.009	4.107	3.565
14	31.32	29.14	26.12	23.68	21.06	17.12	13.34	10.17	7.790	6.571	5.629	4.660	4.075
15	32.80	30.58	27.49	25.00	22.31	18.25	14.34	11.04	8.546	7.260	6.262	5.229	4.600
16	34.27	32.00	28.85	26.30	23.54	19.37	15.34	11.91	9.312	7.962	6.908	5.812	5.142
17	35.72	33.41	30.19	27.59	24.77	20.49	16.34	12.79	10.08	8.671	7.564	6.408	5.697
18	37.16	34.81	31.53	28.87	25.99	21.60	17.34	13.68	10.86	9.390	8.231	7.015	6.265
19	38.58	36.19	32.85	30.14	27.20	22.72	18.34	14.56	11.65	10.12	8.906	7.633	6.844
20	40.00	37.57	34.17	31.41	28.41	23.83	19.34	15.45	12.44	10.85	9.591	8.260	7.434
21	41.40	38.93	35.48	32.67	29.62	24.94	20.34	16.34	13.24	11.59	10.28	8.897	8.033
22	42.80	40.29	36.78	33.92	30.81	26.04	21.34	17.24	14.04	12.34	10.98	9.542	8.643
23	44.18	41.64	38.08	35.17	32.01	27.14	22.34	18.14	14.85	13.09	11.69	10.20	9.260
24	45.56	42.98	39.36	36.41	33.20	28.24	23.34	19.04	15.66	13.85	12.40	10.86	9.886
25	46.93	44.31	40.65	37.65	34.38	29.34	24.34	19.94	16.47	14.61	13.12	11.52	10.52
26	48.29	45.64	41.92	38.88	35.56	30.43	25.34	20.84	17.29	15.38	13.84	12.20	11.16
27	49.65	46.96	43.20	40.11	36.74	31.53	26.34	21.75	18.11	16.15	14.57	12.88	11.81
28	50.99	48.28	44.46	41.34	37.92	32.62	27.34	22.66	18.94	16.93	15.31	13.56	12.46
29	52.34	49.59	45.72	42.56	39.09	33.71	28.34	23.57	19.77	17.71	16.05	14.26	13.12
30	53.67	50.89	46.98	43.77	40.26	34.80	29.34	24.48	20.60	18.49	16.79	14.95	13.79
40	66.77	63.69	59.34	55.76	51.80	45.62	39.34	33.66	29.05	26.51	24.43	22.16	20.71
50	79.49	76.15	71.42	67.50	63.17	56.33	49.33	42.94	37.69	34.76	32.36	29.71	27.99
60	91.95	88.38	83.30	79.08	74.40	66.98	59.33	52.29	46.46	43.19	40.48	37.48	35.53
70	104.2	100.4	95.02	90.53	85.53	77.58	69.33	61.70	55.33	51.74	48.76	45.44	43.27
80	116.3	112.3	106.6	101.9	96.58	88.13	79.33	71.14	64.28	60.39	57.15	53.54	51.17
90	128.3	124.1	118.1	113.1	107.6	98.65	89.33	80.62	73.29	69.13	65.65	61.75	59.20
100	140.2	135.8	129.6	124.3	118.5	109.1	99.33	90.13	82.36	77.93	74.22	70.06	67.33
200	255.3	249.4	241.1	234.0	226.0	213.1	199.3	186.2	174.8	168.3	162.7	156.4	152.2
300	366.8	359.9	349.9	341.4	331.8	316.1	299.3	283.1	269.1	260.9	253.9	246.0	240.7
400	476.6	468.7	457.3	447.6	436.6	418.7	399.3	380.6	364.2	354.6	346.5	337.2	330.9
600	693.0	683.5	669.8	658.1	644.8	623.0	599.3	576.3	556.1	544.2	534.0	522.4	514.5
1000	1119.	1107.	1090.	1075.	1058.	1030.	999.3	969.5	943.1	927.6	914.3	898.9	888.6

Appendix 18 - Meso Level Analysis Esbriet

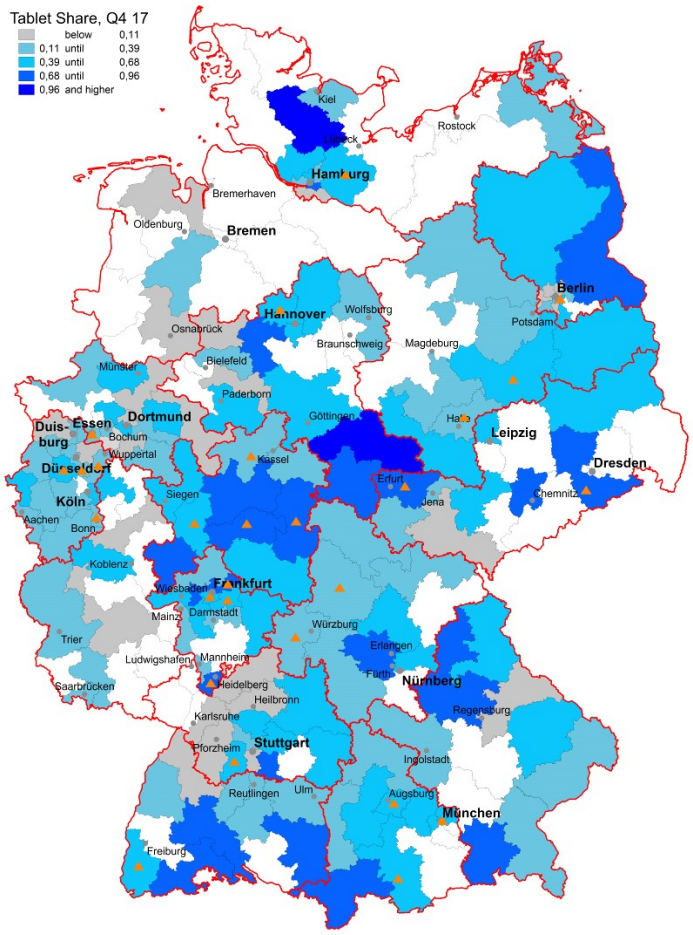
As has been pointed out in the discussion section, variable accuracy forces the level of analysis up onto the meso-level for Esbriet. Last year, the formulation for Esbriet was changed to a tablet form which will eventually replace the former formulation as a capsule. In order to measure the diffusion of this new formulation, a geographic analysis on Großsegmente level was conducted using geographic information software.

The idea is to track the market share of the new tablet vs the old capsule in a Großsegment. Using different colours for different market shares, the map might show if neighbouring areas behave similar, which could be a sign for network effects and clustering around centres. The other way round, it could be that big centres draw in all the patients from the periphery and rural areas are not treating any patients.

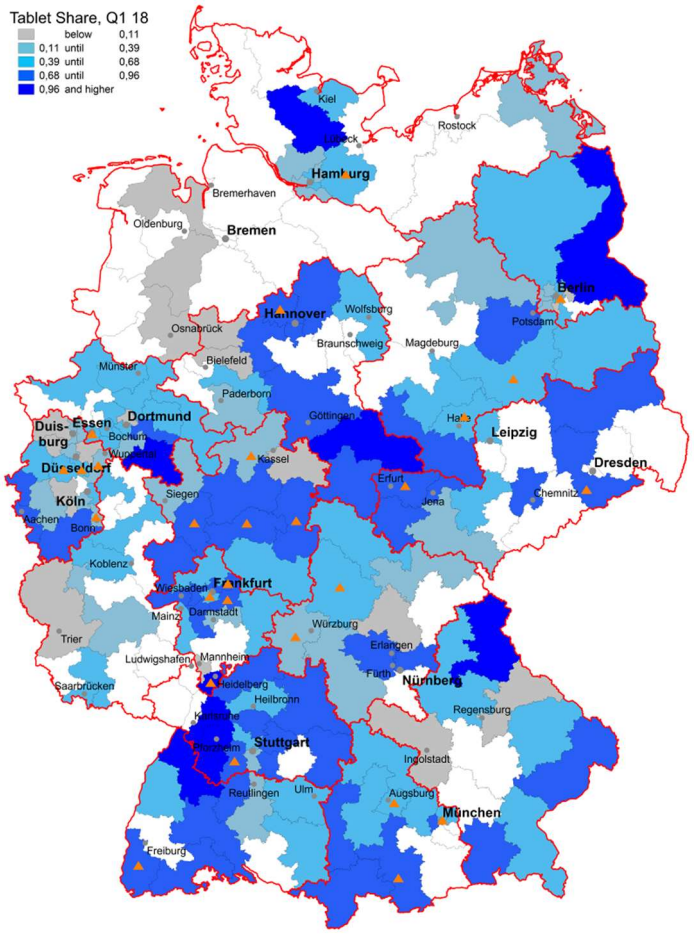
The second important insight that might come is how the areas change over time. Comparing the results of the first quarter of this year to the last quarter of the previous year allows to see which areas are improving or if the development even reverses.

Unfortunately the GIS software most commonly used in the German pharmaceutical environment offers no geographical statistic option like Moran's I. The software EasyMap which has been used to create the maps is not open source and the map data cannot be transferred to an open source software like GeoDa to further investigate the variables.

A brief discussion of the two maps: The darker blue an area, the larger the percentage of Esbriet tablets. White areas indicate no relevant sales. It is clear from a quick glance that centres do not really change their neighbouring areas. More often than not, dark areas are side by side with brighter or even white areas. Comparing the map of Q4 17 to Q1 18 shows that indeed the darker colours are more prominent, so the capsule seems to lose ground. Still, the distribution of dark areas seems more or less random.



1 - Tablet Shares Jan - Mar 18



2 - Tablet Shares Oct - Dec 17

Appendix 19 - Network Pre-Test Ocrevus

The regression model ends up not using any network data. There have been attempts to gather network data, but the information has not been collected extensively enough to be of statistical relevance. A possible approach which might be used in further product launches in similar fashion is to have in-field analysts survey the respective doctors before product launch.

The most extensive research project undertaken so far was called the "MS Survey". In that, 987 neurologists in Germany were surveyed in 2016. Among other things, information about referral networks was gathered. In a pre-test for this thesis, the survey data was used to split geographic regions in Germany into "Opinion Leader" segments and "Nominator" segments. This split was done using question 20 of the survey:

Q20: "Do you rather receive patients for escalation therapy (Tysabri, Lemtrada) or refer patients to a colleague?"
N = 413: I am rather receiving patients for escalation therapy (Opinion Leader)
N = 500: I am rather referring patients for escalation therapy (Nominator)

In the pre-test, an opinion leader segment is simply defined by having at least 2 opinion leaders and no senders in the survey. Any segments containing nominators or having just one identified opinion leader are taken out.
This leaves 59 segments with 154 opinion leaders.

A nominator segment is defined by having at least 2 nominators and no opinion leaders in the survey. Any segments containing opinion leaders or having just one identified nominator are taken out.
This leaves 88 segments with 240 nominators.

The hypothesis is that Opinion Leader Segments will be using more progressive treatment and that effects of social contagion will lead to higher shares of progressive treatemnts in Nominator segments as well.

H_1: Macrosegments with at least two opinion leaders and no followers have higher shares of progressive treatments

H_2: Macrosegments with at least two nominators and no opinion leaders will have higher shares of new treatments than average

The sales data of the choice macrosegments of opinion leaders and nominators were compared to the German average. The share of sales in MS products generated through "New" treatments were compared to the mean of the groups using a two-sample independent t-test.

In order to use this method, sales data were weighted and normalized to account for differences in segment size. The results for the tests with the two samples Opinion Leaders and Nominators were conducted for 2016 and 2017, respectively. The results can be seen in the tables below.

The results show a significant difference in the prescription behaviour of opinion leader segments compared to the average MS prescription in Germany, namely a higher percentage of new, more progressive treatments. The two-tail p-test is significant at the 95% level with p = 0.029.

The tests found no statistical difference in the prescription behaviour of the nominator segments, for which there are several possible explanations:

- The physicians in question treat too few patients to have measurable effects through the dilution of other prescriptions in their segment
- There is an effect, but the segments were not correctly identified (e.g. others in the segment behave differently)
- There is no measurable correlation between opinion leaders and nominators

To conclude: A survey based approach migh be useful to gather network data. To deliver reliable results, coverage needs to be higher than in the case of the MS survey. As four analysts took a year to cover roughly 1000 physicians, this method can only be used in the case of drugs with high concentration in the market. If that happens however, the information might be very valuable.

T-Test Opinion Leader Segments 2016 and 2017

59 "Opinion Leader" Segments	Target physicians	"Opinion Leaders"
Average physician count	6,51	2,61
Standard deviation	4,31	0,74
	2017	2016
Average Share NEW in "Opinion Leader" segments	52,18%	46,25%
Average Share NEW Germany total	47,06%	41,90%

t-Test: Two-Sample Assuming Unequal Variances	2017	
	German avg.	*OL Segments*
Mean	0,470619179	0,521779236
Variance	0,280110577	0,011893971
Observations	822	59
Hypothesized Mean Difference	0	
df	349	
t Stat	-2,196783455	
P(T<=t) one-tail	0,014346466	
t Critical one-tail	1,649231411	
P(T<=t) two-tail	0,028692931	
t Critical two-tail	1,966784557	

t-Test: Two-Sample Assuming Unequal Variances	2016	
	German avg.	*OL Segments*
Mean	0,419048479	0,462537877
Variance	0,226824971	0,014588149
Observations	822	59
Hypothesized Mean Difference	0	
df	239	
t Stat	-1,901295933	
P(T<=t) one-tail	0,029233032	
t Critical one-tail	1,651254165	
P(T<=t) two-tail	0,058466064	
t Critical two-tail	1,969939406	

T-Test Nominator Segments 2016 and 2017

88 "Nominator" Segments	Target physicians	"Nominators"
Average	5,68	2,76
Standard deviation	3,99	1,07
	2017	2016
Average Share NEW in "Nominator" segments	44,69%	39,49%
Average Share NEW Germany total	47,06%	41,90%

t-Test: Two-Sample Assuming Unequal Variances	2017	
	German avg.	*Nominators*
Mean	0,470619179	0,446914401
Variance	0,280110577	0,014087797
Observations	822	87
Hypothesized Mean Difference	0	
df	566	
t Stat	1,057263525	
P(T<=t) one-tail	0,145421183	
t Critical one-tail	1,647550237	
P(T<=t) two-tail	0,290842366	
t Critical two-tail	1,964164101	

t-Test: Two-Sample Assuming Unequal Variances	2016	
	German avg.	*Nominators*
Mean	0,419048479	0,394853556
Variance	0,226824971	0,01463464
Observations	822	87
Hypothesized Mean Difference	0	
df	468	
t Stat	1,148037204	
P(T<=t) one-tail	0,125769844	
t Critical one-tail	1,648116038	
P(T<=t) two-tail	0,251539689	
t Critical two-tail	1,965045852	