Research Document

Assessing the Value, Challenges and Collaboration Networks of Hospital Real World Data for Pharmaceutical Companies

Students

Nine Mennes (MIE)
Vincent Couckuyt (MGM)

Vlerick Promoter

Prof. Dr.
Brecht Cardoen

CEO, LynxCare

Georges De Feu

VLERICK BUSINESS SCHOOL

LYNXCARE

Contents

Authors' Note

Nine Mennes,
Vincent Couckuyt
18th of June 2020

Before diving in, we would like to write our special thanks to several people who made our In-Company Project an enjoyable experience, despite the COVID-19 circumstances we unfortunately faced.

First of all, we want to thank our LynxCare supervisors, Georges De Feu and Kenny Willems, for several reasons. First, thank you for giving us the opportunity to do this wonderful, highly relevant project. We could not have been luckier with the theme, supervisors and all of the opportunities we got to build a network within the pharma and hospital industry. With a highlight planned in two weeks: a presentation of our project results for Pharma.be. When this project first started, we could not have known that especially the pharma sector would be so appealing. Second, our supervisors were at all times present to provide guidance and help. This allowed us to provide an end result with maximum quality, and more importantly, to learn so much from them as we did. Third, we feel honored to have been a part of LynxCare, a startup with an exciting future ahead. We are thrilled to follow up LynxCare's progress in the future and truly wish them the best.

Secondly, we would like to thank Professor Brecht Cardoen for his guidance and intro's to medical specialists in the hospital sector. This gave us very good leads for our study. In addition, we would like to thank him for his methodological clarifications, as well as finding the time to revise our paper. He, too, was always available when we needed help.

Thirdly, we thank Kimberly Pauwels for recruiting us to such an amazing In-Company Project and her guidance throughout the process.

Finally, we thank our friends and family for supporting us throughout the last few weeks.

Executive Summary

Objectives

LynxCare is a start-up that provides data mining solutions for hospital RWD/RWE.

The first aim of the current research is to assess the value, hurdles and collaboration models of Real-World Data (RWD) / Real-World Evidence (RWE) for pharmaceutical companies.

Shortly said, RWD/RWE provide data and evidence on patients collected in a real-world setting rather than under controlled research circumstances. RWD/RWE were unexplored for a long time but have increasingly been finding their way into many use cases for pharmaceutical companies and the healthcare sector at large (see further, cf. Sections 2.2, 4.1, 5.1).

RWD/RWE is something new, and therefore its value for pharmaceutical companies (especially in Belgium), is to date largely unexplored and many research gaps exist (i.e. what collaboration models do pharma companies want?).

The second aim of the paper is to develop a blueprint for a collaboration model between pharmaceutical companies and hospitals for the exchange of RWD/RWE. The third aim is to assess LynxCare's strategic value for the pharmaceutical industry.

Our study aims were translated into the following four research questions:

1. What is the value of RWD/RWE during clinical development, market launch and post-launch according to Belgian pharma professionals?
2. Which collaboration models between pharma and hospitals do currently exist, are desirable for pharma companies, and are manageable for hospitals?
3. What are the preferred types of RWD/RWE sources pharma companies use to support drug pricing and reimbursement decisions?
4. Which role can LynxCare play in the delivery of hospital RWD/RWE to pharma companies?

Methodology

In order to answer to our research questions, we conducted four methodological steps

First, the authors conducted a literature review to familiarize themselves with the current landscape for RWD/RWE. The insights encountered during literature review would inspire for the preparation of questions to ask at pharma professionals during interviews, as well as allow them to take a critical position toward interviewees.

Second, we interviewed pharmaceutical companies to gain insights to their perception of benefits, uses and challenges of hospital RWD/RWE, as well as a collaboration model to exchange data. This was preceded by a literature review, on the one hand, as a guide in questioning pharma professionals, and on the other hand, for the authors to maintain a critical position toward interview data.

Third, we interviewed hospital representatives and a Belgian pharma industry coordinator from the government payer organization RIZIV/INAMI. In these interviews we assessed to which extent the requirements of a collaboration (resulted from the pharma interviews) were feasible for the hospitals and the government payor agency, in order to be able to propose a collaboration model that meets most needs of all stakeholders.

Fourth, we interviewed a LynxCare management member to assess the company's strategic value for the pharmaceutical industry. As such, we aimed to meet our end goal of providing a comprehensive review that included perspectives of multiple RWD/RWE stakeholders: pharmaceutical companies, hospitals, payor (i.e. government payer RIZIV/INAMI), and LynxCare

Study Insights

Results of the current research showed that RWD/RWE for pharmaceutical companies is indispensable during post-market (i.e. when a drug has been launched on the market) to solve clinical or budgetary uncertainties.

Uncertainties lead to a lower net price for pharma companies; whereas resolved uncertainties usually lead to a successful market entry; hence, improved patient care. Thus, **RWD/RWE are indirectly very important to ensure optimal healthcare quality**. Many other use-cases for pharmaceutical companies were also found; enhancing recruitment for clinical trials, assessing patient populations with large needs for treatments etc. (see further, Section 5.1.1).

We also assessed the hurdles of RWD/RWE. Hospitals are an important source of RWD/RWE as they are the custodians of many patient data. To date, collaborations between pharma companies and hospitals have been low-level (individual collaborations, ad hoc single database releases) and unsatisfying for both ends. Legal frameworks make it difficult for pharmaceutical companies to access hospital data and hospitals are impacted by the administrative burden of collecting and aggregating RWD/RWE. This leads to many unused hospital RWD/RWE insights, while the hospital Electronic Health Records are considered the richest, most granular data available in hospitals. With the rising importance of RWD/RWE pharma companies find themselves in need to find solutions to obtain access to hospital EHRs.

Secondly, it is difficult for pharmaceutical companies to obtain representative clinical data to assess their drug's effectiveness and population sizes. In order to gather representative data, RWD/RWE of multiple Belgian hospitals would benefit from being aggregated with one another; as well as aggregated with RWD/RWE from pharmacists and general practitioners. Individual hospital RWD/RWE collections cannot provide such integrated solution. Moreover, hospitals are still setting up protocols and a data infrastructure for RWD/RWE approach. Even if they manage to set up their own data sharing infrastructure, this does not lead to multi-hospital aggregated data. Hospitals have different templates to collect and store data; thus, a uniform coding is required for integration of data coming from multiple hospitals. An independent intermediate should also take responsibility on the validity of the data as well as ensuring the legal steps (e.g. anonymization, aggregation) and compliance. As this is not pharmaceutical companies' core business, nor is it hospitals' core business to own the required data-infrastructure, such job should be outsourced to a third party. It would be inconvenient for all separate pharma companies and all hospitals to invest in such advanced data-integration technology separately. Their budgets should instead be allocated to perform pharma companies and hospitals' core businesses: developing drugs and healing patients.

Thirdly, hospital participants from our study indicated they are still setting up protocols and a data infrastructure for RWD/RWE exchange. In addition, they indicated that legal frameworks about patient data exchange with third parties are to date unclear. While a general workflow protocol is being developed, clarifications should be obtained by e.g. a healthcare interest group such as Zorgnet-Icuro to educate hospital directors on the legal possibilities of RWD/RWE exchange.

LynxCare's Strategic Value for the Pharmaceutical Industry

LynxCare, a start-up focused on mining hospital EHR data could provide a solution, by serving pharmaceutical companies with multi-hospital (and other healthcare data providers) aggregated and integrated data.

Their speed of data delivery is an important factor for pharma companies, who now have to wait multiple years to access clinical outcome data. Bridging this waiting period could lead to significant benefits for pharmaceutical companies; e.g. higher revenues and increases the chances gaining market access for new drugs, which benefits patients in need and society at large.

LynxCare's current collaborations with hospitals offer a unique opportunity to finding a stable middle ground for collaborating with pharma companies, a fair rewarding system being set up that considers their interests and a partner that helps to protect their core business. Hospitals need to understand that allocating their staff to RWD/RWE projects at the moment will negatively affect their business, as RWD/RWE still remain very much time-consuming and outside their field of expertise. Collaborating with a third party such as LynxCare could provide them a chance to increase revenue and access to RWD/RWE research projects, without impacting the quality of their patients' care.

The latter insight applies also to pharma companies: Even if pharma companies hold the keys to scientific know-how, the management capabilities, and technological capacities to develop treatments; the success of a new drug on the market highly depends on the speed to market as well as demonstrating its health benefits (effectiveness), with respect to their competitors. Outsourcing has allowed pharma companies in the past to gain access to new development expertise and span any gaps in manufacturing capabilities to increase speed on go-to-market projects. In addition, outsourcing RWD processing and RWE analysis to LynxCare will enhance pharma companies' operational agility. In a next stage, the government and/or health care interest groups can be included in negotiations to advice on how systemic inequities in the collaboration model or research projects can be addressed by pharma companies, hospitals and LynxCare together.

Strategic Recommendations for Involved Stakeholders

Based on our research results, we have provided each stakeholder group with a set of strategic recommendations with the objective to lead to a smooth hospital-pharma RWD/RWE exchange for all stakeholders

Pharma Companies

- Develop an integrated RWD/RWE strategy, e.g. through real-world data hubs
- Value reputable RWD/RWE sources over contestable sources
- Give clear instructions on required criteria and data to stakeholders

Hospitals

- Increase awareness about need/types of RWD/RWE
- Design internal protocols for proactive RWD/RWE collection
- Educate on the legal framework for RWD/RWE collection
- Embracing the value of an intermediate third-party integrator as ultimately benefiting the patients

Authorities and interest groups

- Provide clarification of laws about data ownership and anonymization
- RIZIV/INAMI and other payors need to proceed with RWD/RWE upskilling programs
- RIZIV/INAMI and other payors need internal education on RWD/RWE sources
- Embrace innovation induced by RWD/RWE

LynxCare

- Focus on data integration from many hospitals and other healthcare stakeholders
- Seize opportunities for rapid RWD/RWE delivery
- Strategic approach toward hospitals
- Take the lead for legal clarification
- Outclass competition by hospital network, medical and IT expertise, and technical capacity

1. Introduction

1.1. Introduction to Company

LynxCare is a Belgian scale-up that offers an AI powered data platform to collect and analyse hospital Real World Data (RWD)/Real World Evidence (RWE).

Attention for RWE/RWD is rising due to restraining healthcare budgets and large variation in patient outcomes (Gerecke, Clawson, & Verboven, 2015). This has led to a healthcare industry that is looking for manageable alternatives for quality care at an affordable rate. With its data-driven technology, LynxCare provides insights that lead to an increased healthcare efficiency and an optimal patient experience.

1.2. Motivation

After the success of LynxCare in the hospital industry, the company aims to address the pharma industry.

Hospital RWD/RWE insights could also benefit pharmaceutical companies in the development of new medicines, the design of controlled research settings, the targeting of patient populations, and with the pricing and reimbursement process. In order to make a successful pharma market entry, initial market research needs to be conducted first. This research should assess the benefits, uses, and challenges of hospital RWD/RWE in pharmaceutical companies. In addition, it should suggest a blueprint for a collaboration model between pharmaceutical companies and hospitals for the exchange of RWD/RWE.

This project is useful on the one hand for the pharma-hospital sector at large to provide insights into RWD/RWE benefits, uses & challenges. On the other hand, it will be useful for LynxCare in particular to gain insights on how their offerings can fill the needs for RWD/RWE in the pharma-hospital sector.

1.3. Problem Statement

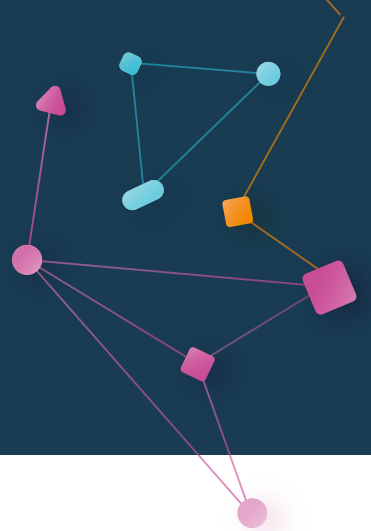
Recently, the value of hospital RWD/RWE for pharmaceutical companies has been receiving increasing attention by many healthcare stakeholders (Annemans, 2016; Gores & Patel, 2018). However, to our knowledge no systematic review has been published about the different benefits, use-cases and challenges of collecting RWD/RWE from hospitals.

The first objective of this paper is to present an integrated approach to benefits and use-cases of RWD/RWE – and in specific, hospital RWD/RWE - for pharmaceutical companies, distinguishing between several application domains: pricing and reimbursement decisions, other applications within the pharma-hospital industry, and other applications within the broad healthcare industry. In addition, through interviews we will list, classify and evaluate the various types of RWD/RWE and alternative medical data sources for pharmaceutical companies currently used in this regard. During interviews with pharmaceutical companies, hospitals and the payers, challenges will become clear.

The second objective of this paper is to design and assess collaboration models for the exchange of hospital RWD/RWE. Up to date, this process has been unstructured and continuous efforts by several stakeholders (e.g., Sciensano) have improved post-launch data collection but have not led to completely satisfactory data supply to pharmaceutical companies.

This paper includes an effort to make suggestions that can help to fill this gap fill this gap. The third objective of this paper - as it is an in-company project - is to assess LynxCare's strategic value for the pharmaceutical industry.

2. Literature Review



The literature review focuses on finding information that would provide an answer to our research questions as they were established in the project charter. Following explorative literature research which revealed more specifically unexplored areas, we have slightly adapted our RQs' scope. The adapted ratio of our four research questions can be found throughout our literature review.

For the purpose of this paper, we start by defining RWD and RWE, by distinguishing between both. However, as there's a thin (mainly conceptual) line between both and we expect participants' definitions to differ and might even bias results (RWD meant by participants as RWE and vice versa), we will not distinguish strictly between both for the purpose of this paper. When we talk about either RWD or RWE, either of both terms could be appropriate.

2.1. Defining RWD/RWE

Many definitions exist that explain RWD. The most straightforward definition of RWD is "any data that is not collected in conventional Randomized Clinical Trials" (Makady et al., 2017) defines RWD as any data that is not collected in conventional Randomized Clinical Trials (RTCs). The difference between data gathered in RCTs and RWD can be illustrated with the difference of efficacy vs. effectiveness. Efficacy describes how medications perform in controlled settings in a homogenous patient population – namely, RCTs (Roots Analysis, 2018; Silverman, 2013). An advantage of controlled RCTs is that confounding factors (e.g., other illnesses in patients) can be minimalized (Meltzer, 2001). As a result, positive effects found on disease burden reduction can be attributed to the intervention of interest, whereas in RWD settings it is not always clear what caused the outcomes. A disadvantage of RCTs' is that it raises the question whether its highly artificial results can be generalized to a wider population in real life circumstances.

Effectiveness, on the other hand, describes how a medication performs in real-world setting within a population that is larger than in RCTs (Meltzer, 2001). Data gathered in this real-world setting are called Real World Data (RWD).

RWD is different from RTCs in the sense that they are collected under real life practice circumstances where other variables cannot be controlled (Makady et al., 2017; Silverman, 2013).

Evidence on efficacy and effectiveness must be seen as complementary to each other; we see the role of RWD becoming increasingly important as complementary evidence to RCTs (Annemans, 2016; Roots Analysis, 2018).

Sometimes it might be useful to conceptualize between RWD and RWE. RWD offers precise information from a patient's treatment and its development (Health & Medicine Week, 2018). Even though RWE is based on RWD, there is a slight conceptual difference. RWE is generated according to a full research plan, with data collection, data-analysis, and a conclusion. RWD, on the other hand, is but one component of the research plan; the simple factual information (e.g., databases). In short, RWE are the conclusions derived from the 'hard data' (RWD), shaped by human judgement (Makady et al., 2017). As mentioned, and motivated, earlier for the purpose of this paper we will not distinguish between RWD and RWE.

It must be noted that RWD/RWE have some advantages in comparison with Randomized Clinical Trials (RCTs). RCTs' homogenous samples and experimental settings threaten external and ecological validity of insights (Makady et al., 2017; Roots Analysis, 2018). External validity concerns the extent to which the results of clinical trials can be held to be true for other cases, for example to different people, places or times (Roose & Meuleman, 2014). Although results might be internally valid, there are a wide variety of factors that need to be considered while treating individual patients, both genetic and environmental (Roots Analysis, 2018). Ecological validity concerns the extent to which test results can be applied to real-life situations outside of controlled settings (Roose & Meuleman, 2014). Often do tests in controlled settings lead to different results and complications than when used in real-life, limiting RCT's ecological validity.

The collection of RWD/RWE addresses the aforementioned complexities and even though it is not a replacement for clinical trials (Annemans, 2016; Health & Medicine Week, 2018), it can be used to complement RCTs (Roots Analysis, 2018).

For the healthcare sector at large, RWD/RWE have the advantage of accelerating innovation and providing better healthcare outcomes (Healthcare & Medicine Week, 2018).

In addition, RWD/RWE have many benefits that are of specific importance to several healthcare stakeholders (Figure 1).

Figure 1

Meta-analysis of benefits of hospital RWD/RWE for different stakeholders (Annemans, 2016; Brooks, 2017; Gores & Patel, 2018; Gregson, Sparrowhawk, Mauskopf, & Paul, 2005; Healthcare & Medicine Week, 2018; Hughes et al., 2016; Roots Analysis, 2018).

Pharmaceutical Companies

- Developing novel treatments
- Assessing long-term effectiveness of drugs
- Receiving reimbursement
- Increasing drug development efficiency
- Increasing ROI
- Distinguishing brand
- Determining safety profiles
- Physician segmentation
- Quantifying unmet need

HCPs

- Choosing right intervention out of mullitple options
- Ensuring reimbursement for patients
- Patient segmentation
- Informing on dosage and application in daily practice
- Information on patients' therapy adherence levels

Patients

- Receiving correct treatment information (e.g. dosage, application)
- Well-considered, informed valuation of treatment options
- Ensuring reimbursement
- Improved health and quality of life

Payers

- Evaluating new treatment's cost-efficiency
- Assessing long-term results
- Broad clinical and economic outcomes
- Ensuring quality healthcare
- Quantifying unmet needs
- Size of target population

Since RWD/RWE offer many benefits to pharmaceutical companies (Figure 1), the use of RWE is increasing throughout a product's entire lifecycle (Gores & Patel, 2018).

Traditionally, RWD/RWE had found their first place in a drug's post-launch phase, to support proving new drug clinical effectiveness in a real-world setting. Today, we see an integrated RWD/RWE approach that is initiated also early on in the clinical development to meet needs of different healthcare stakeholders and to continue throughout the entire lifecycle of a medicine (Gores & Patel, 2018; ICON, 2017).

Albeit the efforts to synthetize evidence from RCTs with observational studies, a chasm in evidence between controlled and uncontrolled studies has been noted (Nordon et al., 2016). During pre-launch RCTs are used to assess the positive efficacy-safety ratio – or, to which extent a drug does more good than harm (Haynes, 1999). However, such exercise shows little about a drug's real-world effectiveness. Despite efforts to bridge RCTs with observational studies (e.g. pragmatic trials, see Appendix 1) discrepancies still remain between scientific evidence from RCTs (efficacy) and real-world studies (effectiveness), this called the efficacy-effectiveness gap. The gap is caused by three main factors: at first different behaviors of physicians toward drug prescription and use, at second the inclusion versus exclusion of confounding factors (i.e., patient characteristics, e.g. age; patient behaviors, e.g. adherence; and environmental factors, e.g. air pollution), and at last by methodologic discrepancies (e.g., study design) (Nordon et al., 2016). The methodologic discrepancies provide an opportunity to look beyond any dichotomy between "standardized" versus "real-life" study designs (Nordon et al., 2016). Many experts believe there is instead an 'explanatory pragmatic continuum' (Nordon et al., 2016). To bridge the efficacy-effectiveness gap, researchers argue that a broad range of pre- and post-licensing technologies will need to be utilized (Eichler et al., 2011).

2.2. RWD/RWE Throughout the Lifecycle of a Medicine

The lifecycle of a drug is characterized by the following four stages: pre-clinical research clinical development, market access, and post-launch, with each their own use-cases for RWD/RWE (Figure 3).

Pre-clinical research can reveal areas of high clinical unmet need (Guinn, Madhaven, & Beckman, 2018), as well as opportunities for compounding (i.e. creation of a drug that fits the unique need of a patient) (Brooks, 2017). Clinical development is a form of healthcare science during which the safety and efficacy of a drug are assessed, usually including three phases of RCTs. At this stage, RWD/RWE can support RCT design and recruitment (Annemans, 2017a). When a drug is proven to be both safe and effective in clinical trials, the drug enters the market access phase, where the new drug is prepared to be launched and commercialized on the market. RWD/RWE on drug performance, i.e. competitor products or results from abroad, can complement RCT results to accelerate market access. Often, RWD/RWE on a drug's performance is not yet available during market access and payors demand firms to collect RWD/RWE in the post-launch. During post-launch, a novel treatment is used in patients in a real-life setting. As such, real-world performance can be measured. These RWD/RWE will often assess a drug's effectiveness in a real-life setting or can help target the right patients for a follow up therapy compliance.

A more elaborate description of each drug lifecycle stage follows, as well as the encountered in literature insights of what crucial factors that may impact drug pricing and which RWE benefits may support new drug development during each stage.

2.2.1 Pre-Clinical Development

Analyzing the status quo on patient needs and current treatments – i.e. the standard of care (see further, cf. Section 2.2.2B) - can be performed already in the pre-clinical development stage, showing which diseases, patients, and current needs that are currently under addressed (Guinn, Madhaven, & Beckman, 2018).

Consequently, pharmaceutical companies have a better understanding of saturated markets, markets not to tackle due to high levels of satisfaction, as well as of emerging markets or markets with high unmet needs, with lots of potential. Revelations of such unaddressed markets ultimately benefits patients in high need of new treatments.

Once a new treatment group has been chosen, the drug can be developed completely in line with the specific needs of the target group, by involving those patients in the process of clinical trials (cf. Section 2.2.2). Such process of customizing drugs to specific patient needs is called compounding (Brooks, 2017).

Types of RWD/RWE that can help in assessing the status quo (Annemans, 2017a):

- RWD/RWE on e.g., the number of complications, disease progression, and costs, enhance
- RWD/RWE from patient communities, social blogs and chat rooms

2.2.2 Clinical development (P1/P2/P3)

Clinical development includes the first three phases of clinical studies – previously referred to as RCTs – to assess a drug's basic efficacy, dosage and side effects (CLINICAL GYAN, 2018; Bahadur, 2008).

They are performed in highly controlled environments and in limited, homogenous populations (Roots Analysis, 2018).

The three phases of RCTs are pharmacology (P1), exploratory (P2), and confirmatory (P3) (Figure 2).

P1: Pharmacology

- The length of the study is several months
- The purpose is assessing safety and dosage (e.g., side effects, tolerability, pharmacokinetics, pharmacodynamics and route of administration)
- Includes on average 20-100 healthy volunteering participants.
- About 70% of drugs are approved to move to next clinical phase

P2: Exploratory

- Samples of about 100 participants
- Participants are healthy volunteers or patients with the condition of interest
- The length of the study is several months to two years
- The primary purpose is to study a drug efficacy; further assessments of safety and dosage
- About 33% of drugs are approved to move to next clinical phase

P3: Confirmatory

- Samples of 300-3000 participants
- Further investigations of efficacy and safety (e.g., side effects),
- The length of the study can lead from 1 year to 4 years.
- About 25-30% of drugs are approved to move to next clinical phase (Phase 4, see further)

Figure 2

RCTs P1/P2/P3 (CLINICAL GYAN, 2018; FDA, O. of the C., 2020; Bahadur, 2008; Pinkhof et al., 2010).

Factors that influence drug pricing during clinical development

During the clinical development phase, RWD/RWE of the drug is usually not available as it is yet to launch on the market.

However, RWD/RWE of the target disease area and related therapies can be gathered to estimate disease burden and budget impact (Barrett & Heaton, 2019), as well as to assist in the design of RCTs.

Increasingly, pharmaceutical companies have been pursuing an early dialogue focused on the payors' or regulators' – Health Technology Access (HTA) bodies (Gores & Patel, 2018). Different EU countries already provide formal early payor guidance structures, such as NICE in the UK, G-BA in Germany, and TLV in Sweden. During this early dialogue, pharmaceutical companies can seek scientific advice and try to identify the value drivers that payors and regulators use to assess the value proposition of a new product. Identified value drivers should then be integrated into the P3 design process to meet payors' and regulators' concerns (Gregson et al., 2005). The advantage is that this can increase chances of receiving market authorization and payors' acceptance for reimbursement during market access.

During early dialogues, information about a drug's clinical trial results, the extent to which it meets with the payors' needs, and how it compares to alternative therapies can be bundled into a value dossier. Usually a value dossier is communicated towards the payor during the market access phase. However, in some cases it is useful for manufacturers to initiate this process already during clinical development. This is particularly important when the current disease burden is unclear and needs to be emphasized or for drugs introductions with a potential large budget impact (because price*quantity) (Gregson et al., 2005).

Benefits of RWD/ RWE during clinical development

RWD/RWE can be integrated into early drug development management (ICON, 2017). For instance, Electronic Health Records (EHRs) or Patient-Recorded Outcome Measures (PROMs) can be used for recruitment optimization. EHRs are the systematized data collections of patient health information stored in an electronic format, while PROMs are standardized, validated questionnaires completed by patients to measure perceived well-being and drug outcomes (Department of Health, 2009).

In addition, RWD/RWE from former studies might improve an RCTs' research design (Annemans, 2017a). RWD/RWE on daily practices (e.g., claims databases) can make RCT's design more pragmatic and less onerous to patients and investigators while EHRs can help with a fast identification of participants (Annemans, 2017a; Chatterjee et al., 2018). This process does not only impact drug pricing due to more reliable evidence but also lowers development costs for the manufacturer (Chatterjee et al., 2018). RCTs that are better designed and tested with the right participant profiles will consequently lead to a better demonstration of drug efficacy. Efficacy is highly correlated to the value of a drug (Kolossa, 2018), thus taking into account RWD/RWE in early stages of a new drug may already impact its value.

In addition, a pharmaceutical company can stimulate disease awareness during early diagnose with HTA bodies and payors, this may support the need for novel treatment options for diseases mostly unknown to payors. This can lead to convincing HTA bodies faster and to grant new drug submission (with proposed value by pharmaceutical) (Hughes et al., 2016).

2.2.3 Market access/launch

During market access, pharmaceutical companies apply a set of strategies to ensure that drugs are offered on the market and adequately priced (Dixon, 2019).

In order to gain permission to introduce drugs to the market, pharma companies must submit a registration dossier to regulatory agencies (e.g., European Medicine Agency 'EMA'), containing all possible information on a new drug's efficacy, safety and tolerability (Dixon, 2019). Once regulatory agencies grant market authorization for new drug, a second dossier is submitted by a pharmaceutical company for pricing and reimbursement to payors and/or national authorities (e.g., RIZIV in Belgium). Based on evidence and pricing dossiers, HTA bodies must make informed pricing and reimbursement decisions with representatives of different healthcare stakeholder groups (Annemans, 2016).

However, RCTs' data often does not suffice for authorities to justify a medicine's price and reimbursement. Additional RWD/RWE is often required from pharmaceutical companies to prove that a product's efficacy effects can be translated into real-world effectiveness (Gregson et al., 2005) and bridge the efficacy-effectiveness gap. In addition, access/launch has evolved into a much more complex process due to continued rising costs putting a government's healthcare budget constantly under pressure (Dixon, 2019; Gerecke, Clawson, & Verboven, 2015). Governments are facing growing safety concerns of latest new drugs developments, an aging population, and increased disease burden that drain new drug budgets (Dixon, 2019). As the institutional environment gets more challenging, healthcare authorities are becoming more cautious regarding their choices on pricing and reimbursements. This also often leads to more in-depth investigations of the value claims for new drugs based on RWD/RWE (Dixon, 2019).

In order to mitigate the efficacy-effectiveness gap, Managed Entry Agreements (MEAs) are set up between pharma-payors to allow coverage of new medicines while simultaneously managing financial or performance-related uncertainties (Wenzl & Chapman, 2020).

With a MEA, a new drug may be allowed to enter the market with a temporary reimbursement scheme, though during a revision after approximately 2-3 years RWD/RWE will be requested to provide answers on current drug related uncertainties (see further, cf. Section 4.1).

Such MEAs are interesting for pharma companies because it allows an (early) entry to market, where otherwise drugs' market entries could be refused. This way pharma companies can manage the trade-off between launching earlier at a lower price versus launching later at a higher price (Gregson et al., 2005).

How RWD/RWE factors impact the market access phase

A. Treatment outcomes

After market authorization has been granted, price negotiations are initiated.

These negotiations will primarily be conducted with payors (Gregson et al, 2005). The baseline for pricing and reimbursement negotiations will primarily be set by RCT results about a new drug's efficacy and safety (Gregson et al, 2005). RCTs are considered to be the highest level of evidence on efficacy and safety because they are designed to be unbiased and exclude systemic errors (Burns, Rohrich, & Chung, 2011). By randomizing participants in treatment groups (experimental + control group), confounding factors are also randomized and therefore neutralized. As such, bias can be minimalized, and efficacy results can be attributed to a drug's performance.

RWE, as mentioned earlier, translates efficacy effects to real-life effectiveness and is therefore often required by payors in addition to RCTs. However, at this point more RWD/RWE on a new therapy are not available yet. Then authorities might insist on setting up an MEA to revise pricing and reimbursement decisions at a later stage when RWD/RWE is collected (Gregson et al., 2005), in particular when clinical effectiveness and/or budget impact uncertainties arise.

Exceptions are when a product had already been launched earlier in other countries or when RWD/RWE is available on competitors' similar products.

B. Standard of care

Healthcare authorities will compare RTC results with the standard of care (e.g. number of complications, disease progression, costs) and give their pricing advice accordingly (Annemans, 2017a). The standard of care specifies the appropriate treatment option for a given condition and is in practice often the price of comparatives in the market. This point of reference not only allows to assess predicted benefits of a drug, it works as a dynamic reassessment tool for the value of a drug (Annemans, 2017a).

Information on a current treatments' healthcare burden can give pharma companies an indication of an acceptable request price for their own medicine.

The effectiveness of a new drug is equal to the price of the reference product and the net value of the perceived differentiation between a new product's benefits outweighing costs stronger than for comparative reference product (Gregson et al, 2005). Pharmaceutical companies must bear this in mind when calculating a new product's price because in exchange for demanding a higher price, payors expect significant improvements in the cost-benefits ratio (see Table 1). RWD/RWE could help to calculate standard of care (Annemans, 2017b).

C. Net impact on the healthcare budget

Although in theory "the higher the value, the higher the price", this principle ignores the built-in limits of some societies' healthcare budget (Annemans, 2017b). With a limited healthcare budget, authorities must also take into account a new product's budget impact and affordability. Spending a large sum on a highly effective new product will obviously be beneficial to an individual patient, however, takes away the opportunity to help other patients (Annemans, 2017b). The ultimate goal of healthcare authorities is to spend their budget wisely in a way that keeps as many citizens as healthy as possible. Horizon scanning and budget impact assessments are therefore required to reveal to which extent a healthcare system can afford a new product.

RWD/RWE can help in deciding the budget impact and disease burden on the healthcare budget (Barret & Heaton, 2019).

The World Health Organization (WHO) and Institute for Health Metric Evaluation (IHME) collaborate extensively to ensure that global disease burden estimates are accessible and accurate.

D. Unmet market needs

When satisfying solutions are missing, patients and physicians often pressure governments and payors to grant market access to innovative therapies that are still in clinical development (Gores & Patel, 2018). Governments and payors have responded to this need with alternative regulatory pathways (Rex et al., 2013). Such regulatory pathways offer pharma companies a legal opportunity to launch on the market while the last phase of clinical trials is carried out. The aim is to facilitate market authorization and access of medicines to patients in areas of high unmet needs.

However, during an early launch, there is more uncertainty about a drug's effectiveness. Such increased levels of uncertainty lead to a lower valuation at earlier launch (Gregson et al., 2005), however when supported with an extensive post-launch data collection the price might ultimately rise (slightly).

Hence, such alternative regulatory pathways in turn require extensive post-launch authorization data and, thus, are a domain of application for RWD/RWE.

Moreover, RWD/RWE become even more important for unmet need in the case of orphan medicines (i.e. medicines developed for small, often underserved, patient groups). Typical for these types of medicines are their high prices and the limited amount of knowledge available (e.g., because of small number of patients to recruit for RCTs) (Isomeri & Hemmilä, 2018).

RWD/RWE serves two purposes for orphan medicines to stimulate earlier access:

1. Electronic Health Records and help finding the right patients for RCTs
2. Satisfying regulators with extensive post-authorization data

E. Pricing model

Countries use different pricing models that can be classified as cost-plus pricing or value-based pricing (Table 1):

Table 1 Cost-plus and value-based pricing models

	Method	Formula and / or example unit	Countries
Cost-plus pricing	Costs of production + profit margin	$	
Value-based pricing	Cost- Benefit Analysis (CBA)	Total costs ($) / Total benefits ($)	Australia, Belgium, Finland, France, Germany, Ireland, Norway, Portugal, Russia, Switzerland, Scotland, Canada
	Cost-Effectiveness Analysis (CEA) / Cost-Utility Analysis (CUA) = treatment impact on life expectancy/Quality of life (QALY)	▲ costs / ▲ effectiveness $ / life years gained $ / QALYs gained	Australia, Belgium, Canada, Finland, France, Germany, Italy, Ireland, Norway, Netherlands, New Zealand, Poland, Portugal, Russia, Spain, Sweden, Switzerland, United Kingdom
	Outcomes-based P&R	Treatment outcomes for a drug, might be	Belgium, France, Denmark, Italy Germany, Netherlands, Norway, Spain, Sweden, United Kingdom

In "cost-plus pricing" R&D investments and the costs of goods sold are reflected in the pricing process. One looks at all of the inherent costs that have been made to produce a drug and adds a profit margin.

A drug's value for patients or society is not taken into account, and, therefore, RWD/ RWE do not impact price in this approach. Although cost-plus pricing was traditionally the preferred method, authors have increasingly been arguing that value-based pricing should be the preferred method for drug pricing (Annemans, 2017b).

In contrary to cost-plus pricing, "value-based pricing" centralizes a medicine's additional value for patients and society (Annemans, 2017b). Additional value then originates from better treatment outcomes (e.g., higher effectiveness) in comparison with the standard of care (see further earlier for definition, cf. Section 2.2.2B). This implies that treatment outcomes and the standard of care are taken into account in a value-based pricing strategy. As discussed earlier, both treatment outcomes and the standard of care can be assessed by the aid of RWD/RWE. We therefore expect RWD/RWE to expand influence in value-based pricing models, as opposed to cost-plus models.

E. Pricing model

A well-known, classic value-based pricing model is Cost-Effectiveness Analysis (CEA). Cost-effectiveness is the ratio between the net cost of the treatment and the net health benefits.

Cost-effectiveness analysis (CEA) is formally required in many countries (Franken, 2014).

Net cost means that additional drug-related costs elsewhere in society are explicitly taken into account (Annemans, 2017b) (infra: Cost-Utility Analysis applies the same metric - $/QALYs gained – for pharmaceutical companies, so for the purpose of this purpose we will not distinguish between CEA and CUA). Larger societal costs can be mapped by including RWD/RWE (Annemans, 2016; Health & Medicine Week, 2018).

Another value-based pricing models is Cost-Benefit Analysis (CBA). CBA considers all the costs and benefits that arise from new drug and discounted to year zero. When total discounted benefits exceed total discounted costs, this is regarded as a positive net present value (NPV). CBA is useful for including benefits and costs indirectly associated to health outcome as for example time taken off from family members' work to care for the patient (Meltzer, 2001).

Recently, European payors and insurers are increasingly tying pricing and reimbursement decisions to patient outcomes to provide a guarantee for care (Blumenthal, Goldman & Jena, 2016; Gandjour, 2017). Such outcomes-based agreements ponder that when a drug's real-world performance does not live up to expectations based on RCTs, the company must, partly or fully, refund the cost of a drug. Outcome-based models can be specified on the level of a medicine but can also be indication-specific or patient-specific (Comer, 2019). Indication-specific distinguishes between treatment outcomes for one product approved to treat multiple diseases ('indications'). Products approved for multiple diseases are often more effective in treating one disease compared with another. In this model, a product's price is based on the results that it delivers for each indication. If a product is highly effective in treating indication A and moderately effective in treating indication B, payments will be higher for indication A.

Patient-specific distinguishes between treatment outcomes for one drug in separate patients (i.e. pay-for-performance, cf. Section 4.1.1(3). Based on electronic health records (EHR) treatment outcomes for individual patients can be recorded. Some patient behaviours, such as non-adherence to a treatment plan, can lead to a refund by the pharmaceutical company who provided the product. The specifics of such outcome-based pricing agreements are set out in a MEA (cf. intro Section 2.2.2).

RWD/RWE could help to calculate costs and effectiveness in a CEA/CUA, and to assess specific effectiveness levels for indications or individual patients in outcomes-based agreements. It is clear that the need of RWD/RWE depends on the pricing model used in different countries and to which extent RWD/RWE is accepted as an input parameter to calculate the benefit. In Estonia, for example, RWD/RWE is considered to be very important to assess clinical effectiveness in addition to efficacy. Therefore, Estonian responsibilities for assessing effectiveness and efficacy are split up: Health Insurance Fund (EHIF) is responsible to advise on cost-effectiveness (Mägi et al., 2018); while the State Agency of Medicine (SAM) will in focus on the results of clinical efficacy when advising the ministry of health.

Benefits of RWD/ RWE during market access

RWD/RWE have proven that they can accelerate the market access submissions (Hughes et al., 2016), as it offers a better understanding of the current standard of care in many of its aspects, especially when combined with comparative trials (Annemans, 2017a).

It does so for example by giving a framework for calculating the current standard of care and shedding light on a therapies' net impact on the healthcare budget. It will also help pharma companies determine a new products' budget impact and cost-effectiveness (Gores & Patel, 2018).

For example, a company wanted initially to invest $3 to $5 million in a traditional multi-centre prospective observational study (Hughes et al., 2016).

Since the therapy was only suitable after a specific expensive diagnostic testing procedure, the company decided instead to use RWE to analyse previous retrospective diagnostic testing results data (Hughes et al., 2016). With RWE, the company obtained more accurate insights, it took two weeks less to launch and reduced the research budget to only 2% of the original $3-5 million.

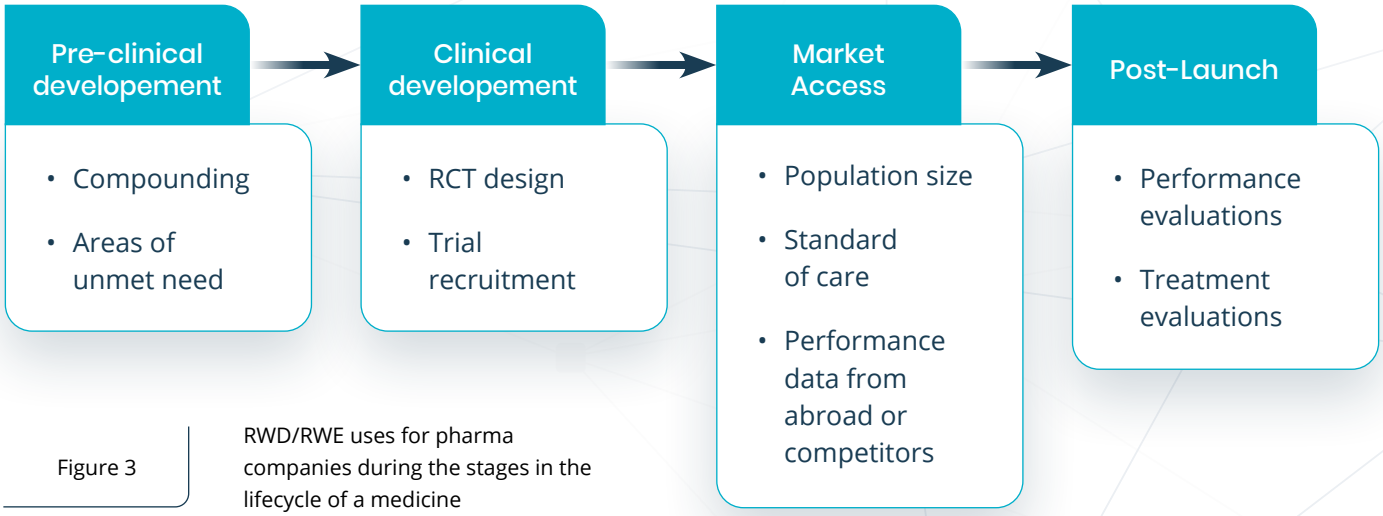


Figure 3

RWD/RWE uses for pharma companies during the stages in the lifecycle of a medicine

2.2.4 In-market/post-launch

After a product has been launched on the market, MEAs often require additional data-collection in order to assess its value for real-world effectiveness.

While clinical studies serve as a good base for a temporary or conditional price, they often provide insufficient evidence to fully justify it. Therefore, price negotiations with HTA bodies (e.g., RIZIV in Belgium) continue after a product's market launch while additional evidence is collected. In case market usage RWD/RWE demonstrates results dissimilar to the RCT results, it can result in price adaptations (Gregson et al., 2005).

Moreover, for chronic diseases it is hard to assess value based on clinical trials because some effects might only appear in the long term. If there's partial evidence that a new product has a significant added value based on clinical trials, firms can get immediate permission to offer their product at a premium price on the condition that follow-up studies are performed (Gregson et al., 2005).

Factors that influence drug pricing during the in-market phase

A. RWD / RWE

RWD/RWE can be used to demonstrate that a drug results on efficacy translate to real-world effectiveness (Gores & Patel, 2018).

Drug prices might be reevaluated and amended as soon as the long-term outcomes are demonstrated.

B. Clinical Phase 4 studies (P4 studies)

Phase 4 studies (P4) are usually conducted after the medicine has been registered and after marketing authorization is granted (Pinkhof et al., 2010).

Clinical phase 4 studies are also known as Post-Authorization Safety Studies 'PASS', market usage studies, post-marketing surveillance trials and post-launch phase studies in scientific literature (European Patients' Academy, 2015). The aim of phase 4 studies is to deliver benefit to patients and to make sure to reap the earlier investments in clinical development (Nell, 2018).

Phase 4 studies can be made up of data mining, collection of outcome data, but also from more familiar clinical trials (e.g. pragmatic trials) and observational studies (cohort studies and case-control studies) (Nell, 2018).

B. Clinical Phase 4 studies (P4 studies)

Phase 4 studies are focused on collecting as much possible real-life data on pharmacovigilance (side-effects that were not seen in earlier clinical phases P1, P2, P3 and risks/benefits over a long period of time) and further therapy optimizing of approved drugs (European Patients' Academy., 2015). These studies usually involve looking into EHRs/EMRs, patient registries, linkage records between databases; this stimulates the refinement, the confirmation or denial and the safety of a drug (FDA, O. of the C., 2020). Phase 4 studies are characterized by continuous research for new drugs indications applied on patients, very large number of patients participating (at least 1000 participants who suffer from a condition are included in study), and the length is long-term and/or extends to the time that the drug stays on the market (European Patients' Academy., 2015; FDA, O. of the C., 2020). About 70%-90% of drugs succeed to remain over time in the market (FDA, O. of the C., 2020). Phase 4 studies are challenging because these studies are at 'the centre of cooperation with marketing, medical, drug regulatory, R&D and legal functions' (Nell, 2018).

Benefits of RWD/RWE for supporting drug pricing during the in-market /post-launch phase

RWD/RWE can confirm post-launch confirmation of drug benefits, to better understand healthcare outcomes (Annemans, 2017a), and in the case of MEAs or product class reviews help maintaining pricing levels. This is achieved by providing evidence of new innovative drugs in real world use (e.g., drug for which patients, dosage, duration) (Annemans, 2017).

This literature has given us a thorough understanding of three main stages in the lifecycle of a drug, as well as the factors that influence pricing and reimbursement decisions. We want to test whether these advantages of RWD/RWE in pricing and reimbursement decisions can be translated to real-life for pharma experts, and, because the landscape of RWD/RWE is changing rapidly, whether new use-cases have been adopted. Therefore, we propose the first research question.

RQ1: What is the real-world value of RWD/RWE during (pre-)clinical development, market launch and post-launch according to Belgian pharma professionals:

1. for P&R decisions?
2. for other use-cases?

2.2.5 Applications RWD/RWE for the broad health care industry

RWD/RWE data use is not limited to pharmaceutical companies but can also serve the healthcare sector at large (e.g., hospitals, payors). In addition, it must be understood that RWD/RWE purposes that serve pharmaceutical companies indirectly serve other healthcare stakeholders, as ultimately pharmaceutical companies design drugs to benefit patients and society at large. In the next paragraph RWD/RWE use-cases for the broader healthcare industry are discussed.

A. Shaping clinical guidelines

Clinical practice guidelines are a method to translate research findings into clinical practice. These guidelines describe appropriate care based on empirical findings and broad consensus, as well as promoting efficient use of resources (Bussières & Stuber, 2013).

RWD/RWE give an insight in real-life empirical findings for numerous patient populations and could therefore provide useful insights into routine clinical practice (Gores & Patel, 2018). This particular use of RWD/RWE is becoming increasingly accepted with HTA bodies. For example, the guidelines for thiopurine usage in Crohn patients were created by the European Crohn's and Colitis Organization was based on RWE. Pharma companies could play a role in this, by helping other healthcare stakeholders when forming clinical guidelines (Gores & Patel, 2018).

B. Following up patient drug usage

First, RWD/RWE show whether drug usage is in line with how it was prescribed. Second, by creating clinical decision support systems, RWD/RWE provide commercial spend effectiveness insights as to how patients respond to drug administration and how patients should be managed (Annemans, 2017a).

C. Stimulating patient therapy adherence

Patient-reported outcomes encompass health data reported by patients, such as quality of life (Arpinelli & Bamfi, 2006). Demonstrating that quality of life has been significantly improved for patients, by following a therapy, might serve as a motivation to others for therapy adherence (Gores & Patel, 2018).

D. Segmentation

The physician segmentation can be improved if RWD/RWE on disease progression models is shared to physicians (Hughes et al., 2016).

E. Evaluation of quality of care

Not only drugs, also procedures executed by HCP's in hospitals can be analyzed through RWD/RWE for their effectiveness. Hospitals can optimize their quality procedures and guide HCP's in better healthcare delivery based on RWD/RWE (Gores & Patel, 2018).

F. Targeted reimburse-ment

Today reimbursement not sufficiently tailored, mainly based on non-granular reimbursement coding that does not reflect clinical reality (e.g., ICD codes).

Availability of RWD/RWE allows payors to put in place targeted reimbursement schemes, e.g. outcome-based P&R models (cf. Section 2.2.3E). Those guarantee reimbursements only for specific populations or individuals, depending on the outcomes (e.g., effectiveness). As a result, healthcare budgets could be allocated in a more effective way, resulting in a more effective spending of the budget and a larger "health-gain" of the population as a whole (Danzon, 2018).

2.3. RWD/RWE Sources

As mentioned before, RWD/RWE are defined as all data and evidence collected outside of RCTs (Makady et al., 2017). As such, RCT data are the only relevant data source drug P&R not to be considered as RWD/RWE.

Different RWD/RWE sources are typically gathered by pharmaceutical companies in the framework of real-life observational studies, for which one could further distinguish between and retrospective and prospective studies (FDA, 2018). Retrospective studies identify the population, exposure/treatment outcomes etc. from historical data, i.e. data generated prior to the start of the study. In prospective studies, the population is defined prior to the initiation of the study, and data are explicitly – i.e., for the purpose of the study – collected from that point onwards.

Noteworthy in the context of RWD/RWE are also "continuous" studies, which involve the continuous capture of RWD/RWE from data generated in clinical practice – the data itself is thus secondary and not collected for the purpose of a study. These can be categorized as retrospective studies, as they do not fall within the prospective study regulations, even though data is collected on a continuous basis.

1. Hospital data

Hospital data are all data collected in hospitals and typically provide information on patient demographics, diagnoses, medical procedures, admission sources, discharge statuses, duration of stay, and charges (AHRQ, 2015a). Medical measures that can commonly be provided by hospitals are (AHRQ, 2015b; Guinn, Madhavan, & Beckham, 2018):

- Patient safety measures. E.g., the number of patients with surgical complications
- Effectiveness measures. These are clinical measures, E.g., percentage of patients that survived a heart attack
- Patient-Reported outcomes measures (PROMs). See further (This section, n°7)
- Efficiency measures. E.g., average length of stay
- Equity measures. E.g., Electronic Health Records (EHRs)

These data can in Belgium the following RWD/RWE is found in hospitals:

- Electronic Health Records (EHRs): Structured and unstructured information; from notes from clinical encounters including consultation, discharge, surgery, treatment, diagnoses. These data are largely unstructured, whereas the structured data is not uniformly coded.
- Imaging reports
- Lab data
- Minimal Hospital Databases (MHD database): claims data; clinical data extracts from EHR. The disadvantage of clinical MHD is that granularity of EHR data is lost, while extracting data causes large delays on data delivery to pharmaceutical companies (see Table 5 in Section 4.2).
- Genetic & biometric data

2. Claims data ("payors' data")

Claims databases contain data from claims that healthcare providers submit to payors when a patient uses health services.

Claims data – or reimbursement data – are electronic data records on patients' doctors' appointments, bills, health insurance records, and other patient-provider communications. These systems are primarily in place for billing and administration purposes but can also be used by pharmaceutical companies to provide long-term RWD/RWE on disease burden (Umuhire, n.d.).

In Belgium, The InterMutualistic Agency (IMA) collects, consolidates and aggregates claims data from all 7 separate health insurance agencies ("mutualistic agencies"), before passing it on to the RIZIV. These claims data include information on all transactions made within in the healthcare industry (e.g., billing information), as well as demographic information per individual. Billing information show the date, location/institution, healthcare provider, and cost. As such, detailed information is available per individual, per expenditure, per institution, and per healthcare provider (e.g., doctor).

Specifically, IMA offers a database "CIVARS" for Chapter IV and VIII drugs. It contains all electronic data exchanges between physicians and mutualistic agencies on doctors' approvals for Chapter IV and VIII drugs given to individual patients.

3. Clinical registries

Clinical registries are organized data collection systems that use observational methods to collect outcome data for a particular disease, condition or exposure.

The goal of registries is to improve healthcare quality and to inform value-based pricing models. Treatment outcomes can be evaluated for a population in a real-world patient setting over varying periods of time (Blumenthal et al., 2016).

Examples of well-known Belgian registries is the Cancer Registry. Most of the Belgian registries are bundled by an organization named Sciensano on a platform Healthdata.be. The platform stores data of multiple health registries in a single Internet-based platform. Access can be requested by pharmaceutical companies. Sciensano also assists in the setup of custom registries for specific studies, e.g. in the context of MEA's.

4. Mortality and population data

Mortality and population statistics are kept by governments. In Belgium, population and mortality data are made public by a federal government initiative Statbel in an online database (www.statbel.fgov.be).

5. Social media data

Patients can exchange their experiences health-related information with their peers on social media, in chat rooms, and patient communities (Annemans, 2018). For instance, adverse drug reactions are often involved in online discussions and can be extrapolated using data mining techniques (Yang, Yang, Jiang, & Zhang, 2014).

6. External laboratory data

Laboratory tests are used in various stages of all fields of clinical medicine and are an important addition to other types of measurements as a source of information on a patient's health status (Solnica, Dabrowska, & Sypniewska, 2010). Laboratory metrics, such as biomarkers data, are used not only during clinical development, but also in real world practice when investigating real patients. Such lab metrics can either be measured within hospitals, but also in external labs.

7. Survey data – PROMs

In addition to survey data collected in hospitals, online medical surveys (Houston & Fiore, 1998), or other surveying methods can be used to measure patients', caregivers', physicians' and others' feedback. A metric that is often included in medical surveys is satisfaction measurement.

PROMs measure effectiveness of a treatment from a patient's perspective rather than a clinical perspective. E.g., a survey measuring pain and mobility.

8. Wearables data

Wearables are electronic devices that are placed on the surface of the skin to measure heart rate, pulse, and other physiological data. E.g., Fitbit

9. Pharmacy data

10. Phase 4 of Clinical studies (P4) — See Section 2.2.3B

11. Investigator initiated studies

Contrary to clinical studies, investigator-initiated studies (IIS) arise from research goals/questions pondered by independent researchers (Perkmann et al., 2013).

In addition, IIS are guided by an already existing theory rather than a need for evidence for commercial purposes. These can be organized in highly organized settings comparable to RCT, as well as in more real-world settings. Academic studies are a type of IIS, initiated by an academic center.

12. Marketing studies

Medical marketing research companies provide pharmaceutical companies with expertise to understand the health care industry.

Their aim is to get access to a wide range of medical professionals including doctors, nurses, patients, payors and others. These stakeholders deliver insights into the medical, pharmaceutical and health care industry through interviews, focus groups, and surveys (Quirk's Staff, 2018). These insights are translated into reports that are provided to the pharmaceutical companies.

13. Expert reviews

Expert reviews are journals that serve the clinical research community by providing commentary, analyses and debates performed by medical professionals.

Examples of such journals are "Expert Review of Medical Devices" and "Expert Reviews in Molecular Medicine". Their advantage is offering accelerated publication

These are the different RWD/RWE sources pharma companies can use to gather information to support a drug's pricing and reimbursement decisions. We must now look at the benefits, use-cases and drawbacks of each RWD/RWE source. Hence, we formulate the second research question:

RQ2: What are the preferred types of RWD/RWE sources pharma companies use to support drug pricing and reimbursement decisions?

Even though many RWD/RWE sources can provide information to pharma companies, hospital data has been found difficult to access while containing the purest clinical outcome data, indispensable to assess the value of pharmaceutical products. In what follows, we aim to assess how pharma companies currently retrieve hospital RWD/RWE.

2.4. Collaboration models between pharma companies and hospitals

Very little has been discussed on collaboration models between pharmaceutical companies and hospitals for the exchange of RWD/RWE.

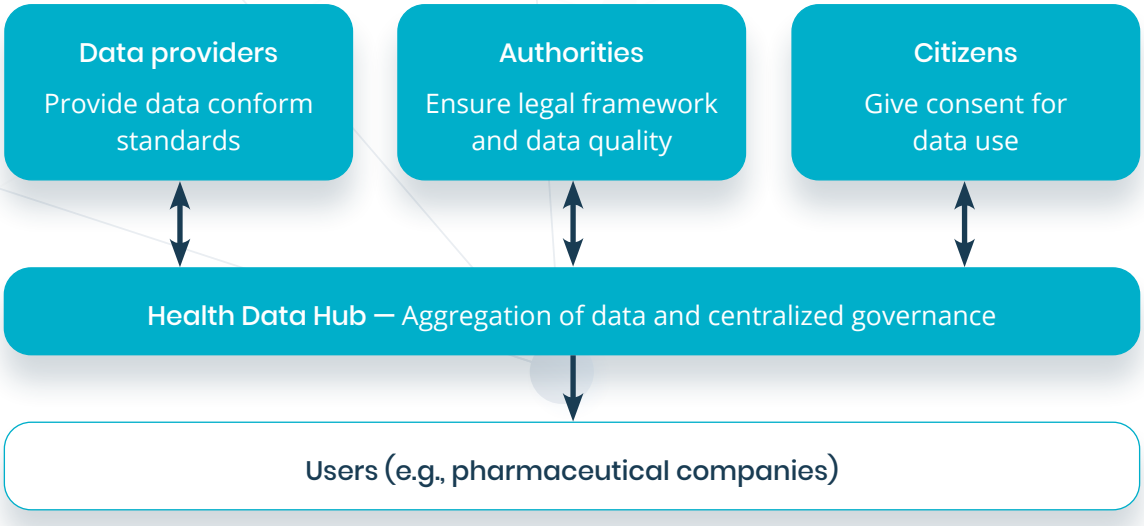
Structured direct collaborations seem not to be implemented yet on a large scale, although efforts are increasingly made in several countries to set up better data infrastructures, and in France even a first large RWE data hub project. RWE data hubs act to simplify the complexity of data exchange between pharma and hospitals and perform as an intermediary between involved parties. They involve a limited number of centers per country with which pharma has a structural collaboration and continuous access to RWD/RWE that together form a representative image of the population. Next to data hubs, national data infrastructures and CROs might also offer indirect sources of collaboration between pharma companies and hospitals for the exchange of RWD/RWE. Each of these alternatives is discussed in the following paragraph.

2.4.1 Data hubs

In France, a Health Data Hub was set up in 2019 (Aureen, Paris, & Lopert, 2019), with the goal to "facilitate interactions between owners of health data, health data users, and citizens, under high security conditions", as they understand this is essential for innovations in the healthcare industry. The full model is shown in Figure 4 (Bouet, Floch, Guerrier, & de Neuville, 2019).

Figure 4

Health Data Hub, a French initiative. Source: Bouet, Floch, Guerrier, & de Neuville, 2019



2.4.2 National data infrastructure

When governments in countries set up legal frameworks and systems to facilitate the exchange of health data, this also benefits pharmaceutical companies. Several European countries are taking the lead to set up legal frameworks, such as the Nordic countries and France.

In the Nordic countries, the development of a unique identifier together with a long tradition of population-based health registries has facilitated record linkage across databases and countries (Aureen, Paris, & Lopert, 2019). In addition, the government gathers and provides RWD/RWE datasets to the public.

In France, the Système National des Données de Santé (SNDS) was created in 2016 by the French government to aggregate three databases (Aureen, Paris, & Lopert, 2019): SNIIR-AM (i.e. nationwide database on patient demographics and claims data), PMSI (i.e., public and private hospital data), and a causes of death database.

In Belgium, the Healthdata.be platform has been set up by the government with the objective to centralize health data that is currently stored in multiple health registries into a single digital platform. In addition, this platform has improved data collection by offering customized data collection services to pharmaceutical companies.

Whether these improved legal frameworks should be considered a collaboration model is debatable. But it is clear that they facilitate aggregated data access and exchange.

2.4.3 Contract Research Organizations (CROs)

Another type of indirect collaboration between pharma and hospitals is the use of Contract Research Organizations (CROs). Pharma companies can outsource research activities to CROs, e.g. clinical research (P1/P2/P3/P4).

Some CROs manage almost all aspects of a clinical studies, offering services such as project management, database design and build, data entry and validation, coding, statistical analysis, validation programming, safety and efficacy summaries, and final study reports (Stone, 2019).

CROs are called upon to reduce costs for companies developing new drugs and to reduce the need for companies to have the time and human resources readily available 'in house' (Cook, 2016). An example of a CRO is IQVIA. In addition to their CRO services, IQVIA also offers standardized reports on the health industry.

Although we found some collaboration models most of them work on a project-by-project basis and do not provide structural access to RWD/RWE, and little to no literature or commercial sources were found on the topic. The recently initiated (2020) French Health Data hub can be seen as a structural RWD/RWE model, however it is too soon to evaluate its practical applicability. We therefore believe that this is mostly unexplored ground and aim to assess what a desired collaboration model for pharma companies and hospitals in the exchange of RWD/RWE. Therefore, we formulate our third research question:

RQ3: Which collaboration models to generate RWD/RWE between pharma and hospitals:

- A do currently exist from the experience of Belgian pharmaceutical companies?
- B are desirable for pharma companies in the future?
- C are manageable for hospitals in the future?

In function of the response to research question three, we must assess the value of LynxCare in a collaboration model between pharma and hospitals. This might be in a more leading or supporting role. Therefore, we formulate our fourth research question in an open, highly explorative manner:

RQ4: Which role can LynxCare play in the delivery of hospital RWD/RWE to pharma companies?

3. Methodology

3.1. Design

3.1.1 Semi-structured interviews with 4 stakeholder groups

A qualitative method of semi-structured interviews was chosen as the study topic was complex and partly unexplored (e.g., collaboration model) (Bowling, 1997).

Primary data on several topics of interest was collected during interviews with four stakeholders (see Figure 5 for topics discussed with each stakeholder).

Following a literature review and an introductory interview with an acquaintance from the national association of the pharmaceutical industry (Pharma.be), our interview guide for pharma companies was developed. An example of an important, yet abstract, variable in our study was measuring the role of "RWD/RWE in P&R", which needed to be operationalized using proxies. Examples of proxies for the variable "RWD/RWE in P&R" (the list is not exhaustive but merely illustrative) can be found in Table 2 (see appendix 2 for full pharma interview guide).

Based on our pharma interviews that took place from the fourth until the sixth week, we performed an intermediary analysis to assess preliminary results on collaboration models. Afterwards, collaboration models suggested by pharma companies were discussed on their merits during our hospital interviews.

In addition, we shed light RWD/RWE sources from hospitals' perspective as and we quizzed them on their understanding of the legal framework (see Appendix 3 for full hospital interview guide, see Appendix 4 for quiz results). A second intermediary analysis (including a SWOT analysis, see further) revealed interesting topics to discuss with LynxCare supervisors. In addition, we questioned them about technical opportunities of their model (see Appendix 5 for full LynxCare interview guide). Lastly, we interviewed a payors' organization associate. In our pharma interviews we were suggested to involve government payors RIZIV/INAMI within our study design. We bundled pharma companies' concerns about the governments' role within the collaboration model for RWD/RWE, with questions about MEAs and the value of RWD/RWE (see Appendix 6 for full payor interview guide).

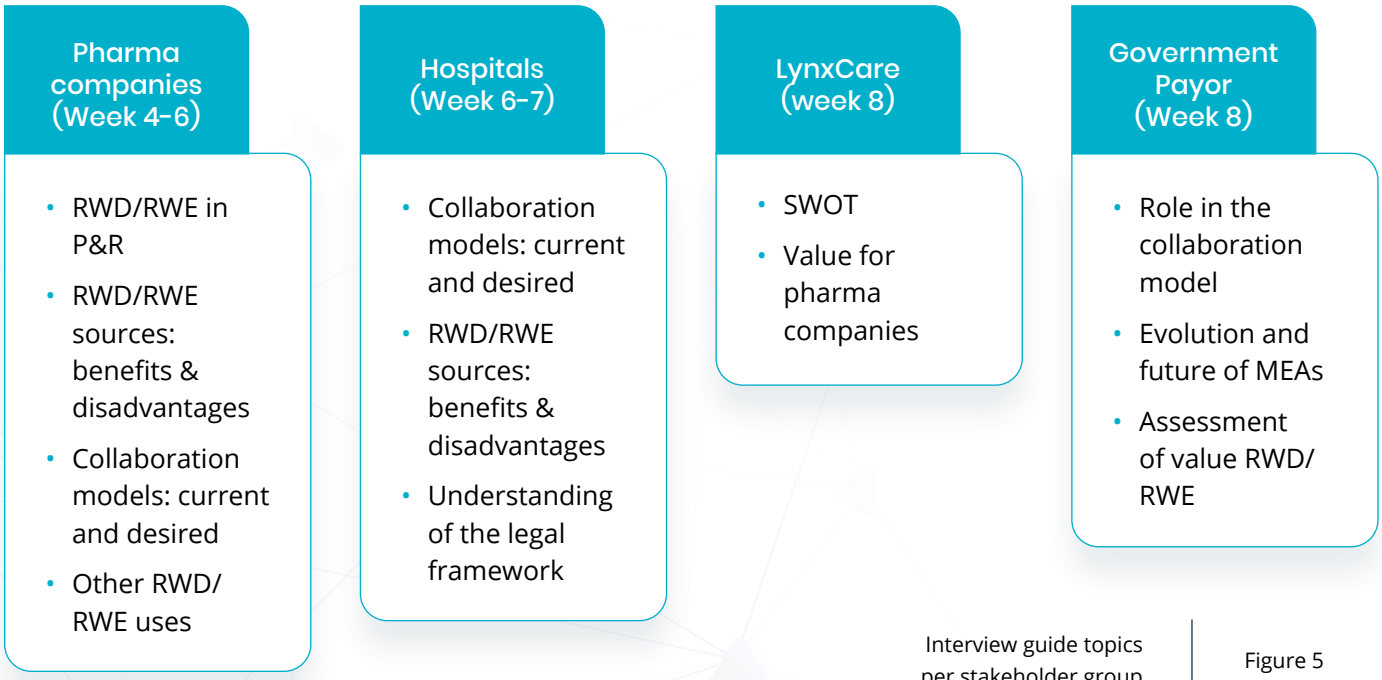


Figure 5 Interview guide topics per stakeholder group

The pharma interview guide was piloted with two RWD/RWE managers from a large pharma company. Vlerick and LynxCare supervisors gave a qualitative assessment on our interview guides for each first interview with one of our stakeholder groups (with the exception of LynxCare).

During the pharma and hospital interviews we received additional suggestions to improve our questions and topics to discuss. All feedback was taken into consideration and amendments were made to the interview guide after each interview. Therefore, our interview guide could at all times be seen as a work-in-progress rather than a finished whole (interview guides in appendixes were of the middle interview in each stakeholder group, e.g. "the average"). The initial plan was for our interviews to take 1h, however in reality interviews often took longer because of extra anecdotes, or interesting topics that were added to the discussion and were on average 1h17.

Table 2 Example of operationalizing variables: proxies for variable 'RWD/ RWE in P&R'

Theme 2: Clinical development
"How can RWD/RWE be used to support the design of RCTs?"
Theme 3: Market access
"How can RWD/RWE be used to demonstrate effectiveness during market access?"
Theme 4: Post launch
"What is the importance of RWD/RWE in the value dossier?"

3.1.2 RWD/RWE Sources Table: structuring and restructuring

We aimed to arrive at a general view of RWD/RWE sources used by pharmaceutical inductively.

As such, we started from an almost blank table in our first pharma interview (Table 3, which was based on our introductory interview with Pharma.be). The table was supplemented with RWD/RWE suggestions after each interview and showed to the next participant to give feedback on each sources' benefits and hurdles. During interviews, participants made remarks about the poor structure of our table. First, we heard that we were mixing raw data sources with digital interfaces, clinical studies etc. Second, we received the remark that RCTs are not an alternative to RWD/RWE but complementary and as such it did not make sense to structure our table as in Table 3. Third, we noticed that definitions of RWD/RWE differed between participants. Our conceptual definition reads that RWD/RWE equals all data and evidence gathered in real-life, i.e. all data collected outside of RCTs, thus our initial table structure was incorrect (i.e. 'alternatives to RWD/RWE' column could by definition contain only RCTs). As a consequence, we did extra literature review and restructured our RWD/RWE sources table (see Table 5 in Section 4.2).

Table 3 — RWD/RWE sources table draft from pilot pharma interview, which was amended heavily throughout subsequent interviews and during analysis. Final result: Table 5

RWD/RWE Sources	RWD/RWE Sources
• Registries (E.g., Cancer Registry)	• RCTs
• Patient Reported Outcomes (PROs)	• Expert reviews-
• Zorgnet Icuro	• …
• Sciensano	
• IMA-data	

Because of the inductive build-up of Table 5 and limited time during hospital interviews, we provided all participants with the opportunity to validate our final RWD/RWE sources Table (Table 5) after finishing all interviews.

3.2. Sampling, recruitment and participants

The selection of participants was based on convenience and snowball sampling. Our LynxCare supervisors and Vlerick supervisor already had an extensive network in the pharma and hospital industry and referred us to Belgian managers highly involved in the subject of RWD/RWE.

We assumed that these were the ideal candidates to interview, as managers generally have much experience and knowledge in their field.

Therefore, we concluded that a convenience sample was sufficient for our research aim and started recruiting from our supervisors' networks.

Prospective participants were recruited by email in Belgian divisions of pharma companies, Belgian hospitals, and a Belgian payors' institution between April 2020 and June 2020. Mails of invitation included an introduction to our project, i.e. an in-company project thesis for Vlerick Business School that was completed for LynxCare, as well as a brief description of our study aims and what was expected from candidates. Finally, we requested them to participate or refer us to another person within their organization that could help us.

After study participation confirmation, a video call of 1h was scheduled in Microsoft Teams/ Zoom, and participants received a temporary version of the interview guide (as this was always a work in progress), and a digital informed consent form. The informed consent form included the researchers' information, information on why the research was being carried out and what would happen. Informed consent forms were completed by participants by responding to our email with their explicit consent. In addition, participants were asked permission to record prior to their interview, while ensuring them their recording would afterwards be deleted and anonymity would be maximized.

Although participants understood that their participation did not have any direct benefits for them, we noticed an enthusiasm to be a part of our project. This enthusiasm stemmed from a collective need for a business model and faith in the opportunities offered by RWD/RWE and LynxCare to meet this need.

Study participants included multiple stakeholder groups

Pharma company RWD / market access experts (12):

We interviewed 12 Belgian pharma company experts of 7 international pharma companies.

We assumed that RWD/market access experts would have gained much experience within the pharma sector and would have sufficient expertise on RWD/RWE topics to provide us with meaningful answers. Nevertheless, in 4 of our 8 pharma interviews, our participants suggested one of their colleagues assisted them during the interview (2 market access leads, 1 payer value lead, and 1 health economist). As this would give us more nuanced and correct information, we accepted these requests and did 4 double-interviews.

Hospital experts (5):

We interviewed 5 participants from 4 large Belgian hospitals.

Our sample included 2 General Directors, 1 Health Innovation & Research Manager, and 1 Research & Training manager. The latter suggested one Valorization Manager to participate in the interview. Again, this would give us more nuanced and correct information, hence, we accepted the request.

Government payers (1):

Although it had not been our initial plan to involve the government in this study, one of our study goals was to provide a comprehensive review of all stakeholders' positions.

During our pharma interviews, multiple participants mentioned the importance of the government in a collaboration model. As such, we interview one reference within RIZIV/INAMI.

LynxCare (2):

Within LynxCare we interviewed two managers (general and financial).

3.3. Qualitative data-analysis

During our analysis, we focused on both synthesizing information that could directly answer our research questions, as well as discovering interesting patterns of information also of interest within our research framework.

As such, we combined a more closed and open approach to our data. The former could lead us to finding more generalized assessments whilst the latter would result in interesting topics for discussion.

3.3.1 Data pre-processing

All interviews were recorded and transcribed. Interview transcripts were sent to participants for control and feedback. Corrected interview responses were arranged in four Excel sheet matrixes for analysis. The Excel sheets were set up in respondence with the topics and questions from the first interview of each stakeholder group.

Interview data was de-identified, meaning that the participants' names and companies were omitted from the analysis files. We updated the document on Microsoft Teams so every researcher was able to contribute interviewing data and have access to the others' data.

3.3.2 Data-analysis transcripts

Thematic content analysis was performed to find, analyse and report patterns within the data (Bree & Gallagher, 2016). The researchers closely examined the data in the transcripts to identify common themes during the interviews. This process had already started during the iterative analysing-interviewing process, and, as such, new themes and questions were identified during interviews (and new literature review) and afterwards added to the interview guide for the next participant.

After 6 pharma interviews, we did an extensive intermediary analysis. The goal was to see which answers we heard repeatedly, which led to a more focused questioning in the last 2 interviews.

3.3.3 Table 5: RWD/RWE Sources

RWD/RWE sources were supplemented to Table 5 after each pharma interview, as well as their benefits and hurdles.

As such, each participant could build on the knowledge of the previous interviews and make corrections when necessary. We entered definitions or brief explanations of each RWD/RWE source based on information that was mentioned during the interviews, integrated with extra RWD/RWE source information found online (i.e., government websites).

The RWD/RWE Sources Table (Table 5) was largely created and completed based on primary data from our interviews (i.e., explicit requests to complete the table, as well as, RWD/RWE source related information that was implicitly mentioned throughout the interviews). However, as we got many remarks (cf. Section 3.1.2) we restructured Table 5 based on literature review and internet searches. We compared what was said in pharma and hospital interviews and came to general conclusions as well as contradictions.

The RWD/RWE Sources table (Table 5) was sent to all of our 17 pharma and hospital participants, of whom 6 gave feedback (4 pharma participants; 2 hospital participants).

3.3.4 LynxCare SWOT

To assess the value of LynxCare's business model within the pharmaceutical industry we performed a SWOT.

A SWOT analysis is a strategic planning technique used to evaluate how closely a business is aligned with strategic roadmaps and solutions. We started by identifying LynxCare's strengths, weakness, opportunities and threats according to the following scheme (Figure 6). Strengths and weaknesses were assessed from LynxCare's perspective, while opportunities and threats were assessed from the perspectives of pharmaceutical companies and hospitals.

After identifying LynxCare's strengths, weaknesses, opportunities and threats, these four elements were compartmentalized into four categories: Strength-opportunity strategies, strength-threats strategies, weakness-opportunity strategies, and weakness-threats strategies (Following the scheme presented in Figure 7). Our strategic integration of the SWOT as well as practical strategic recommendations can be found in our discussion (Section 5.2.1).

We considered other strategic tools such as 5 forces analysis, business model canvas and internal value chain analysis but concluded that it was too soon for these methods.

These can be applied at a later stage, while the purpose of this study was an exploratory assessment of the value of LynxCare in the pharmaceutical industry.

Figure 6 SWOT step one: strengths, weaknesses, opportunities and threats identification

		External	
		Opportunities	**Threats**
Internal	**Strengths**	**Strength-Opportunity strategies** Which of LynxCare's strengths can be used to maximize the identified opportunities?	**Strength-Threats strategies** How can LynxCare use its strengths to minimize the identified threats?
	Weaknesses	**Weakness-Opportunity** What actions can LynxCare take to minimize its weaknesses using the identified opportunities?	**Weakness-Threats strategies** How can LynxCare minimize its weaknesses to avoid identified threats?

Figure 7 SWOT step two: subcategorizing strengths, weaknesses, opportunities and threats in internal and external subcategories

3.3.5 Collaboration models pharma-hospital

One of the objectives of our interviews was to come to a collaboration model between pharma and hospital sector.

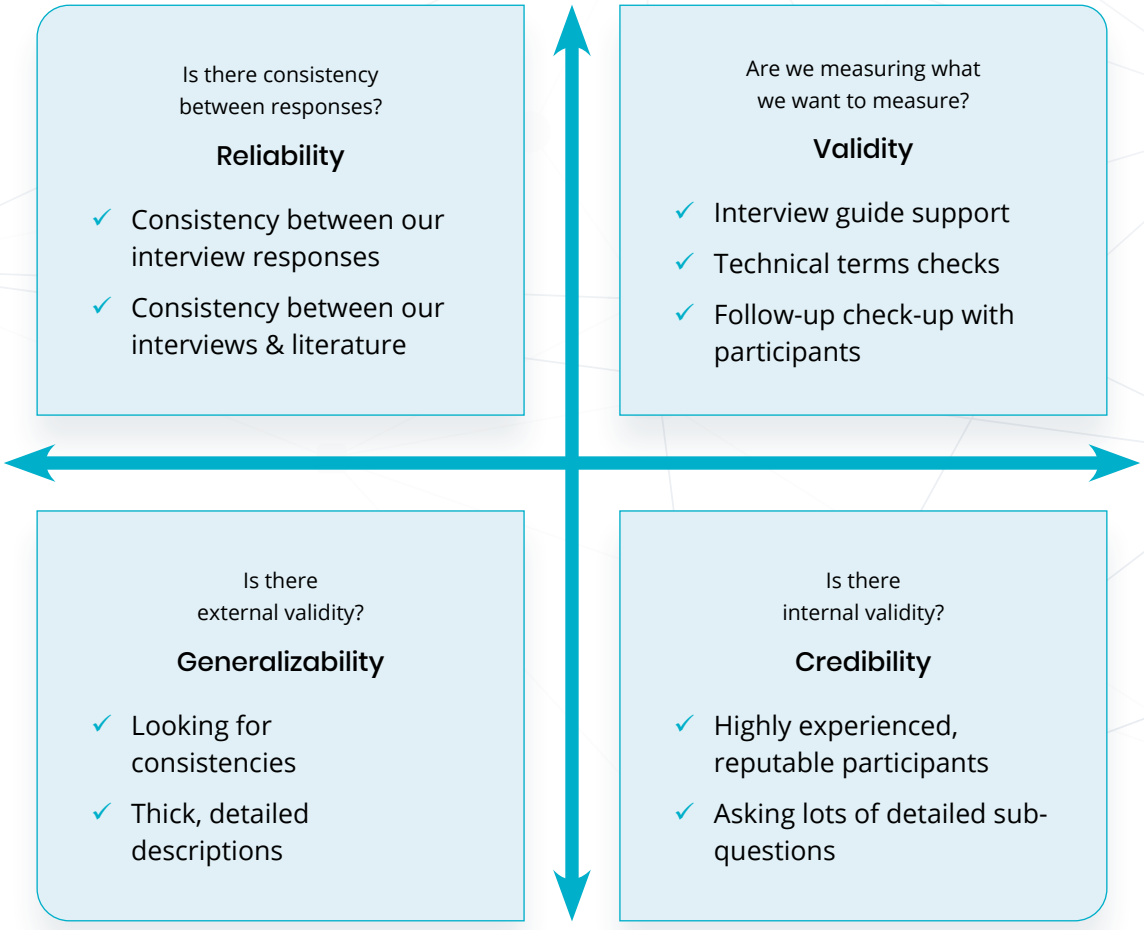
We first interviewed pharma professionals about current collaboration alternatives, their frustrations, and a desired collaboration model. Afterwards we interviewed hospitals to check whether such desired collaboration model would be practically and ethically manageable.

Ultimately, we analyzed collaboration models from both sides and came to an integrated manageable suggestion for LynxCare in the discussion (cf. Section 5.4.1).

3.4. Validation checks

Figure 8

Validation checks based on reliability, generalization, validity and credibility



1. Reliability

Reliability questions whether there is consistency between responses. This does not mean that every participant should give the exact same answer to each question, however, there must be some level of common ground in responses. Consistency is guaranteed by two measurements we have taken: we compared participants' responses to one another, and we compared participants' responses to the literature. In cases of inconsistencies we zoomed in on these issues in consequent interviews to resolve them.

2. Generalizability

Generalizability is classically no top priority in a qualitative design with a small sample. However, inferred theory building should always be a research objective. Therefore, we will attempt to generalize based on information that is very consistent between literature and interview data, or that is provided with solid, detailed descriptions in interviews. For more peculiar but interesting responses, we must provide rich and thick descriptions in our results so that the reader is aware of contexts where the knowledge might be applicable.

3. Validity

✔

We validated our measurements in order to guarantee that we were indeed measuring what we wanted to measure.

First, to design our interview guide we had support from highly knowledgeable people: a PhD expert at pharma.be (for our pharma interview guide), our LynxCare and Vlerick supervisors, an another Vlerick professor whose specialized in research and the pharmacy industry, and during a pilot interview with RWD/RWE managers in a large pharmaceutical company. Second, our interview guide included an introduction with a list of definitions of terms that would be discussed as we made use of many technical terms (e.g., RWD/RWE, value dossier). During the interview, common understanding of these terms was also tested by giving a short description of what was meant by each term so that we were sure we were measuring what we wanted to measure. Third, we sent each participant a transcript, as well as some key take-aways we had during the interview and requested for feedback on our interpretations. Fourth, a draft of our paper, including our study results, was validated by two pharma participants as well as an acquaintance at Pharma.be; the RWD/RWE sources table (cf. Table 5) was validated by 4 pharma participants and 2 hospital participants (6 in total).

4. Credibility

In pharmaceutical companies, we interviewed managers highly involved in the subject of RWE/RWD: RWE managers, market access mangers, a health economist, a solution specialist, and a payer value lead. We assumed that these were the ideal candidates to interview, as managers generally have much experience and knowledge in their field. In hospitals, we interviewed 2 General Directors, 1 Research & Training manager, 1 Valorization Manager, and 1 Innovation & Research manager. In LynxCare, we interviewed a founder and board member who knows the business model and strategy very well. In the payors' organization, we interviewed the pharmaceutical medicine's market access coordinator who.

Therefore, we concluded that, although we were using a convenience sample, we were in touch with the most credible mix of people that was available for our research aim.

4. Results

4.1. Assess the value of RWD/RWE throughout the life cycle of a medicine

In the following paragraph, RWD/RWE uses discussed by pharma participants have been categorized in P&R (4.1.1) vs. other use-cases (4.4.2). A summary of use-cases is given in Table 4.

	Pre-clinical development	Clinical development	Market launch	Post-launch
P&R (4.4.1)		• Positioning • Calculating standard of care	**Value dossier:** • (effectiveness & side effects) • Disease burden and budget impact	**MEA:** • Clinical uncertainties (effectiveness & side effects) • Budgetary uncertainties • Pay-for-performance **Class revisions:** • cf. value dossier
Other use-cases (4.4.2)	• Identifying areas of clinical need	• RCT design • RCT recruitment • Early dialogue • Measuring current patient flows		• Logistic and operational • Marketing processes

Table 4 Summary of RWD/RWE use-cases through the life cycle of a drug for pharma companies

4.1.1 Drug pricing & reimbursement

RWD/RWE uses for pricing & reimbursement (P&R) during clinical development, market launch, and post market phase:

1) RWD/RWE uses for P&R during clinical development

Positioning to narrow down the scope of the target group: Early thinking about positioning; "in which subpopulations will we receive reimbursement for our drug?". Narrowing down the scope of the population based on RWD/RWE, because in a broad population pharma companies assume that they will not receive reimbursement. Value of a drug increases when it has more favorable results and by targeting subpopulations a drug can be tailored based on their needs and lead to the best results. For instance, a pharma company could narrow down its target population for a new epilepsy treatment to the most severe cases of epilepsy, involve only that type of patients in RCTs and consequently fully tailor the drug treatment to the subpopulation. As a result, RCTs will lead to high quality results in a subpopulation and lead to full reimbursement at an acceptable price level.

Calculating standard of care: In a cost-effectiveness model the price of the current standard of care can be used to determine own drug pricing. Indeed, a cost-effectiveness analysis looks at how effective the current product is in relation to its price. Then based on the relative benefit of pharma's new product, an appropriate price level can be determined.

2) RWD/ RWE uses for P&R during market access

During market access, RWD/RWE is mainly used within the framework of value dossiers submitted toward the EMA and national submissions for P&R with the payors. The following use-cases are most prominent during this phase:

Assessing effectiveness and side effects: Sometimes RWD/RWE on a drug's effectiveness and side effects are available during the initial reimbursement request, from competitors or from earlier launches abroad (e.g., Belgium is often a late launcher). RWD/RWE on effectiveness and side effects provide more information about a drug's real-world value and are therefore taken into consideration when giving market authorization and/or negotiating P&R. if this is already available during market access, pharma companies include it in their value dossier and P&R submissions. However, often RWD/RWE on effectiveness is not available yet during the initial reimbursement request because it involves a completely new drug.

Role of RWD/RWE increases in the value dossier when limited number of patients are available. RWD/RWE can then help to assess the effectiveness/value/added value. Indeed, effectiveness can then complement the limited RCT results on efficacy.

2) RWD/ RWE uses for P&R during market access

Estimating disease burden and budget impact: To estimate disease burden and budget impact, RWD/RWE on incidence and prevalence of a condition (e.g., data from Belgian Cancer Registry) could be used. The budget impact analysis can assess the difference between a world in which a patient has access to the new treatment versus a world in which a patient does not have access to the new treatment. The budget impact of that decision for society as a whole is being calculated.

Limitations are preventing pharmaceutical companies from finishing such estimations during market access: 1) Collecting RWD/ RWE takes time, involves loads of protocol writing and internal procedures within pharma companies. E.g., after market authorization it is legally possible to perform a P4 study, however, this takes significant time and resources to design and execute. Often there is too little time to organize RWD/RWE collection before reimbursement submission; 2) IMA-data and some registries (e.g., Sciensano registries) used to obtain RWD/RWE for estimating disease burden and budget impact can only be accessed within a legal framework (e.g., MEAs), making it impossible to collect data before market launch; 3) There is an inconsistency in what the authorities ask and what data access is granted to provide the answers they require.

3) RWD/ RWE uses for P&R during post-launch

Participants indicated that RWD/RWE use is currently most prominent during the post-launch phase, within the framework of MEAs. It is a rather new phenomenon to replace previous (non-contractual) individual price revisions.

The rationale behind setting up MEAs is to allow companies to still bring their products to the market, even though there might be clinical or budgetary uncertainties at the moment of the reimbursement decision. The confidential nature of the agreement allows the companies to provide a discount, without impacting reimbursement decisions in other EU countries.

MEAs are very important for the pharmaceutical industry because without them, many innovative medicines wouldn't be able to come to the market in Belgium. MEAs can be proposed by the Commission of Reimbursement of Medicines (CRM; Dutch: CTG) when there are clinical and/or budgetary uncertainties, or for pay-for-performance contracts.

Clinical uncertainties mainly involve answering the following question: "can patient clinical outcomes retrieved from RCTs be translated to real-life healthcare practice?" Examples of patient outcome uncertainties: effectiveness, side effects. But clinical uncertainty can also be related to real-life usage of drug: time in-between incidence and drug intake, duration of treatment, etc.

Budgetary uncertainties, on the other hand, include patient population size, duration of treatment, number of responders to the treatment (very important parameter in a heath-outcomes based contract, wherein you only get reimbursement for the patients that respond to the treatment). Pharmaceutical companies are then often required to collect RWD/RWE to support future P&R decisions.

3) RWD/ RWE uses for P&R during post-launch

Pay-for-performance: An upcoming, interesting subtype of MEA is pay-for-performance contracts, which are outcome-based P&R models (cf. Section 2.2.2).

In a pay-for-performance contract pharmaceutical companies are reimbursed based on individual health outcomes on the level of the indication or the patient. Most prominent, and interesting to payors, are patient-based pay-for-performance contracts: if a drug has a significant effect, they reimburse; if it does not, they don't.

Idealistically they praise such "simple" concept; however, there are some practical limitations to its simplicity:

1) Incompleteness of registries; for pay-for-performance to become operational, high quality clinical and outcomes data is indispensable. For many indications, current RWD/RWE solutions fail to provide the required completeness of data.

2) How does one decide whether a drug has a significant effect? E.g., in oncology one could propose to reimburse when a treatment has regression – reduction of a tumor. However, putting such oncological theory into practice is challenging because how to assess the volume and frequency of a reduction.

3) Inefficiencies of cash flows. When a treatment does not work, and, thus, payors do not pay for performance, at that moment the bills have already been paid by hospitals to pharmaceutical companies. This implies an administrative burden for hospitals to receive reimbursements from pharma companies. As a consequence, hospitals are not enthusiastic about the idea.

Another, less prominent, application of RWD/RWE than MEAs are for class revisions; when drugs have been launched on the market for some time, but the commission of ministers decide to revise the reimbursement criteria and drug prices for an entire class of products. Example of product classes are antibiotics, hemophilia products, or all diabetes medication. Within a class many new drugs might be launched throughout the years causing an abundance of regulations. In addition, medical progress, and scientific progress in general, give rise to a need for harmonization of product classes. In Belgium, one class a time is updated every 1-2 years and these revisions are imposed on pharmaceutical companies (i.e. collaboration is mandatory). During class revisions, pharma companies have to resubmit their value dossier and include all RWD/RWE that is available on the medicine (e.g., effectiveness, prevalence, incidence). Class revisions can lead to decreases in list prices.

Ultimately, the role of RWD/RWE in the pricing and reimbursement remains limited until the post-launch phase. Participants agreed that RWD/RWE need is currently the largest during the post-market phase as it is required within legal frameworks (i.e., MEAs) to solve two types of uncertainties: budgetary uncertainties or clinical uncertainties.

Uncertainties are most prominent in three types of drugs (and often one drug is a combination of them): 1) innovative drugs, 2) expensive drugs, and 3) orphan drugs. In innovative drugs this is the case because there is a new molecule for which its clinical value needs to be explored in real-world settings. Orphan drugs also need to be explored by collecting RWD/RWE as they often launch earlier in areas of high unmet need through accelerated registration and reimbursement procedures, based on early phase (and

3) RWD/ RWE uses for P&R during post-launch

sometimes single arm) clinical trials. Results of Phase 3 trials are often not known yet during the initial reimbursement procedure. Finally, expensive drugs have a large budget-impact and, therefore, payers demand RWD/RWE on e.g., number of patients, to ensure clarification of budgetary uncertainties. Thus, for such drug types an extensive RWD/RWE collection could be required and MEAs are increasingly becoming systematic procedures: "When there are large uncertainties, because companies want accelerated access or because certain medical conditions have limitations, MEAs are indispensable. MEAs allow the government to deal with uncertainties while keeping budget-impact in check [Pharma respondent F]."

Keeping budget-impact in check is indeed very important to payors and authorities, as the Belgian healthcare budget is under enormous pressure. As a consequence, MEAs are primarily perceived by most pharma companies to lead to budget discussions rather than price discussions, although both are interconnected (Figure 9). Budget discussions include reaching an agreement on a maximum budget to be spent by payors on a product/product class for a given number of patients. In that situation, prevalence has a larger impact on budget than on price. However, indirectly prevalence also impacts price, as Budget = Price (Net Price) x #Patients. Thus, a lower maximum budget leads to a lower price per package.

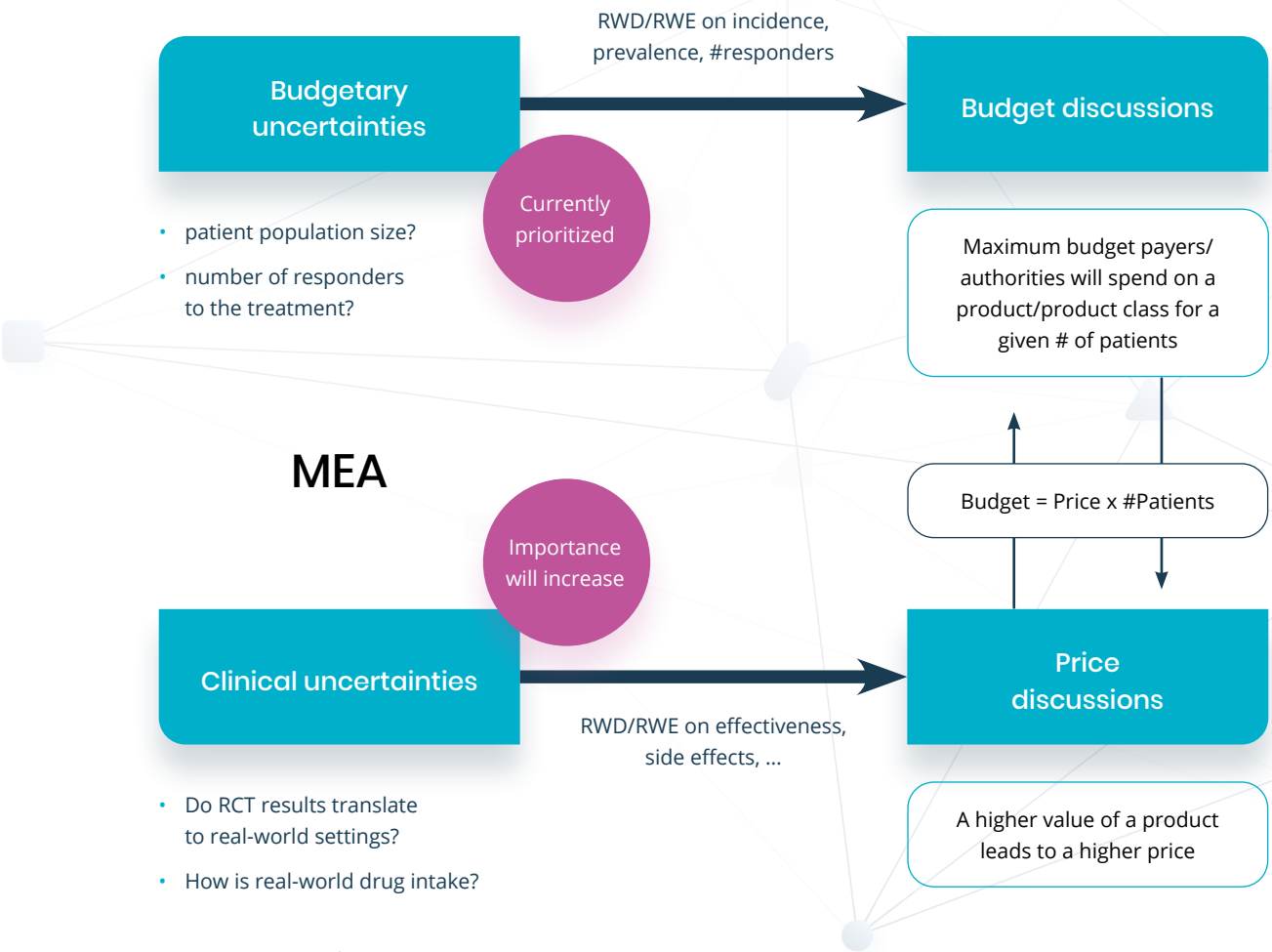


Figure 9 Budgetary and clinical uncertainties lead to budget and price discussions in an MEA

3) RWD/ RWE uses for P&R during post-launch

An important nuance to be made here is the difference between list price and net price per package. The list price is agreed upon during the initial reimbursement procedure with the CRM and in general does not change afterwards. In the framework of an MEA, however, clinical and budgetary uncertainties (temporarily) lead to lower reimbursements than the full list price per package. This discounted price is called the net price. The difference between the list price and the net price are the agreed upon confidential discounts. Discounts are required from pharma companies by payors and might in some cases decrease when clinical or budgetary uncertainties are resolved. Some pharma companies believe MEAs are used by payors to enforce discounts in confidential agreements (i.e., "behind the scenes") on the official list price:

[Pharma respondent C]: "Ultimately, RIZIV (i.e., the payors) will pay less than what is stated on a package. And why is this difference important between list price and net price? If we would put the discounted price on the package, our headquarters would never allow us to launch in Belgium. We are forced by the authorities to set a low confidential net price in order to guarantee market access to the drug".

The outcome of MEAs can be to move into definite contracts and discounts can ultimately be (partly) canceled by resolving uncertainties with RWD/ RWE. Usually, discounts are not canceled out however, and instead pharmaceutical companies still have a to give a significant discount to be able to receive definitive reimbursement. In exceptional cases the discount might not be as severe as in the contract, but usually it is. One of our participants testified that their pharma company had a large project for resolving clinical uncertainties with the payors. Thanks to RWD/RWE, they succeeded to get of their managed entry agreement and move into a definite reimbursement contract. Not all participants have been this lucky, and some indicated that the discounts requested by the payer in Belgium are increasing over time, which might lead to unsustainable situations in the long term. Companies might not be able to provide the requested discounts anymore and lead to negative reimbursement decisions, leading to no patient access in Belgium.

Even though RWD/RWE-based budget discussions are currently prioritized in MEAs, this does not imply that the value of RWD/RWE on clinical variables in price discussions is negligible. A high clinical value (i.e. high effectiveness and low side effects) justifies a higher price. High value is still mainly determined by RCT results but increasingly RWD/RWE on e.g., effectiveness rather than stand-alone efficacy impacts price decisions. By solving clinical uncertainties based on RWD/RWE, pharma companies can limit, to some extent, discounts given on their list price. As a consequence, high quality RWD/RWE on effectiveness leads to a more realistic drug value as it reflects the real-world effectiveness. Collecting quality RWD/RWE on clinical variables should therefore be seen as a means to on the one hand strengthen a pharma company's negotiation power to maintain a correct reimbursement level rather; so that drugs can be launched in the market to help patients in need.

In conclusion, pharma experts have been experiencing an increasing impact of RWD/ RWE in P&R decisions, mainly to feed budget discussions. To assess clinical value and consequently an appropriate price level, RCTs are still considered the leading factor. They assume that the payors will always prioritize RCT results and that RWD/RWE could never replace RCTs. RWD/RWE usually consider much lower patient numbers than RCTs, proving less robustly a drug's value to the payor.

4.1.2 Other RWD/RWE uses in the lifecycle

In addition to P&R use-cases, participants noted that RWD/RWE has many important use-cases to them outside of direct P&R context (indirectly they might be related). Benefits of RWD/RWE start during pre-clinical development.

1) RWD/RWE use-cases (non-P&R) during pre-clinical development

During pre-clinical development RWD/RWE is used by pharmaceutical companies to identify clinical needs. They try to asses in which subpopulations (e.g., epilepsy) is there a "need" for a therapy. Consequently, they think about how they can meet an unmet need: "what drug can we design that meets this population's needs?" Choosing for unsaturated markets is a strategic or ethical choice by pharmaceutical companies.

2) RWD/RWE use-cases (non-P&R) during clinical development

Developing clinical guidelines – improving design of RCTs (P1/P2/P3): RWD/RWE on daily practices (e.g., claims databases) can help in developing clinical guidelines, making RCT's design more pragmatic:

A. RWD/RWE show how patients are currently treated to make research design as 'real' as possible. E.g., Learning how long it currently takes for patients to heal as this has implications for the length of your study.

B. Assessing feasibility of a study in a center; are the right resources present in a center to do a certain study design? e.g. based on RWD/RWE of earlier studies.

Supporting early dialogue with authorities: related to the previous point, RWD/RWE can help in improvement of RCT design during early dialogue.

In this phase, pharmaceutical companies are considering trial outcomes that authorities find important and designing RCTs in such a way that will answer their questions. RWD/RWE can lead negotiations about design of RCTs. For instance, RWD/RWE can inform on the number of patients available to recruit for an RCT. When few patients are available, pharma companies can present the RWD/RWE on patients available for recruitment to the authorities and propose an alternative study design to collect the required data.

2) RWD/RWE use-cases (non-P&R) during clinical development

A second use during early dialogue is an early consideration of RWD/RWE collection protocol once a drug is launched in the market. E.g., assessing which parameters that would be important to follow up due to uncertainties (survival rates, neurological research). Early RWD/RWE protocol design leads to an accelerated RWD/RWE collection during post-launch, which facilitates and accelerates P&R discussions and ultimately, patients in need get quicker access to new treatments.

Early dialogue with payors is still unconventional in Belgium. Nevertheless, pilot projects are taking place in Belgium (Uneta, MOKA group), centered around orphan drugs. European initiatives for early dialogues are also increasing, in which different stakeholders are involved by EMA: national payors, patient organizations, clinical experts, and pharmaceutical companies. RWD/RWE was always put on the table during early dialogues to assess what was already known about a drug, and what would be required to collect once a drug launches in the market. E.g., which parameters that would be important to follow up (survival rates, neurological research…). In addition, pharmaceutical companies sometimes asked the payors for information on the standard of care, however, payors could not meet this need due to a lack of RWD/RWE. If data would be available easier from hospital databases, unions of oncologists, and other data sources, it would be easier for the payors to answer to this need. However, when payors request information on the standard of care from pharmaceutical companies, they did their homework properly and were able to assess the standard of care based on interviews with clinical experts, opinion leaders or from clinical guidelines. This has never been an issue.

Recruitment for RCTs (P1/P2/P3): It is always difficult finding the right patients to recruit for RCT trials. An RWD/RWE-based platform to find the right patients/physicians would be ideal, to locate the right people with for instance light, moderate, severe renal insufficiency.

Measuring patient flows: E.g., measuring how many patients would be eligible for treatment with a certain drug with RWD/RWE on incidence and prevalence.

3) RWD/RWE use-cases (non-P&R) during post-launch

Logistic and operational: "RWD/RWE are important to plan stock orders. With COVID-19 the importance of maintaining sufficient stock became very clear: face masks, testing stock etc. [pharma respondent E]"

Marketing processes: RWD/RWE on e.g., sales data, number of patients, motivations for drug usage, patients characteristics, epidemiology data and RWE on e.g., insights on population level acquired through market research, are used to find the right patients in the right life stage eligible for a particular treatment. Period X vs. Period Y in the life stage of patients might make a large difference. E.g., chemotherapy fit for a new treatment in period X but not in period Y in the same patient.

4.2. RWD/RWE sources currently used by pharmaceutical companies

Which RWD/RWE sources pharma companies prefer depends on the information that needs to be obtained, for instance to answer remaining uncertainties in an MEA

All RWD/RWE sources listed in Table 5 have been found to have their particular uses, benefits and hurdles from the perspectives of both pharma companies and hospitals. Every RWD/RWE source has its importance and would otherwise not have been mentioned by our participants. Nonetheless, this does not imply that every source is equally as essential. In what follows, we discuss the RWD/RWE sources with the highest value.

The IMA-database is very useful because it offers much information, can be used for incidence, prevalence, and consumption data of medication. The latter is the most important reason to use IMA data in MEAs: pharmaceutical companies can track via IMA data how many patients used their product, in which indication (if more indications are reimbursed) and what the treatment duration is. A first limitation of IMA-data is the limited use of the database, as information can only be obtained under strict circumstances (e.g. MEAs). Second, IMA-data allows limited diagnoses because it lacks clinical outcome data. To reach diagnoses, IMA-data must be linked with other databases e.g., healthdata.be, PRO(M)s. Third, IMA-data must be requested one year before the analysis to allow IMA to plan for the analysis resource-wise; Moreover, these are not real-time data (i.e. there is a delay on the data of about 7 months).

In general, for hospital data, pharma experts prefer to use standardized industry reports published by a third party rather than doing their own RWD/RWE collection. Standardized reports include information from multiple hospitals that has been collected, bundled, and aggregated. This is labor intensive and time-consuming work that pharma companies prefer to outsource. However, often such reports do not include specialized, in-depth information, which requires pharmaceutical companies to perform their own clinical research or to set up a collaboration with a CRO for clinical research (see further, Section 4.3.1(2). Moreover, standardized reports often contain findings from abroad (non-Belgian data) which limits their representativity for Belgian populations. While this used to be no problem for authorities, nowadays they increasingly insist on Belgian RWD/RWE, causing standardized report's use to slowly decrease. Lastly, data in such reports are often collected under dubious circumstances (e.g. contacting physicians under the radar without any quality checks on the data), raising questions about its scientific value.

Expert reviews/opinions are also often used, but often in a more practical form than what we found during our literature review, i.e. scientific journals for expert reviews. In practice pharma RWD managers directly contact expert

doctors and ask them questions such as "What % of your patients do you believe use medicine X?". Expert reviews then include a quick, top of mind insight of a single doctor into patient care trajectories (i.e. general sequence of events and turning points during a treatment). This allows pharma companies to learn about patient flows and which type of research and diagnoses to perform on patients. The disadvantage is a limited validity of data, it is really an opinion without scientific evidence. One should never base important decisions on expert reviews/opinions. When expert reviews are compared with physicians' real-world behavior, it becomes clear that there's a discrepancy between what they say and what they do.

Hospital experts assumed the EHR (Electronic Health Record) to be the most resourceful, granular data source for pharma companies. When we asked pharma participants to complete Table 5 with RWD/RWE sources, not one participant explicitly mentioned EHR.

This does not imply that they were unfamiliar with the EHR, as it was continuously mentioned during other questions from our interview guide. An explanation is that pharmaceutical companies cannot directly access the EHR and consequently, do not consider it as a usable RWD/RWE source. Instead, they must use secondary extracts form the EHR to access clinical data and outcome data. Pharma companies indicated that there is indeed a large need for clinical data on incidence, prevalence, drug use, number of patients, patient characteristics, and even more importantly, outcome data. Outcome data on death rates, overall survival rates, progression etc. are very much desired, however, difficult to access. Those parameters are currently assessed by pharma companies using clinical registries and interfaces (e.g., healthdata.be, CIVARS, Death Registry) but those sources obviously impose several hurdles. Also, MHD and IMA-data provide extracts from the EHR but cannot offer an equal level of granularity. Ideally, pharma companies would be granted access to look into anonymized EHRs and get insights into EMRs and PROMs/PREMs.

Hospital4: "if pharma companies would get the opportunity to launch her queries into all of the EHR s in the country, they would be willing to pay an immense amount of money for that privilege".

Nevertheless, the EHR cannot directly be accessed by pharma companies as this is prohibited by law. Pharma companies can get access to EHR data through a third party, such as a CRO.

Many of the alternatives have a significant administrative burden for hospitals: registries, MZG-data, IMA-data, P4 studies. They must each time ensure anonymization and aggregation of all data as a result of GDPR rules.

These rules state that pharmaceutical companies can only access EHR raw data under supervision of hospitals, which prohibits pharmaceutical companies to perform analyses on the data. Hospitals have to respect these rules but are frustrated by all of the additional administrative burdens they are put up with.

A remarkable observation we have made during our interviews is that pharmaceutical companies were very well aware of the different RWD/RWE sources. When asked about it, pharma participants gave extensive descriptions, use-cases, benefits and hurdles. In contrast, during hospital interviews participants admitted lacking sufficient knowledge to provide us with such detailed answers. They recommended we would speak with DPO's, data nurses, data coordinators etc. within their hospital that were able to provide us with more information. We found this striking as we interviewed decision makers in hospitals, implying that RWD/RWE sources and optimization are not placed on top of their agenda.

This is problematic, as they make the decisions about it.

In addition, a similar observation was made during our interview with the governmental payor respondent. During this interview, we did not show Table 5 with RWD/RWE sources, however, we asked our participant whether he was well aware of the possibilities of each source. He, too, admitted that he was not up to date on which sources provided which type of information. Again, we found this striking since he was responsible to make RWD/RWE collection requirements in MEAs.

RWD/RWE structure in different countries: The RWD/RWE sources found in Table 5 are typically Belgian and RWD/RWE infrastructures differ between countries. Some countries, e.g. Finland, Norway, Denmark, Germany, adopt an infrastructure that is considered to be ahead of Belgium's (e.g. public RWD/RWE access). Adoption in Belgium is moving slower as each stakeholder (group) is progressing separately and RWD/RWE collection is seen as merely a responsibility of the industry. Instead, participants believe different stakeholders must communicate, and each stakeholder needs to understand broad application domains and benefits of RWD/RWE.

RWD/RWE Source	Benefits	
	Pharma perspective	Hospital perspective
Hospital data		
Electronic Patient Dossier data (EHR data) An EHR bundles all medical records of a patient on a central digital platform. Medical records include treatments, drug usage, reference letters, study results and radiology images.	1. Big potential to gain better insights for pharmaceutical new drug developments: for patients' identification, optimizing study designs, deciding study population size, reduce clinical uncertainty, reduce budget uncertainty. 2. Insights into patient diagnoses, clinical pathways, drug dosages 3. High naturalistic validity	1. Is the most granular, rich form of hospital data. 2. Contains clinical outcome data 3. EHR offer extra tab spaces where full description of patient and symptoms can be added. 4. Hospitals management, ethical committee and DPOs are present to protect and maintain control over data
Minimal Hospital data (MHD) (Minimale ZiekenhuisGegegens/ MZG-data) Legally required registrations of hospital data. Contains two types of data: 1. Clinical data (summaries from EHR data) 2. Claims data (e.g., honorarium)	1. Representative data (99% of the population)	1. Representative data (99% of the population)
Claims data		
InterMutualistic Agency data (IMA-data) IMA collects, consolidates and aggregates claims data from 7 separate Belgian health insurance agencies ("mutualistic agencies"). Data include information on all transactions made within in the healthcare industry (e.g., billing information) as well as demographic information per individual. They integrate billing information from hospitals, pharmacists, GPs etc. IMA owns different databases: healthcare, medicines (i.e. Farmanet), and population characteristics.	1. Consumption data of drugs used within hospitals and public pharmacies (pharmaceutical companies can track via IMA-data how many patients used their product, in which indication, and duration of treatment) 2. Representative data (99% of the population) 3. Affordable	

Table 5 RWD/RWE sources mentioned by pharma and hospital participants during interviews with their benefits and hurdles from the perspective of both pharma vs. hospital side

RWD/RWE Source	Benefits	
	Pharma perspective	Hospital perspective
Hospital data		
Electronic Patient Dossier data (EHR data) An EHR bundles all medical records of a patient on a central digital platform. Medical records include treatments, drug usage, reference letters, study results and radiology images.	1. Pharma cannot access directly, can only access raw data under supervision of hospitals or through processed data delivered by third parties 2. Delays in providing EHR data for research purposes 3. Limitations to EHR data: missing data points, quality depends on willingness of physicians to input data (correctly). E.g. in psychiatry correct data input has been found to be an issue	4. No workflow in place yet for EHR data exchange with third parties 1. Cannot give pharma companies direct access to raw EHR data 2. Some hospitals are protective over third party usage and third-party data interpretations
Minimal Hospital data (MHD) (Minimale ZiekenhuisGegegens/ MZG-data) Legally required registrations of hospital data. Contains two types of data: 1. Clinical data (summaries from EHR data) 2. Claims data (e.g., honorarium)	1. Delay on data (1-2 years) 2. Limited granularity/detail 3. Might not always reflect clinical reality	1. Delay on data because EHR needs to be transferred into MHD 2. EHR granularity/detail is lost due to summarizations 3. Data delay leads to biased hospital budget estimates 4. Does not help to perform accurate diagnosis.
Claims data		
InterMutualistic Agency data (IMA-data) IMA collects, consolidates and aggregates claims data from 7 separate Belgian health insurance agencies ("mutualistic agencies"). Data include information on all transactions made within in the healthcare industry (e.g., billing information) as well as demographic information per individual. They integrate billing information from hospitals, pharmacists, GPs etc. IMA owns different databases: healthcare, medicines (i.e. Farmanet), and population characteristics.	1. No clinical data 2. Limited diagnostic data (sometimes contains information on indication/ diagnose drug is prescribed for) 3. Only accessible in post-market 4. Only accessible for a running dossier, when RIZIV specifically requires information 5. Lengthy request process 6. Big delay on data (6-9 months)	1. EHR granularity/detail is lost due to summarizations 2. Cannot be linked with external data (e.g., when patients are dismissed from hospital and continue treatment with regular pharmacists) 3. Labour intense process

RWD/RWE Source	Benefits	
	Pharma perspective	Hospital perspective
Clinical registries/ interfaces		
Belgian Cancer Registry Registry contains summaries of data collections on novel cancer diagnoses in Belgium and their follow-up. In addition to their generic reports, more specific cancer data requests can be made by third parties.	1. Representative data (99% of the population) 2. Potential to be rich data source (e.g., IKNL in the Netherlands) 3. Potential for longitudinal data series 4. Can be used for budget impact (#patients)	
Tool for Administrative Reimbursement Drug Information Sharing (TARDIS) An online application/ interface used by physicians to enter patient data related to certain pathologies, in exchange for individual drug reimbursement authorizations.	1. Representative data (99% of the population) 2. Potential to be rich data source 3. Potential for longitudinal data series 4. Comprehensive outcome data	1. High interest in reimbursement studies with RWD, because they can offer insights and profit for finance department in hospital settings
Claims data		
CIVARS An online application/ interface used by physicians to enter patient data related to certain pathologies, in exchange for individual drug reimbursement authorizations for Chapter IV drugs (for in hospitals and retail pharmacies)	1. Defining patient population (e.g., information on number of treatment approvals for patients with certain predefined criteria)	

RWD/RWE Source	Benefits	
	Pharma perspective	Hospital perspective
Clinical registries/ interfaces		
Belgian Cancer Registry Registry contains summaries of data collections on novel cancer diagnoses in Belgium and their follow-up. In addition to their generic reports, more specific cancer data requests can be made by third parties.	1. Cancer Registry does not answer specific data requests from pharma companies. Consequently, pharma dependency on willingness of physicians to request access to register. 2. Administrative burden on physicians to insert high quality data (e.g., no missing data points), and on other hand to request access for pharma companies 3. Big delay on data (2 years) 4. Important measurements are missing (e.g., mutations)	1. Administrative burden to fill in the forms (double data entry next to the EHR)
Tool for Administrative Reimbursement Drug Information Sharing (TARDIS) An online application/ interface used by physicians to enter patient data related to certain pathologies, in exchange for individual drug reimbursement authorizations.	1. Dependent on willingness of physicians for to give access, provide high data quality (e.g., no missing data points) 2. Administrative burden on physicians 3. Big delay on data (2 years) 4. Important measurements are missing (e.g., mutations) 5. To date only applied in rheumatology	1. Administrative burden to fill in the forms (double data entry next to the EHR)
Claims data		
CIVARS An online application/ interface used by physicians to enter patient data related to certain pathologies, in exchange for individual drug reimbursement authorizations for Chapter IV drugs (for in hospitals and retail pharmacies).	1. No certainty on number of patients that have effectively been treated (only approvals) 2. No information on patients registered with predefined criteria without treatment approval 3. Only accessible through IMA or RIZIV 4. Limited to Chapter IV drugs	1. Administrative burden to fill in the forms (double data entry next to the EHR)

RWD/RWE Source	Benefits	
	Pharma perspective	Hospital perspective
Clinical registries/ interfaces		
Zorgnet-Icuro publications Zorgnet-Icuro is a Belgian hospital umbrella organization with a plausible project to consolidate minimal hospital data, such as MZG-data.	1. Potential to become a data/project coordinator – role for connecting pharma to correct data providers	1. Could provide guidance to hospitals as many hospital directors are members of Zorgnet-Icuro
Healthdata.be An online platform set up by Sciensano, that allows third parties to access Belgian clinical registries. Approximately 15 registries run through this platform. In addition, healthdata.be sets up customized registries for specific ad hoc requests from RIZIV in MEAs.	1. Facilitator; allows pharma companies to uniformly access registries, allow GDPR approvals 2. Architecture: standardization in data collection 3. Experienced with MEAs 4. Willingness to collaborate with pharma and to keep data up to date. 5. Customized registry requests: possibility to obtain epidemiological and outcome-based information	
Mortality/population data		
Statbel data Statbel publishes population and mortality statistics on the Belgian society via statbel.fgov.be. The organization also accepts microdata requests (i.e. pseudonymized study data) from third parties.	1. Oversight of death causes in Belgium	
Social media data		
Social listening Consulting web forums, health blogs, and social platforms to find deeper patient insights and prolonged discussions on medications and symptoms.	1. Lots of qualitative data	

RWD/RWE Source	Benefits	
	Pharma perspective	Hospital perspective
Clinical registries/ interfaces		
Zorgnet-Icuro publications Zorgnet-Icuro is a Belgian hospital umbrella organization with a plausible project to consolidate minimal hospital data, such as MZG-data.	1. Not operational yet 2. Only Flemish hospitals 3. Technological limitations	1. Each hospital should maintain control over their own data, no interest in another central data platform. Hospitals are already increasingly setting up federated data networks themselves (i.e. centralized data from friendly, geographically proximate hospitals).
Healthdata.be An online platform set up by Sciensano, that allows third parties to access Belgian clinical registries. Approximately 15 registries run through this platform. In addition, healthdata.be sets up customized registries for specific ad hoc requests from RIZIV in MEAs.	1. Expensive RWD projects for pharma 2. Depends on governmental grants 3. Sciensano is slow = Lengthy data collection process 4. Labour intense process to organize RWD projects with Sciensano 5. Only accessible by legal requirement (MEA) from RIZIV 6. Incompleteness of registries (mainly applicable to ad hoc registries) as hospitals are not willing to do double data entry, creates too much of administrative overload	1. Too much governmental and political influences 2. Administrative burden to fill in the forms (double data entry next to the EHR)
Mortality/population data		
Statbel data Statbel publishes population and mortality statistics on the Belgian society via statbel.fgov.be. The organization also accepts microdata requests (i.e. pseudonymized study data) from third parties.	1. Anonymity; no common identifier for some statistics (i.e., Morality cause cannot be linked with other RWD sources)	
Social media data		
Social listening Consulting web forums, health blogs, and social platforms to find deeper patient insights and prolonged discussions on medications and symptoms.	1. Relevance perhaps not optimal	

RWD/RWE Source	Benefits	
	Pharma perspective	Hospital perspective
Laboratory data		
Predictive Tests for a Therapeutic Response registry (PITTER-registry) Example of a registry that runs through healthdata.be that collects laboratory data (among others). It includes the data collection of reimbursed Chapter VIII treatments and their associated molecularly laboratory tests.	1. Information on laboratory tests 2. Looks promising for pharma companies with products that require laboratory testing	
Survey data		
Patient Reported Outcome Measurements (PROMs) PROMs provide a patient's perspective on health outcome endpoint data, such as physical functioning, psychological well-being, global health perception and other subjective outcomes.	1. Insight into patient information 2. Existence of scientifically validated PROMs scales (e.g., PROMIS, ICHOM)	1. Relevant patient-perspective insights
Wearables data		
Wearables data Wearables are electronic devices that are placed on the surface of the skin to measure heart rate, pulse, and other physiological data. E.g., FitBit	1. Ease of data collection, real-time	1. Automated real-time tracking of data
Pharmacy data		
Association of Pharmacists Belgium data (APB-data) Database for Belgian pharmacies.	1. Provides access to Farmanet (i.e. is the same data) 2. Easy to build dossiers, also outside MEAs	

RWD/RWE Source	Benefits	
	Pharma perspective	Hospital perspective
Laboratory data		
Predictive Tests for a Therapeutic Response registry (PITTER-registry) Example of a registry that runs through healthdata.be that collects laboratory data (among others). It includes the data collection of reimbursed Chapter VIII treatments and their associated molecularly laboratory tests.	1. Not accessible yet for pharma companies because currently in the making in laboratories 2. Most participants were unfamiliar with PITTER	
Survey data		
Patient Reported Outcome Measurements (PROMs) PROMs provide a patient's perspective on health outcome endpoint data, such as physical functioning, psychological well-being, global health perception and other subjective outcomes.	1. Methodologic limitations: self-reports instead of hard evidence 2. Not used in Belgium for reimbursement purposes because not prioritized by CTG 3. Of little value if not combined with clinical outcome data	1. Many providers, needs to be coded, stored and re-sent to the EHR in a uniform way
Wearables data		
Wearables data Wearables are electronic devices that are placed on the surface of the skin to measure heart rate, pulse, and other physiological data. E.g., FitBit	1. Not much used in practice 2. Privacy issues related to "tracking", need for third party	1. Data is not really 'anonymous' – software provider can track location if patients do not switch of location sharing in phone settings 2. Need to calibrate for correct measurements 3. Value of wearables application is disease dependent
Pharmacy data		
Association of Pharmacists Belgium data (APB-data) Database for Belgian pharmacies.	1. Anonymity, i.e. hard to link with other RWD sources 2. Expensive	

RWD/RWE Source	Benefits	
	Pharma perspective	Hospital perspective
Studies		
Clinical studies (P4) with RWD/RWE Post-market measuring of a new product's safety and efficacy. Combination of characteristics from both RCTs and RWD (e.g. pragmatic studies), which makes them a very strong source of evidence. These can also be initiated by the hospitals or universities; in which case they are called "Academic" RWD/RWE studies".	1. Observational data (solving efficacy-effectiveness gap, information on QALY) 2. Prospective data generation 3. Pragmatic studies have high level of evidence (e.g., causality)	1. Workflow for clinical studies is formally in place in hospitals
Marketing studies		
Market research Marketing research organizations create surveys (i.e. drivers for drug prescription, advantages/disadvantages of drug intake, number of patients with a certain indication) and forward these to 15-20 physicians. Physicians respond to these questions based on personal top of mind experiences, in exchange for an incentive. E.g., Cegedim	1. Easy, low-cost alternative to gather RWE	
Standardized market reports Reports that are compiled by market research providers and offered on a large scale to the pharma industry.	1. Efficient method for standardized information collection (third party multicenter data aggregation)	

RWD/RWE Source	Benefits	
	Pharma perspective	Hospital perspective
Studies		
Clinical studies (P4) with RWD/RWE Post-market measuring of a new product's safety and efficacy. Combination of characteristics from both RCTs and RWD (e.g. pragmatic studies), which makes them a very strong source of evidence. These can also be initiated by the hospitals or universities; in which case they are called "Academic" RWD/RWE studies".	1. Very expensive (>€100.000) 10-15 hospitals: €150.000-€200.000 2. No priority on CTG level (they prioritize RCT results). 3. Pragmatic studies have lower level of naturalistic representativity than in uncontrolled RWD settings	1. Administrative burden to fill in the forms (double data entry next to the EHR) 2. Low/negative ROI for hospitals compared to P1/2/3 studies
Marketing studies		
Market research Marketing research organizations create surveys (i.e. drivers for drug prescription, advantages/disadvantages of drug intake, number of patients with a certain indication) and forward these to 15-20 physicians. Physicians respond to these questions based on personal top of mind experiences, in exchange for an incentive. E.g., Cegedim	1. Methodologic limitations: difficult to assess validity (subjectivity) 2. High clinical uncertainties, especially for in-depth insights (i.e. as to understanding these top of mind insights) 3. Some market research organisations face GDPR issues (went directly to physician, without involving the hospital nor the EC)	1. Little general knowledge about this practice 2. Perception hospitals on market research providers: too commercial; a few large hospitals refuse to collaborate with them 3. Some market research organisations face GDPR issues (went directly to physician, without involving the hospital nor the EC) 4. Hospitals evaluate to "ban" these direct-to-physician phone screenings, these should go via the hospital clinical trial unit
Standardized market reports Reports that are compiled by market research providers and offered on a large scale to the pharma industry.	1. Standardized' = insufficient detail for in-depth, customized data analyses 2. Data from some large hospitals is missing	1. Perception hospitals on market research providers: too commercial; a few large hospitals refuse to collaborate with them 2. GDPR issues; some data are obtained without the necessary permissions 3. Are often foreign reports; therefore, limited level of representativity for Belgium

RWD/RWE Source	Benefits	
	Pharma perspective	Hospital perspective
Expert reviews		
Expert reviews/ expert panels Authoritative opinions provided by doctors and healthcare experts (opinion leaders) on conditions and treatments. E.g., pharma companies ask physicians general questions about their patients.	1. Quick, high-level insights in patient care trajectories 2. Obtaining specific clinical insights to complement general evidence from literature	
General Practitioners (GPs)		
Intego Healthdata.be registry. Intego links data from GPs systems (EMRs) with IMA-data, as well as directly questioning patients with PROMs. Contains: 1. Epidemiological information 2. Diagnoses	1. Not much known about this initiative	
Network of General Practitioners (SGPs) Healthdata.be registry. Collects and provides epidemiological information and treatment information by 120 GPs in Belgium about 8 health problems (infectious and non-diseases).	1. Not much known about this initiative	

RWD/RWE Source	Benefits	
	Pharma perspective	Hospital perspective
Expert reviews		
Expert reviews/ expert panels Authoritative opinions provided by doctors and healthcare experts (opinion leaders) on conditions and treatments. E.g., pharma companies ask physicians general questions about their patients.	1. Opinions = subjective (no hard numbers in reports) 2. No real evidence	
General Practitioners (GPs)		

During interviews, the need for hospital data for pharmaceutical companies became clear. In hospital settings, it is easier to follow up drug usage and consequent healthcare outcomes in patients.

In real-life this is harder to assess because when a patient consumes drugs with a regular pharmacist, usually this is not followed by measurements. This indicates a need for hospital data wherein drug use can be linked to clinical outcomes. In what follows we discuss the current options for pharmaceutical companies to access hospital data (in particular, EHR data is of interest, see Table 5).

4.3. Collaboration models pharma-hospital

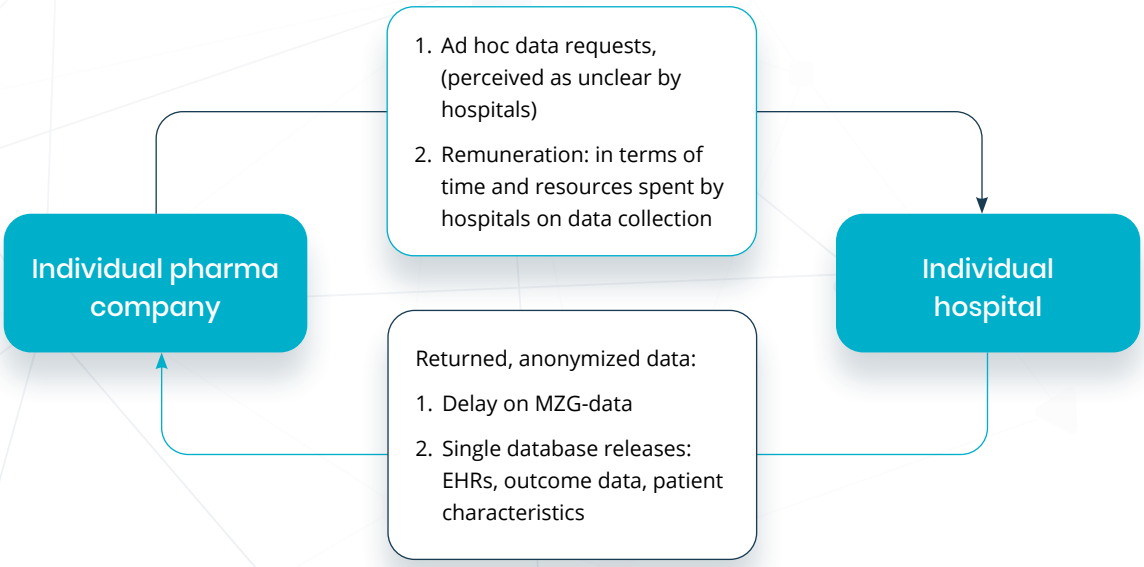
4.3.1 Current models: directly in on-on-one data exchanges, and indirectly through CROs

1) Direct Collaborations

From both pharma and hospital interviews, we learned that the current collaboration models look like the following:

Figure 10

Current collaboration model between hospitals/centers and pharma companies



Structural collaborations at a large scale do not exist yet in Belgium between pharma companies and hospitals.

However, pharmaceutical companies indicate a need for improved collaborations with hospitals as certain large hospitals refuse to collaborate with CROs, and certain specialized information cannot be obtained from standardized market reports.

Data requests take place per project instead, and generally take place as small, ad hoc, single database releases in individual collaborations between pharma and hospitals (Figure 10).

"Often it comes down to a good relationship between a pharma company and a physician. That physician then gives you access to a dataset he/she owns [Pharma respondent C]". This means that at the moment collaborations do not take place at the level of the hospital, but more at the level of individual physicians or departments.

Some collaborations even happen under the radar of hospital directions. A hospital director confirmed this hypothesis: "Clinical studies also used to be unreported toward the ethical committee and federal agency, I could not imagine that anymore today. However, I'm having a déjà-vu for RWD requests now [Hospital respondent 1]".

Nevertheless, pharma participants indicated that some hospitals directions are more open to EHR data exchanges than others, while these exchanges are actually legally prohibited. In addition to ethical constraints, direct collaborations with individual collaborations with physicians include some disadvantages for pharmaceutical companies:

- Communication difficulties – unclear data collection protocol (i.e. Pharmaceutical companies cannot access the documents and cannot pinpoint what is specifically needed, consequently data requests are perceived as unclear by hospitals)
- Time-consuming
- Delay of release of data results
- Register dependency
- Enormous administrative burden
- No traceability back to patient profiles
- No claims data

During the interviews, a clear need for a more structured, streamlined process of data exchange from both sides was indicated. Governmental initiatives have been taken to make the data collection process happen more structured and at high-level, by means of:

Sciensano

Sciensano is a research institute sponsored by Belgian government, its main aim is to collect and maintain an overview of medical data. Quite some efforts happened to establish its online portal healthdata.be, however Sciensano disadvantage is that they depend on government grants to expand its operations and multi-stakeholder projects. The financial aspect is very critical here. Currently, processed (coded) registers and medical data are released with 2 years or even with longer delay in comparison to its raw recorded data sources in hospitals. While other countries are starting to embrace for their medical research institutes the usage of automated and continuously updated Blockchain Technology, Sciensano lags behind by still manually updating and uploading CSV files every time to their portal.

Forming consortiums

The formation of consortiums is to reduce the presence of current mentality of 'ad hoc - 1 pharma company working with 1 hospital' in order to reach for a higher level of sharing of data. Some pharma companies are even willing to contribute huge financial investments in a common shared budget pot to give an extra boost for data to be developed properly at once. This would give a first step towards the shared risks and benefits mentality that unconsciously all stakeholders need to guarantee their livelihood in near future.

This could help multiple research studies to achieve more significant results and support enhanced drug development. The potential and expertise for this exist in Belgium, a first taste of this potential of collaboration can be seen in bladder cancer project "Athena" taking place with governmental VLAIO subsidy worth of 16 million euros to be invested on RWD/RWE studies by AZ Delta & UZ Leuven hospitals, and opportunity to invited pharma industry to share their expertise as well.

Reference hospitals

Registries are organized in reference hospitals – hospitals officially acknowledged for specific indications. These registries allow more structural individual collaborations between a hospital and a pharma company for e.g., orphan diseases.

However, pharma companies do not seem fully satisfied with the present initiatives. We heard some practical restrictions that prevent pharma companies from using hospital RWD/RWE:

- Data quality (granularity of data, details missing, etc.)
- Disarray on the application of privacy rules (GDPR)
- Protectionism from hospitals in sharing data with commercial parties
- Availability of accessible structured data is limited
- Integration of different data providers and platforms is missing, between different hospitals but also with the healthcare service at large (e.g., pharmacists)
- For certain diseases no data available on the standard of care, so no baseline exists for new drugs to be compared with
- Significant delays on data requests

In hospitals as well, there is a need for a more structured collaboration and technology to facilitate swift, compliant data-exchange, at a fair price.

A general workflow (i.e. protocol) must be put in place to streamline data-exchange for RWD/RWE with third parties. Hospitals need to find an internal system to involve all responsible staff members at the right timing. Such workflows are known for clinical studies (i.e. called 'database research workflows') and should now be streamlined for data. In addition, hospitals require a remuneration in line with market value of data (i.e. % of revenues obtained by pharma companies as a result of hospital RWD/RWE).

2) Indirect collaborations: CROs

Pharma companies can indirectly collaborate with hospitals through Contract Research Organizations (CROs). Pharma companies opt for CROs when they want to set up larger studies or more complex data requests whereby it would be inconvenient for pharma companies to do it themselves (e.g. time and resources, privacy regulations). CROs set up the study protocol for data collection in hospitals, i.e. creating a clinical protocol in parallel with EHRs (Figure 11). This offers a solution to the communication issues between pharmaceutical companies and hospitals mentioned earlier: CROs are specialized in transforming pharma data requests into protocols for hospitals and are therefore easier to understand for hospitals. Moreover, CROs follow up strictly on data quality, collaborate with data nurses, and can obtain permission to look into EHRs. Such tasks are less evident for pharmaceutical companies, as pharma companies A) cannot legally access EHRs, and B) lack the specialized, temporary manpower to create and negotiate strong study protocols, and follow up on quality data input. The latter would require pharmaceutical companies to hire new employees, who would be unemployed when a research project is finished. In contrast, CRO has a huge organization to support in the collection of clinical data and the processing of new clinical data. An important motivation for pharma companies to collaborate with a CRO is quicker access to MHD-data than in a direct request

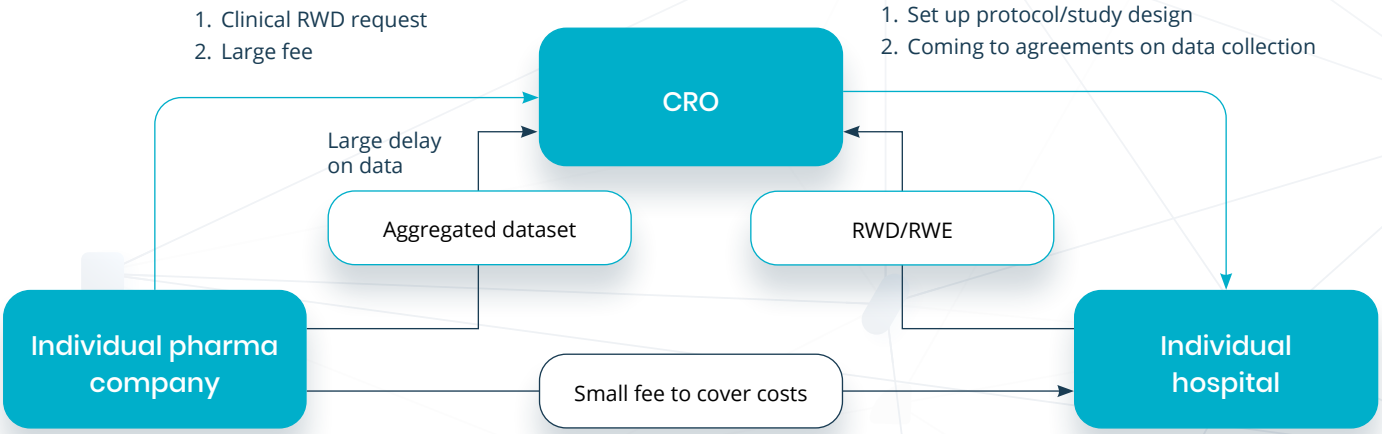


Figure 11 Process of working with a Contract Research Organization (CRO)

CRO's collect data from (multiple) individual hospital(s) which they often collect through an eCRF (electronic Case Report Form), saving RWD/RWE on their own server. After data aggregation, the entire aggregated dataset is delivered to the pharma company.

2) Indirect collaborations: CROs

That being said, working with a CRO goes parallel with the necessary hurdles.

1) For pharma:

- Very expensive (>100.000€ for a single study)
- Time-consuming: data only available much later

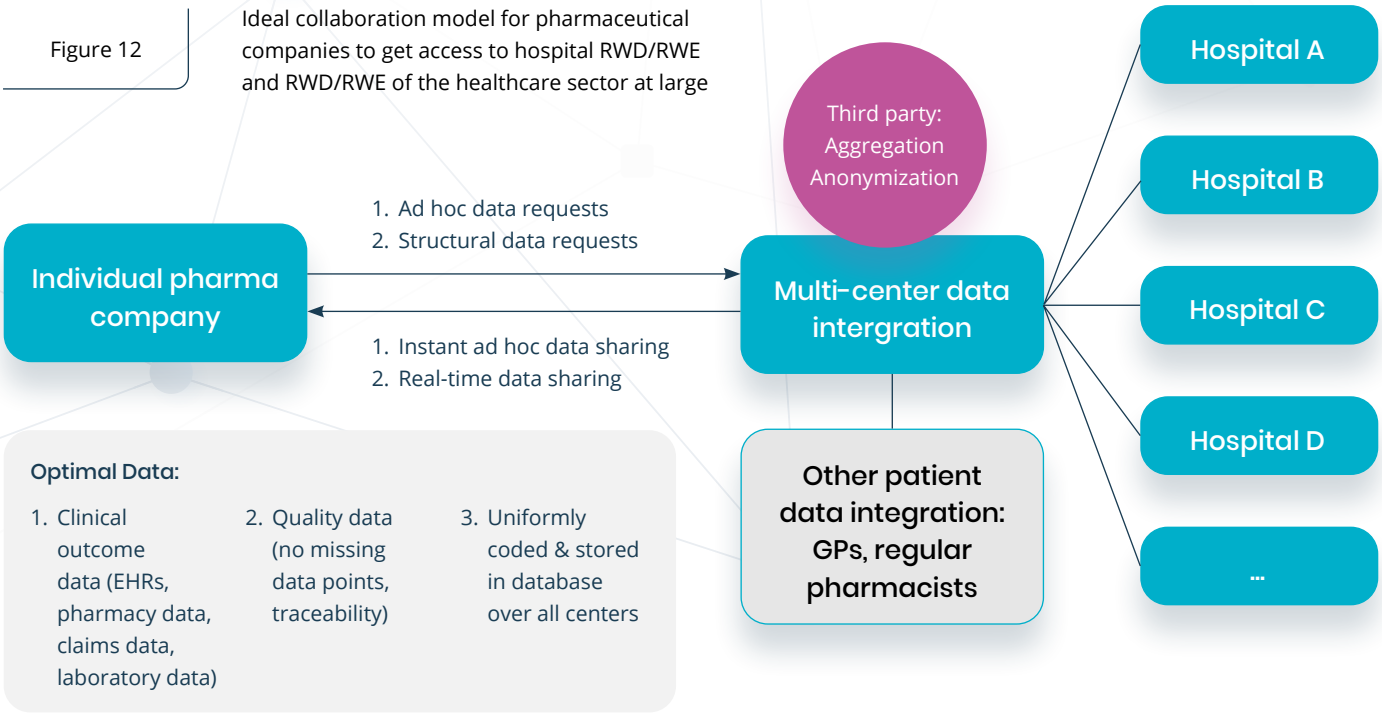
2) For hospitals:

- Compensation ends up largely with CRO, hospitals want their fair share of the deal
- Experience with CROs (e.g. IQVia) that did not hold up their end of the bargain when it came to agreements on data uses. Ended up using the data for other projects than what was agreed on. This has resulted in a reputation of being 'too commercial' (i.e. too money-focused, without respect for patient rights).
- Whereas pharma participants assumed that CROs performed the data collection work (i.e. accessing EHRs, working together with data nurses to control data quality), hospital participants reassured that the actual work ends up on their plate: "The IT department and physicians perform the work, CROs don't actually do the labor, they negotiate and make agreements with hospitals [hospital4]". As a result, added value of collaborating with CROs is limited for hospitals despite the added labour.

4.3.2 Desirable for pharmaceutical companies in the future: fully integrated health data

Figure 12

Ideal collaboration model for pharmaceutical companies to get access to hospital RWD/RWE and RWD/RWE of the healthcare sector at large



Authorities: ensuring clear legal framework

Figure 12 shows the construction of an ideal collaboration model for pharmaceutical companies deducted from our interviews:

Participants prefer receiving aggregated and anonymized data rather than data analyses. This allows them to perform their own ad hoc analyses. However, data analyses services were welcome as an extra service for some participants.

Mainly structural collaborations (i.e., structural data requests) are required, but in addition some pharma participants also wanted to maintain the option for ad hoc data requests. They want the option to choose this per product/project.

- Structural collaborations for data streams that will be needed for a longer period. For instance, a contract for 3 years for a product with the option to stop the collaboration after 3 years if the data is no longer needed
- Ad hoc data is needed for new drugs

Collaboration through a third intermediary party: multi-center data integrator. Some pharma companies first indicated to prefer a direct collaboration because this allows them to communicate more specific personal preferences to hospitals content wise. However, these participants soon realized that a direct collaboration was idealistic and not practical for multiple reasons. First, it is not a pharmaceutical company's core business to collect data in multiple hospitals, to be responsible for anonymization, to invest in advanced data analysis technology. Second, this would prevent them from accessing the EHR. A third intermediary party is more practical to account for multicenter data collection, anonymization, aggregation, analyses, and statistics. Additional requirements for participation with a third intermediary party:

- High quality data; this requires involving physicians who initially enter the data within the collaboration model
- Representative data: minimally 10-25 large centers need to be part of the project to create a representative research sample. For orphan drugs about 5 specialized centers suffice for representativity.
- The option to discuss analysis results with hospitals. E.g., to understand peculiar outcomes that were obtained digitally in conversations with the data provider source.
- Collaborations based on mutual trust. Hospitals are afraid that pharma analyses merely serve commercial interests but must understand that they primarily serve patients' interest, also through a third party. If pharmaceutical companies cannot provide the required data to the payor, there is the risk that the product will be de-reimbursed, hence that patients cannot access the drug anymore. Hence, it is of direct importance to both patients as well as physicians to collaborate in the RWD collection.
- Cost-efficiency: A third party needs to develop a protocol and routine to analyze unstructured and structured hospital data. As a consequence, they can become cost-efficient and lower their price toward pharmaceutical companies.
- Integration with other patient data: When patients leave the hospitals and continue their treatment with a regular pharmacist, these data cannot be linked to hospital data. This makes it hard for pharmaceutical companies to assess the full patient trajectory. Ideally, consumption data from within hospitals is linked with pharmacist and GP data.

The role of authorities (CTG/RIZIV) should remain limited according to pharmaceutical companies. Authorities need to ensure a clear legal framework for data governance: defining criteria and a roadmap (i.e. steps to take) for data requests. Some pharma participants, however, expressed their frustration about the payors, who demand RWD/RWE without providing a practical option to access the required data. They envisioned a more proactive role for the authorities in providing data access and delivery. However, other pharma companies indicated that this would imply authorities getting involved and complicate the data request procedures. Governmental interference was a synonym for delay and complexity to them. Authorities already play their role through Sciensano and Zorgnet-Icuro. Their main focus should be to improve these initiatives and further limit interference. For instance, Zorgnet-Icuro could be used to implement a standardized governance for data requests in all Belgian hospitals.

4.3.3 Manageable for hospitals in the future: transparent, fair, and protocolized

The collaboration model shown in Figure 12 was shown to hospitals and they were asked to give their opinion:

— Anonymization: does not exist according hospitals, they would rather call it pseudonymization. E.g., a wearables company can trace patients' location, implying they could more or less identify the patient. In hospitals' opnion, this anonymization/ pseudonymization remains a responsibility of the hospital's DPO/clinical data coordinator.

— Instant ad hoc data sharing: this is technologically possible; however, data sharing decisions need to obtain permission from several parties within hospitals. Hospitals, physicians, and patients all have ownership over (parts of) the data. By the time all of those approvals are acquired one can no longer speak of 'instant data'.

— Third party as a shield between pharma and hospitals: hospitals want to maintain the option to directly interact with pharma companies. This interaction is important to discuss general outcomes, as well as peculiarities and animalities in data.

\+ Third party integration: most hospitals saw an important role of a third-party integrator in the process: whereas hospitals are convinced that necessary tools (e.g., technologies, IT department) for their own data aggregation are present within hospitals, no one took the responsibility for data integration over multiple hospitals, which presents an opportunity for LynxCare. Hospitals also indicated that a third party is perceived as being more neutral than pharma companies (i.e. who are often perceived as too commercial).

Additional requirements for hospitals:

- Transparency: related to maintaining the option for dialogues with pharma companies, hospitals require a transparent model, where they have an overview of current projects: who is using which data, for which purpose.
- Protocolized: Hospitals need to develop a protocol to streamline data-exchange for RWD/RWE studies; A general internal workflow within each that indicates who needs to be involved in the process of data-exchange when, and what for. As soon as this is put in place, they will be more open to answer RWD/RWE requests.
- Fair financial rewards: Are important to hospitals as healthcare budgets are under pressure. The financial rewards should be divided between hospital, departments, and physicians. Hospitals currently receive only a fraction of the market value when collaborating with CROs for clinical studies. They indicated that they would like to see an increase in remuneration that is in line with the market value of the data, rather than with labour hours spent to deliver the data = revenue sharing model per project.
- Internal data generation: Data generation should remain an internal task executed by hospital staff (e.g., physicians, data nurses, IT department). However, to guarantee data quality, hospital staff needs to be incentivized for spending their time on inputting data.
- Value-based healthcare: insights obtained from the data to serve pharma companies could also be valuable to hospitals to improve quality of care and internal operations. LynxCare's services provide benchmarks over all participating centers, disease-specific insights, quality measurements, technological means to help hospitals building up RWD databases. One participant, however, indicated that these factors are valuable but should not be used as leverage to lower financial rewards.
- Using RWD for other research projects (e.g. authorship): this is an important factor for University Hospitals (Dutch: "Universitaire Ziekenhuizen"/UZs) to generate scientific publications, but less so for General Hospitals (Dutch: "Algemene Ziekenhuizen"/AZs).

Including hospitals' objections and requirements, we built Figure 13 to reflect a collaboration model considered manageable by hospitals.

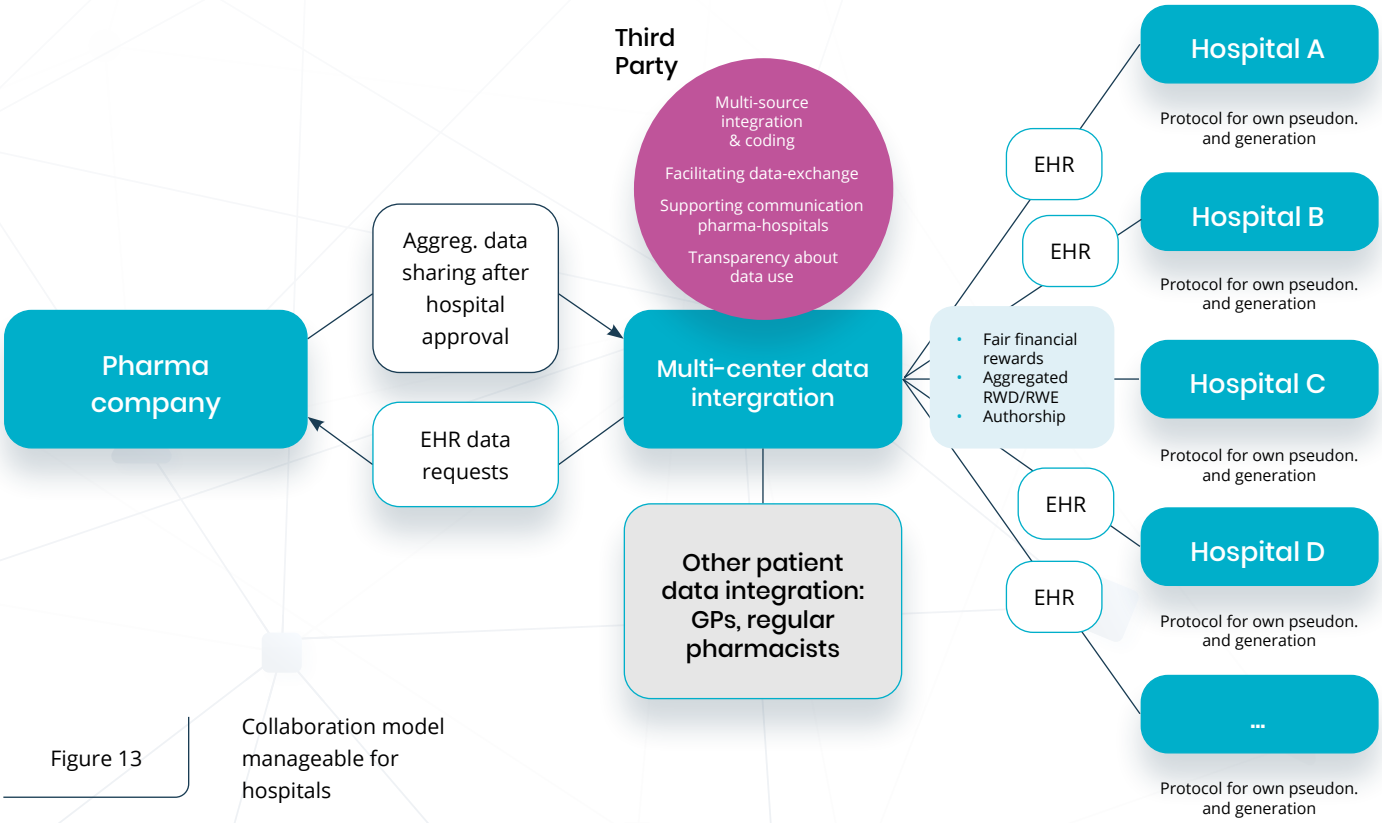


Figure 13 Collaboration model manageable for hospitals

Authorities: ensuring clear legal framework

4.3.4 Role of government

While most study participants (hospitals and pharma companies) advocate that government should provide an improved legal framework and leave the rest up to private parties, other study participants (hospitals and pharma companies) argued that the government should go beyond and take a more proactive role.

It is difficult to move towards a collaboration model between hospitals and pharma without involving the government and ideally an updated overview of registers in a collaborative model. Authorities and HTA bodies (CTG-CRM for Belgium) need to become more realistic about what pharma companies feasibly can and cannot answer in terms of information to gain market access. In the defense of governments and their HTA bodies (CTG-CRM for Belgium), their high requirements originate from good intentions to give new medical drugs market access only if proper scientific evidences can be provided and to prevent the Belgian population safety to be harmed from medical drug side effects (e.g. hydroxychloroquine still in market as rheumatic treatment despite many documented side effects). A recent study even showed that of all the medicines on the market, half of those medicines do not do what they are intended for. Sometimes you just do not have a cure for certain diseases, very few alternatives, and people are inclined to give drugs just because we do not wish to leave the patient untreated. There are many medical drugs therefore that remain on the market despite scientific indications show they do not help relieve patients of pain or other symptoms.

Pharma perspective	Hospital perspective	Government perspective
• Providing legal framework • Take a more proactive role and offer more guidelines • Be realistic on feasibly what pharma companies can and cannot answer in terms of information to gain market access • Reduce '1 on 1 mentality' & reach for a higher (consortium) level.	• Providing legal framework • Take a more proactive role and offer more guidelines • High requirements originate from good intentions to only allow drugs on markets with proper scientific evidences and to safeguard population health outcomes	• Providing legal framework • High requirements originate from good intentions to only allow drugs on markets with proper scientific evidences and to safeguard population health outcomes

Table X Missing Text

What the (Belgian) authorities ought to do

HTA bodies need to ensure that pharma companies will provide more RWD/RWE in near future to support their new drug claims when requesting for market access and reimbursement.

This will to lead to better public health outcomes measurements being recorded over time. This will also benefit payers since they desire approving new drugs that are applicable in everyday real life and that can be generalized to wider patient population (Patsopoulos, 2011). HTA bodies can ensure all this by offering more instructions when discussions arise, for example on what they deem is the right study population size. By giving more instructions, the authorities will solve a lot of future issues that raise up from clinical uncertainties and health budget challenges. Over time, this will benefit authorities as well to help create the base upon which collaboration for RWD per projects can be transferred to a higher level, even perhaps towards national RWD datahubs formation. For Belgium, it is unclear how much cooperation has already taken place between Zorgnet-Icuro, Sciensano, Réseau Santé Wallon and INAH for RWD projects. The authorities should interpret the fact that pharma companies and hospitals are starting to set up multiple individual RWE projects (related with high costs and time-consuming) as to get involved. Authorities can take an advisory role in discussions between pharma companies and hospitals on matters of how to spread the costs and to share of profits fairly.

It is a necessary that the Belgian government rethinks the current legal framework as hospitals are financially struggling and are currently taking up a mindset of not sharing the collected raw patient data (as they are legally entitled) but may relinquish too fast the opportunity to share processed data.

Hospitals feel that by taking this mindset they are safeguarding their last bargaining chip in a struggle to gain a voice in research projects with pharma companies and receive more financial resources to maintain properly operational. The Belgian government should implement control systems in the legal framework to make sure GDPR is being respected at all times by the diverse parties in collaboration models, this will increase the trust for hospitals to work again with pharma companies and third parties. The bad perceptions that certain commercial third parties have given to the RWD sector at pharma companies and hospitals should of course be considered and not forgotten. Yet the past experiences should no longer affect future collaboration opportunities for other commercial third parties as LynxCare as they also deserve a fair chance to show their expertise to hospitals and pharma companies.

What the (Belgian) authorities ought to do

The Belgian government should fund much more their research institute Sciensano (Healthdata.be).

The additional financial means could help speed up attempts to map all data on a central umbrella consortium overviewing data portal. This will contribute also to reducing current mentality of 'ad hoc - 1 pharma company working with 1 hospital' in order to reach for a higher level of sharing of data. Not all stakeholders would agree with this, especially for the short-term there could be high costs potentially to share together, but in the long run stakeholders would benefit from the creation of multiple synergies between pharma companies, hospitals, third parties RWD companies and governmental active guidance. The potential for this does exist in Belgium. In the past many patient registries and administrative databases existed, but their existence and how to access were known by only a few people. In Belgium, eventually government decided to use the FAIR principles (Wilkinson et al., 2016), Findable, Accessible, Interoperable, Reusable, as a guide when creating healthdata.be and with the hope to increase the number of users of these databases (Sciensano, 2017). These databases are regularly updated by Sciensano which monitor the Healthdata.be platform.

4.4. Collaboration models pharma-hospital

From the interviews we conclude a clear need for a third-party integrator for several reasons:

1. Neither pharma companies nor hospitals' core business is to have the technology and focus on data integration from multiple healthcare sources, which is a unique value proposition that third parties can provide.
2. Governmental initiatives have so far been helpful in collecting data from registries (Healthdata.be), however have not yet succeeded to meet all of the wishes from pharmaceutical companies for RWD/RWE

We have deducted requirements for collaborating with a third-party integrator from the pharma and hospital interviews (see Figure 14 for a summary). The requirements were organized in a Strengths and Weaknesses within our SWOT analysis based on industry and LynxCare assumptions and knowledge we had gained during the course of this project. Opportunities and Threats do not necessarily indicate requirements as such but more of the opportunities and threats from either hospitals' or pharma's point of view. The accuracy of the initial SWOT analysis was assessed during our LynxCare interview. For a summary of the SWOT see Figure 14. Each of the strengths, weaknesses, opportunities, and strengths, is discussed in detail in the following paragraph.

		Hospitals	Pharma
S	1. Technical capacity for high quality structured, unstructured, and nominal data	✓	✓
	2. Broad RWD/RWE coverage and integration	✓	✓
	3. Medical & IT knowledge combined	✓	✓
	4. Focus on RWD/RWE mining (core business)	✓	✓
	5. Image of reputable company	✓	✓
	6. Agility		✓
	7. Legal framework and procedure	✓	✓
	8. Near real-time		✓
	9. Ethical mindset (transparency – fairness)	✓	✓
W	1. Limited experience in pharma industry		✓
	2. Unclear selling proposition	✓	
	3. Primary data capture / completeness of data		✓
O	1. Full hospital data infrastructure	✓	✓
	2. Full healthcare sector data infrastructure		✓
	3. Positioning as a hospital partner	✓	
	4. Need for financial resources	✓	
	5. Need for rapid, high quality data delivery		✓
	6. Early market launches abroad		✓
	7. Offering a network of hospitals	✓	✓
T	1. Conservative attitude against 'selling data'	✓	
	2. Suspicion of third parties	✓	
	3. Legal unclarities		
	4. No protocol in place yet for structural RWD exchange	✓	✓
	5. Competition from other startups	✓	✓

Figure 14 SWOT LynxCare, summary of the requirements mentioned by pharma and hospitals

4.4.1 Strenghts

1. Technological capacity for high quality structured, unstructured and nominal data

LynxCares primary and foremost strength is their capability to unlock and mine EMR data. Without the ability to unlock EMR data, their only alternative would be to mine alternative RWD/RWE sources, which are difficult to enter as a commercial party.

LynxCare thanks this unique strength to their history as a startup that initially only served hospitals' interests and could therefore gain their trust.

In addition, LynxCare has made large investments in advanced data mining technology. They guarantee a data quality level >90% for unstructured and structured data:

- Unstructured data (e.g., EHR): LynxCare has the technological capacity and the experience to mine unstructured data, such as the EHR. Their experience has been built up by their data mining services they have been providing to hospitals in recent years.
- Structured data (e.g., IMA): LynxCare has recently built technological capacity to mine structured data, which they will now start building experience for.
- Nominal data (e.g., text data): Hospitals mentioned that there is a high need to analyze nominal data, LynxCare can answer this high need by means of text data mining and some basic functionalities in LynxCare tool that give out codes to facilitate identification, collecting, processing and analyzing nominal raw data.

LynxCare performs this data mining on their own internal servers, on a cloud outside hospital premises. The output is structured, aggregated, pseudo-anonymized & coded evidence. They have legal ground for this within their contracts.

2. Broad RWD/RWE coverage and integration

If a party were to come up with a solution to integrate a large number of RWD/RWE sources, pharma companies would be willing to collaborate. A requirement is that LynxCare can supply all data from start to end, without missing parts in the data process.

LynxCare has the advantage that its starting point is the EHR, which is the basis for many other RWD/RWE Sources from the table. Most of those data sources in the table (e.g., registries, MHD data) are used to obtain indirect EHR data because direct data obtaining is very challenging. In addition to the EHR, LynxCare can also access other data sources, so these can be integrated into their model if necessary.

The opportunities for LynxCare, for each required RWD type, are shown in Table 6. However, LynxCare's true added value lies in becoming a full end-to-end platform, which is not captured in this table. Since every business starts small, we discuss the level of opportunity of offering separate data sources: At the moment LynxCare is strong for clinical data, epidemiological data and outcome data, as these are all present within the rich EHR. LynxCare is also currently running a project with the pharmacy sector, which will start soon, to integrate claims data from regular pharmacists into their offer. The only RWD type missing in their offer is the billing data from hospitals, which LynxCare does not have access yet today. Increasing hospitals willingness to provide access to their billing data is currently on top of LynxCare's priority list. Consequently, they will be able to integrate billing data from hospitals with EHR data.

Table 6

RWD types required	Current RWD/RWE source	LynxCare's offer	Level of opportunity
Clinical data Patient data on indication and drug dosage.	P4 studies Expert reviews Registries EHR	EHR	(Lower level of evidence than P4 studies, more expensive than expert reviews and registries)
Outcome data Treatment outcomes (complications, effectiveness, side effects).	P4 studies Registries Expert reviews	EHR	= (fast, easy to access, naturalistic validity)
Epidemiological data: 1. Prevalence 2. Incidence	IMA Registries P4 studies	EHR	+ (accessible)
Claims data from pharmacists: Billing information.	APB IMA	(APB)	+ (accessible)
Claims data from hospitals Billing information from hospitals.	IMA	/	0

Most essential RWD types required by pharma companies, the RWD/RWE source currently used to access RWD types, LynxCare's alternative, and the level of improvement LynxCare provides in comparison with the current RWD/RWE source

3. Medical & IT knowledge combined

A requirement that is important for both the hospitals and pharma companies is an integration of medical and data/IT knowledge within one company. Hospital experts have been witnessing many data/IT startups who lack medical knowledge and are therefore not suited to analyze EHRs:

Hospital 4: "You need a party with both IT and EHR insights. Moreover, this party should have a critical perception toward aggregated EHR data. Often integrators assume they possess enough clinical insights. But no. When it comes down to understanding data and variables, they lack medical background. For instance, a certain terminology used in a data request by pharma might have a different meaning in the EHR."

A third-party integrator must be capable and willing to interpret each line of the EHR correctly. First, variables within the EHR must be interpreted according to its clinical meaning. Therefore, a strong medical background is required. Second, there must be willingness to interact with different stakeholders from within the hospitals to guarantee correct interpretations. For instance, three different temperature measurements (e.g., morning, noon, evening) could be present in three different EHRs under the same variable name "temperature". The third-party integrator is then responsible for capturing this nuance by interacting with the clinical data coordinator/ DPO/data nurses/physicians. Consequently, a correct data interpretation leads to accurate analysis results.

LynxCare offers expertise from the medical side: 1/3rd of their company are either Doctor of Medicine (MDs) or Doctor of Pharmacy (PharmD), plus 1 Doctor of Biomedical Sciences. The other 2/3rd of the company carry the IT knowledge: e.g., data scientists, developers, business engineers. This combination meets the requirement of hospitals and pharmaceutical companies for accurate medical data analyses. The algorithm extrapolates the data from MHRs, performs quality checks and anomalies are discussed with hospital representatives during checks and balances.

4. Focus on RWD/RWE mining (core business)

An advantage that LynxCare has over their established competitors is an exclusive focus on RWD/RWE. RWD/RWE is something relatively new, that has emerged during the last decade. Established competitors have centered their main focus around clinical studies (P1/P2/P3/P4) and are therefore less specialized in data-integration.

Also, LynxCare offers a more advanced data mining capacity than their competitors (e.g., IQVia and Zorgnet-Icuro).

5. Image of reputable company

Having a clean reputation came forward as an important requirement for both pharma and hospitals. The latter placed a lot of emphasis on this as they have had bad experiences with LynxCare's competitors in the past. Certain competitors have been accused of being 'too commercial' and of selling data outside of contractual agreements. Consequently, their reputations have been contaminated and they have lost their trust in the pharma and hospital industry.

LynxCare already has built a reputable image in the hospital sector by delivering data consulting services. In addition, they have had the chance to build a network within the hospital sector.

6. Agility

With its exclusive focus on RWD/RWE, LynxCare is far more agile in succeeding an RWD/RWE integration project than its more versatile competitors. In addition, with its private company structure it is more agile and quicker than governmental initiatives such as Zorgnet-Icuro, who are moving too slow according to pharmaceutical respondents.

7. Legal framework and procedure

An important requirement for a third-party integrator is a strong legal framework and the ability to work with contracts. Hospitals fear that once third-party integrators access data outside of hospital premises, they will lose ownership and control over the data. The former is guaranteed because of legal ground provided by contracts for hospitals that protect hospitals' interests. They remain co-owners of patient data (next to the patients and physicians) and receive a fair share each time data insights are required by pharmaceutical companies.

This is essential as patient data are a delicate subject and their privacy must be maximally protected. LynxCare collaborates with a legal advisor to ensure a fully legal approach and have support in dealing with contracts

An important requirement for a third-party integrator is a strong legal framework and the ability to work with contracts. Hospitals fear that once third-party integrators access data outside of hospital premises, they will lose ownership and control over the data. The former is guaranteed because of legal ground provided by contracts for hospitals that protect hospitals' interests. They remain co-owners of patient data (next to the patients and physicians) and receive a fair share each time data insights are required by pharmaceutical companies.

This is essential as patient data are a delicate subject and their privacy must be maximally protected. LynxCare collaborates with a legal advisor to ensure a fully legal approach and have support in dealing with contracts.

8. Near real-time

Pharma companies struggled with delivering RWD/RWE in time and are in favor of a more real-time data delivery. The latter is offered by LynxCare, who succeeds in providing data analyses within 2-3 weeks.

8. Near real-time

LynxCare understands the sensitivity of working with patient data. They have experience with working with EMRs and have developed a consciousness that these data need to be well-protected. Their technology is well-secured and LynxCare is determined to be ethical: approach the correct audience within hospitals, understand data ownership does not belong to them but to patients and hospitals, and the importance of transparency toward hospitals. LynxCare is prepared to renegotiate their rights and obligations for every new pharma project, so that hospitals maintain an overview of what their data is used for, by whom, and when.

4.4.2 Weaknesses

1. Limited experience in pharma industry

Neither pharma nor hospitals mentioned the importance of experience in the pharma industry as an important factor in their interviews.

However, established names such as IQVia were mentioned multiple times during our interviews and they have the advantage over LynxCare that they are experienced within the pharmaceutical industry.

2. Unclear selling proposition

Hospital experts noted that the selling proposition was unclear because LynxCare initially introduced themselves as a hospital serving startup, whereas it would now serve two markets. This led to some confusion:

Hospital 4: "LynxCare's first service was data consulting, supporting our hospital in building a data infrastructure. Now afterwards, that same party says they will provide data aggregation services for pharmaceutical companies. This means they are combining two separate services, which makes us uncomfortable. They are internally too informed for the position of data integrator for pharma companies".

3. Primary data capture / completeness of data

Pharma companies demand an optimal data quality: no missing datapoints + traceability of data.

LynxCare cannot guarantee completeness of data because they do not offer an application for primary data capture. Instead, they analyze secondary data from EHRs and therefore rely on the quality of data input by physicians in hospitals. An inherent limitation of EHRs is their missing data points, credibility of information, and the lack of validation tools to assess credibility.

4.4.3 Opportunities

1. Full hospital data infra-structure

The pharma industry wants a full hospital data infrastructure in which at least most large hospitals participate and preferably also the smaller centers, as well as the officially appointed reference centers (see earlier, Section 4.3.1).

LynxCare is currently working with about 20 hospitals, of the 103 large hospitals in Belgium. There is still a great opportunity to expand.

2. Full health-care sector data infra-structure

In addition, pharmaceutical companies aspire that the data from hospitals can be linked to regular pharmacies (i.e. pharmacies outside hospital doors) and general practitioners. Eg. When a patient leaves the hospital and continues his treatment with a regular pharmacist, it must be possible to link the consumption data from the hospital to the regular pharmacist consumption data (i.e. obtained from pharmacist claims data).

This linkeage can be very important for pharmaceutical companies as they aim to map the entire treatment process of patients.

As linking consumption data from hospital pharmacies with regular pharmacist data is a rather straightforward procedure this would be a quick win for LynxCare (See further for recommendations LynxCare, Section 5.2.1).

3. Positioning as a hospital partner within pharma collaboration model

Hospitals tend to feel excluded from the interaction between pharma companies and intermediate parties (CROs, third party integrators).

A more inclusive approach would require transparency, so that hospitals are aware of what is happening with their data and so that they are included in the data exchange process. This means that a third-party integrator should not position themselves as a shield between hospitals and pharma companies but rather as a facilitator of the interaction between both.

4. Hospitals' need for financial resources

The hospital sector is facing financial challenges. Collaborating with a third-party integrator would not only benefit their own patients due to additional high-level insights but would also be an amendment to their financial gap. Hospitals did explicitly mention that these resources were of high importance to them, but also that a mere compensation for the delivered labour would not suffice. They emphasized their awareness of the market value of their data and their need for a more market conform pricing. A high remuneration would open many doors.

4. Hospitals' need for financial resources

We heard different suggestions to develop a fair financial model (cf. Section 5.1.3):

- Two hospitals suggested to LynxCare perhaps instead of the "fair-share revenue scheme" to introduce a long-term access fee for pharma companies to gain a clear overview of a processed data page (from small and easily clinical collected data);
- For bigger special projects (e.g. anatomo pathological data for cancer) to be paid by a payment/commission per project and gain sole access from pharmaceutical side to data until the end of project, this guarantees lower risks for all involved stakeholders that data will less likely be leaked out or damaged.
- An intermediate third party must enter into dialogue with hospitals to get a better idea of what they perceive as a fair reimbursement for their data. Nonetheless, hospitals must also remain reasonable and understand that currently EHR insights are simply lost and that no hospital has taken any responsibility to integrate all hospital data, nor has the government. LynxCare is prepared to take on this challenge and to enter into dialogue with hospitals to fairly reimburse them for their data.

5. Need for rapid, high quality data delivery

During market launch: Data is required on a drug's budget impact and disease burden. A practical restriction is that there is not always sufficient time to complete such task before or during the pricing & reimbursement submission. Pharma companies need to write a protocol to collect IMA-data and MHD-data and wait until data is delivered to them afterwards. Due to data delivery delays, this task is often postponed until after market launch as pharma companies want to receive reimbursement as soon as possible.

Post-market: Pharma companies are increasingly facing the obligation from the payors to provide high quality RWD/RWE within 2 years (i.e. MEA). This short contract period is a hurdle for pharma companies who currently need several years to gather RWD/RWE due to delays of 1-2 years on many RWD/RWE sources (see IMA, MHD in Table 5). Insufficient RWD/RWE collection leads to new temporary contracts with new, less desirable price negotiations. Another adverse outcome of delayed RWD/RWE acquisition is that data might be outdated by the time of delivery: "e.g., we need RWD/RWE to define the standard of care, but in oncology the standard of care changes dramatically over the course of 2 years [Pharma participant B]".

6. Early market launches abroad

Multinational pharma companies often launch their new products earlier in some countries than in others. Consequently, RWD/RWE from abroad is sometimes available from countries that launched earlier. Pharma companies indicated when this happens, they always include RWD/RWE from abroad in the value dossier during their authorization process.

This leads to two opportunities for LynxCare: 1) Collaborating with foreign hospitals and mining their early launch RWD/RWE, and, thus, offer it to Belgian pharma departments, 2) Collaborating with departments of pharma companies abroad to offer Belgian early launch RWD/RWE. The latter could be a quick win for LynxCare; however, Belgium is often at the later side of the spectrum for launching new products.

7. Offering a network of hospitals

Offering a network of hospitals increases hospitals' bargaining when negotiating prices with pharmaceutical companies. Individual hospitals have low bargaining power because they are one of many hospitals, while there are only a handful of large pharmaceutical players active in Belgium. When pharma companies dislike the offer proposed by hospitals, they opt for another hospital to request data. Hospitals can avoid such situations by combining forces through LynxCare.

4.4.4 Threats

1. Conservative position against 'selling data'

Hospitals are opposed to the idea of "selling MHRs" to pharma companies and feel the responsibility to protect patient data. Some hospitals indicated that they will not let EMRs leave their building (i.e. hospital's internal server). This poses a threat to LynxCare as they cannot run their queries on a hospital's internal server.

However, they indicated that a fair price could lead to a more open stance from their side. When the remuneration for the data is more in line with its market value (i.e. higher), the extra resources could lead to major data structure improvements in hospitals. This practice would ultimately benefit the patients, while a small amount denies the possibility of doing so. To our opinion this is attitude is ambiguous from an ethical perspective: "selling data is wrong, unless it comes at the right price".

2. Suspicion of third parties

A threat related to the aversity of selling EMRs is that hospitals are suspicious of commercial third parties, and trust is at stake. If trust were to be broken due to suspicious practices or dossiers (e.g., double selling data out of contract), large hospitals might fully shut down collaborations, as has happened to other competitors.

Some hospitals indicate that they would rather directly communicate with pharmaceutical companies without a third party. However, hospitals' core business is to heal patients rather than spending their time and resources on collecting and aggregating RWD/RWE form the entire healthcare sector.

3. Legal unclarities

The legal framework for clinical studies is clear to hospitals (i.e. GDPR). However, there seems to be some confusion as to whether GDPR rules for clinical studies are also appropriate for raw data collection by pharmaceutical companies.

3. Legal unclarities

Interpretations of those rules differ between LynxCare's legal consultant and hospital directors. Whereas LynxCare is convinced that GDPR rules apply to raw data, hospital directors were either convinced that the rules for raw data were stricter, or undecided/awaiting clarifications. Especially for selling patient data hospital participants wonder whether this is still within the logical expectations of a patient, that he/she gives when entering the hospital.

The absence of a clear, uniformly interpreted legal framework for RWD collection and exchange with pharma companies can pose a threat for LynxCare: hospitals might be reluctant to collaborate.

4. No hospital protocol in place yet for structural RWD exchange

The internal structure for clinical studies is in place in hospitals. Nonetheless, when it comes to the issue of outsourcing raw data analysis, finding an ideal structural workflow is still challenging for hospitals. Hospital participants indicated that finding a good workflow is a work-in-progress: data coordinators are trying to set up a structure where all hospital stakeholders are aware of what is expected from them, when, and how.

The absence of a workflow currently poses a threat for LynxCare: hospitals are not fully ready to take on large data projects where synchronized workflow is required.

Currently there is some frustration from hospitals in how individual physicians are approached without the approval of a clinical data coordinator/DPO/responsible director. Hospital managements and ethical committees often feel disrespected when pharma companies and/or third parties directly talk to doctors or hospital pharmacies without their consent. Pharma companies and/or third parties answer to this concern by mentioning that it makes no sense to go to an ethics committee or management without a concrete project. Pharma companies and/or third parties feel they need to always start a conversation with a doctor, look at the medical missing interests, what are the possibilities and make a concrete plan before you can talk to the management or ethics committee. This tactic may benefit pharma companies and/or third parties when the doctor and/or hospital pharmacist understands their innovative vision and gives also an internal push forward to get research studies approved. Even when pharma companies and/or third parties have built up already a relationship with hospital management and ethical committee members, often they forget that hospitals management and ethical committee approval procedures need to be respected as they will have also the last say for a research project approval. Asking hospital managements' and ethical committees' permission to approach the doctors and/or hospital pharmacies instead of approaching them without consent will give hospitals an emotional feeling to be respectfully included in the research projects and help build back the trust between pharmaceutical and medical sectors.

5. Competition from other startups

Hospital experts mentioned their collaborations with other data startups (e.g., Telemis, Ontoforce, ...). This means that LynxCare has some competitors to be aware of. However, these startups' business models do not involve RWD/RWE, which proves our point that LynxCare's value proposition and technological capabilities remain unclear to hospitals. Hence, clarification on LynxCare's part is deemed necessary.

5. Discussion

Our discussion starts with a general discussion of our main research results (more scientific outlook).

Based on our results, we give strategic recommendations for different stakeholders that can aid in making this RWD/RWE evolution a success in general. We finish by discussing the limitations of our current paper, as well as our advice for future research.

Side note: all findings in the discussion reflect results from our interviews, unless clearly indicated to come from our literature review or unless accompanied by a source.

5.1. General discussion

5.1.1 RWD/RWE uses during a drug's life cycle

Even though RWD/RWE has only emerged during the last decade, the phenomenon has grown as an important factor for multiple applications throughout a drug's life cycle. Our interviews indicate the importance of RWD/RWE for pharmaceutical companies is most prominent in the post-launch phase within the framework of an MEA contract (to assess clinical and budgetary uncertainties related to a new drug, before moving into a definite reimbursement). A white paper by Hughes et al. (2016), that indeed indicates that RWD/RWE's largest value is in during post-launch, found that RWD/RWE usage for clinical uncertainties could save a pharma company about $200-$600 million due to safety and value demonstration. Our current research showed that RWD/RWE is mainly required during post-launch to feed budget discussions. The implications for post-launch budgetary uncertainties in financial terms could therefore be even more impactful (i.e. than the $200-$600 savings found by Hughes et al., 2016). Participants indicated that too much uncertainty could lead to a denied definite reimbursement, thus leading to large losses for companies.

RWD/RWE is also increasingly used to assess clinical uncertainties during post-launch (e.g., effectiveness in real-world). At market launch, clinical value is already calculated based on RCT results (e.g. efficacy and safety). Still, clinical uncertainties arise because of the efficacy-effectiveness gap: RCTs can assess efficacy, or the "effectivity under controlled, randomized, optimal research settings" but cannot ensure such results will remain when applied in real-life (i.e. cannot assess effectiveness). The gap needs to be bridged by pharmaceutical companies with an RWD/RWE collection. In orphan drugs the clinical value of RWD/RWE even increases as little data on efficacy can be collected during RCTs due to a lack of patients available for recruitment. As a result, assessing thoroughly its effectiveness in real-world is indispensable for payors before going into a definite reimbursement.

MEAs, which are built around collecting RWD/RWE, are becoming the standard for innovative, expensive and orphan drugs.

An interesting, to date largely unexplored type of MEA are pay-for-performance contracts. These are on the table internationally and an assessment of their value needs to be made. So far, payors are excited about the concept on the condition that solutions are found to meet their concerns (for concerns see earlier, Section 4.1.1 p.32); for each concern we suggest a solution:

1. Initiatives such as LynxCare can provide a solution for the incompleteness of registries by providing high quality clinical and outcome data.
2. Assessing whether an effect is significant or not is indeed difficult for complicated metrics such as the assessment of tumors. However, in the case of simple metrics or surrogate metrics pay-for-performance could be very valuable. E.g. Hepatitis C significance of treatment can be assessed with a simple metric: lab results will either indicate that the virus has disappeared or not. When uncertainties involve more complex measures, surrogate metrics (i.e. proxies to measure complex phenomenon, that are very close but easier to measure instead) can be used to assess significance of treatment effects. Simple metrics and surrogate metrics facilitate the implications of pay-for-performance in practice to all stakeholders.
3. The administrative burden for hospitals is also an understandable objection, but such administrative work can be outsourced to a third party. The third party then takes a small commission on reimbursements obtained by pharmaceutical companies. In the end, this would be in all stakeholders' best interest. Hospitals now do not receive reimbursements for treatments without effect, while this option would not increase the administrative burden, while largely insuring their investments in innovative medications. A small medical start-up for instance could take up the administrative work for some extra income.

Evolutions such as the increasing importance of MEAs and the emergence of pay-for-performance lead us to believe that RWD/RWE will become more important in the future. Even more so when once RWD/RWE can be unlocked and collected, when its quality increases, when its value is better estimated and understood (e.g., by payors), and when all these improvements can reveal new domains of application. In addition, secondary use of big data is a societal trend and will even become more important with the advancement of technological innovations such as Artificial Intelligence that allow to make sense of large amounts of unstructured data.

Lastly, we believe that RWD/RWE can increase new drug's speed to market; RCTs are a lengthy process and we already see for e.g., orphan drugs that Phase 3 can be postponed until after market launch. A similar procedure could be copied in other innovative or expensive drugs in the future. An increased speed to market has two advantages for pharmaceutical companies: 1) creating accelerated value for patients and benefiting society as a whole, which is in line with the main raison d'être of pharmaceutical companies; 2) an increased speed to market will increase revenues, which will satisfy shareholders.

RWD types required	Pre-clinical development	Clinical development	Market launch	Post-lauch
P&R (4.4.1)		• Positioning • Calculating standard of care	Value dossier: • Performance data from abroad or competitors • Disease burden and budget impact	MEAs: • Performance evaluations • Budgetary evaluations • -(e.g. applied in a Pay-for-performance) Class revisions: • cf. value dossier
Other use-cases (4.4.2)	• Identifying areas of clinical need (= compounding)	• RCT design • RCT recruitment • Early dialogue • Measuring current patient flows		• Logistic and operational • Marketing processes

Table 7 New use-cases of RWD/RWE for pharma companies found in interviews are indicated in green

RWD/RWE uses found in our literature review were all mentioned during the lifetime of the interviews with pharmaceutical companies. Hence, RWD/RWE uses are applied quickly by the industry.

They even added RWD/RWE uses that we did not come across during the literature review (Indicated in Table 7 in green), such as positioning, measuring current patient flows, budgetary evaluations during post-launch (instead of only during market launch), class revisions, logistic/ operational, and marketing processes.

However, the use-cases of RWD/RWE were also discussed during hospital interviews and then we did not come across all applications for the broad healthcare industry found within our literature review: E.g. stimulating patient adherence, physician segmentation, and evaluation of quality of care can be application domains in hospitals in the future.

5.1.2 How improved hospital collaboration models could improve RWD/RWE delivery

The previous paragraph emphasized the increasing need of RWD/RWE for pharmaceutical companies. However, during interviews the diffused and difficult to access character of such data sources became apparent (cf. Table 5, Section 2.2). The richest, yet most difficult to access, data source for clinical outcome data is the EHR, retrieved within hospitals. Many of the other sources in Table 5 are extracts/ summaries from EHR data, hence cannot provide the same granularity. Furthermore, when pharmaceutical companies succeed to access hospital data (e.g. through single EHR database releases via physicians) – which is rather uncommon -, they experience this data is largely unstructured and embedded in different data formats, making it difficult for pharmaceutical companies to analyze and aggregate the data from multiple hospitals. Lastly, anonymization has been found problematic due to ethical constraints within hospitals who believe such low-level database releases are more of a pseudonymization than anonymization. All these burdens account for low quality and completeness of data. In addition, physicians are tired of the administrative burden that is caused by additional data requests from pharmaceutical companies without being properly incentivized. These findings revealed the need for a better collaboration model with hospitals in the future to retrieve EHR.

But even more importantly, no source exists yet that integrates data from different RWD/ RWE sources. Pharma companies would like to see lineages between EHR outcome data, clinical data, epidemiological data and claims data. A possibility to link all of these sources would be the National Insurance Number (Dutch: "Rijksregisternummer") which is always present in all RWD/RWE sources. This is a better alternative than using patients' names, however, we do realize that the National Insurance Number only party anonymizes aggregated data as when the party who owns the data has access to a source that links National Insurance Number with names. Nonetheless, when the data aggregating party is prohibited from accessing the identification source that links National Insurance Numbers to names, this would be a considerably anonymous, or pseudonymized, option.

In conclusion, a solution is needed that better unlocks EHR data to increase speed and accessibility, taking away the need for other derivative data sources and limiting the administrative burden for hospitals. In our assessment data hubs (i.e. third parties who integrate, aggregate and anonymize data from different RWD/RWE sources) can provide a business model solution to unlock EHR data, to limit administrative burden for both hospitals and pharmaceutical companies, while aggregating data retrieved from multiple hospitals and other RWD/RWE providers.

To address these issues, pharmaceutical companies currently consult CROs. CROs support pharmaceutical companies in setting studies in hospitals by offering services such as project management, database design and build, data entry and validation, coding, statistical analysis, validation programming, safety and efficacy summaries, and final study reports for clinical studies (Stone, 2019). However, when working with CRO's, there is still a delay on data as a fully-fledged study is set up, most of the data gathering is done manually thus it generates a big cost (which prevents using CRO's for gathering RWD at scale), hospitals complain about the administrative burden this generates both in terms of follow up as in terms of answering data requests from CRO's, the format doesn't allow for additional/more granular data capture if needed in a second phase, and most importantly, these studies do not allow for a continuous data capture aggregated over multiple centers.

As such, pharmaceutical companies desire a third party, that can collect, anonymize, and aggregate multi-hospital data that is shared with them within structural collaborations and ad hoc data projects. Performing data analyses could be an additional service offered by that same or a complementary third party, but pharmaceutical companies prefer raw data releases so that they can perform their own post hoc analyses. Moreover, pharmaceutical companies favor quick, high quality data. This third party should include EHR in their model as this is the most rich, granular data source, especially for outcome data.

5.1.3 Role of LynxCare within the pharma industry

LynxCare's business model offers two types of value for the pharmaceutical industry:

a. Unlocking EHR data

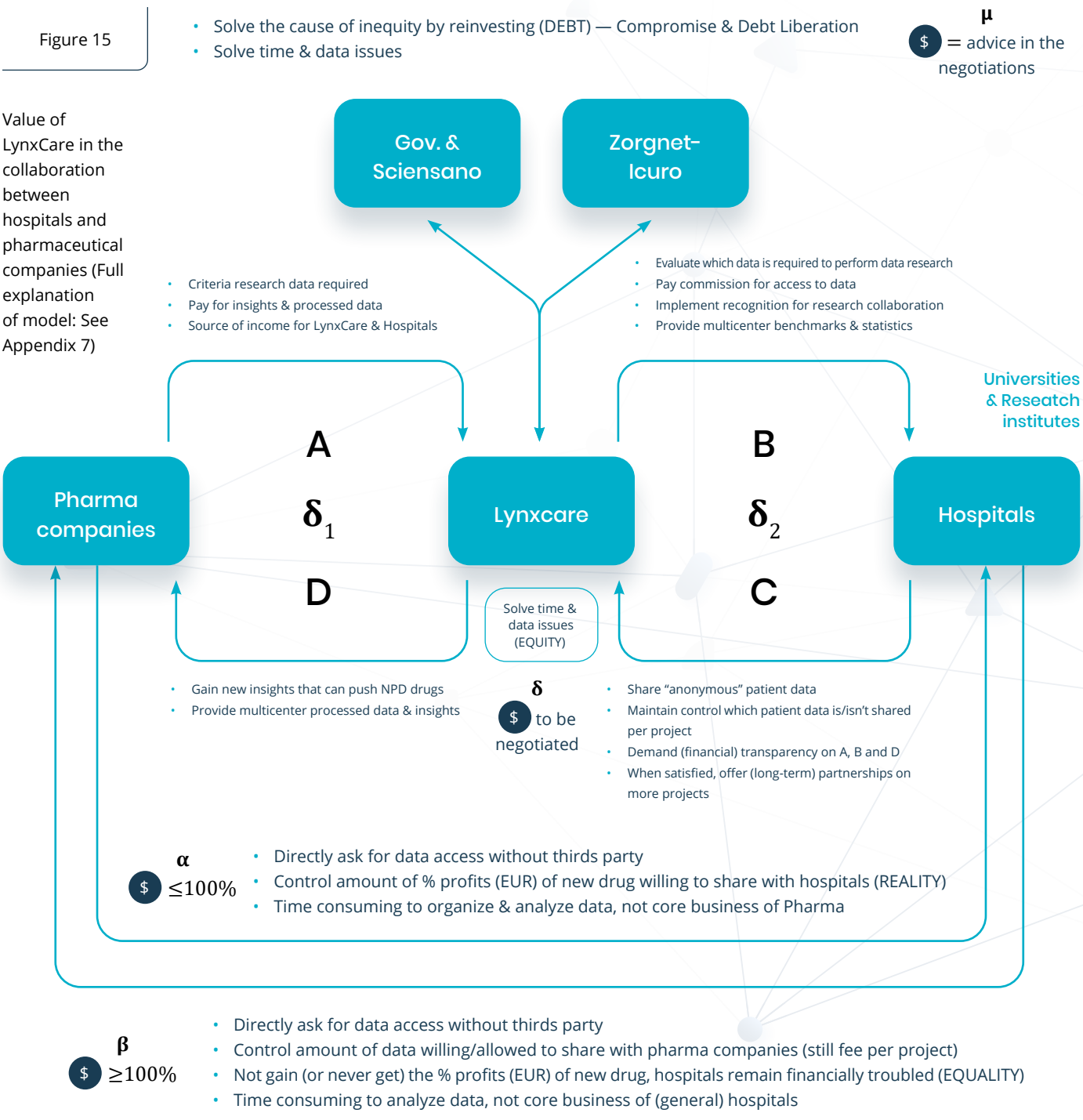
EHR data is currently "locked" for pharmaceutical companies as they cannot directly access it due to legal and technical constraints. LynxCare unlocks EHR data by transferring raw data from hospital servers to a cloud outside hospital premises. Consequently, the data is processed in a structured, aggregated, pseudonymized, and coded format.

b. Aggregation of multiple data sources (hospitals, pharmacists)

This is very valuable for pharmaceutical companies as they experience difficulties when cooperating with multiple hospitals that it is too cumbersome, not cost-efficient (i.e. requires too much time for little data) and data consistency (data should be coded, structured the same way) over all centers is very important to maintain. In addition, aggregated RWD/RWE provide pharmaceutical companies with more representative data and the possibility to follow up their patients for a longer period (e.g. when a patient leaves the hospital but continues treatment with regular pharmacist).

Figure 15

Value of LynxCare in the collaboration between hospitals and pharmaceutical companies (Full explanation of model: See Appendix 7)



In addition, LynxCare's model offers four types of value for hospitals:

a. Searching for a middle ground

Hospitals are astonished by some pharma companies approaching them and asking to gain access to data free of charges, when they have to explain to other pharma companies that the raw data is not direct accessible to them by current law standards or that processed data is not ready at their disposal when visiting hospitals.

Hospitals often feel that the amount of skills and time that needs to be invested from medical staff to collect their required raw data and/or processed data is not always being respected and/or fairly financially rewarded, e.g. recognizing a brain tumor by a brain head surgeon on an MRI is not an easy task in comparison to checking a chest CT scan by master medical students. Hospitals believe they are being neglected when authorities enter negotiations with pharma companies. As many hospitals are financially struggling, hospitals are taking a mindset that they should hold back the data to offer themselves a last bargaining chip when negotiating directly with pharma companies before collaborating directly with them. Some hospitals are starting to process and to analyze the raw data themselves instead of collaborating with pharma directly or through a CRO. In both ways, hospitals are holding the data as a bargaining chip as hospitals now deem fair that by a "fair-share revenue scheme" they should receive a portion of the pharma companies' profits for launching new drugs on the market that were developed thanks to their hospitals (collected and processed) data. [Figure 15: Black arrow going to the left — Mentality: EQUALITY β = Hospitals viewpoint is that the one providing the raw data to proceed further to processed data has the last say and advocating towards a 'revenues-fair share' model].

Some pharma companies do not see the logic in this argument, pharma companies are inclined to think they are the ones taking all the risks when developing and researching on a new drug. [Figure 15: Black arrow going to the right — Mentality: REALITY α = Pharma companies' viewpoint is that the one providing the money for processed data has the last say in financial matters].

Though, at first it is important for as much pharma companies as hospitals to agree upon on a middle ground, which ought to be both of their staffs/stakeholders are being paid for their performance and time invested in collecting and processing the data. At second, some hospitals insist on receiving a portion of the pharma companies' profits for launching new drugs on the market that were developed thanks to their hospitals (collected and processed) data. From their perspectives, it was even suggested pharma companies may be holding back their capital gains and therefore the loss of trust between them continues to increase.

b. Not their core businesses & setting priorities

Yet the above-mentioned loss of trust may unconsciously originate actually from the difference in their core businesses. Hospitals are where people who are seriously ill or injured are examined, treated and cared for, where one or more forms of medical specialist help and the related nursing and care services can be provided day and night (Pinkhof, 2010).

Recently hospitals in Belgium have acquired the status of being defined as companies, but hospitals are still challenged with finding the balance between attempting to make profits, providing optimal patient care and scientific research (especially in the case of university hospitals). In hospitals interviews, patient care was mentioned as their main focus, but to remain operational making profits and conducting research studies were becoming as equally important; in the context of other questions within hospitals interviews, we noticed that the financial theme was often being emphasized in their answers. From this, we believe the current priority for hospitals is to find new financial income streams; data collecting, processing and analyzing answers this need, however processing the raw clinical data is not part of their core business. Pharma companies put their emphasis on developing pharmaceutical drug care for the individual patient with an eye for rational and user-friendly pharmacotherapy (Pinkhof, 2010). Hospitals often forget about pharma companies that "they hold the scientific know-how, the management capabilities, and the physical and technological capacities to develop treatments. Pharma companies have doubled down on developing products that help protect public health and find cures to diseases. On one level, it has endeavored to live up to this promise through massive investments in R&D. In a free-market society where every company tries to be better and faster than its competitors, pharmaceutical companies armed with intellectual property rights and, in many cases, the right to set prices, have developed, produced, and marketed products that have made people heathier. For that, we should be thankful." (Massachusetts Institute of Technology, 2020)

Also pharma companies are being challenged with finding the balance between helping patients (by means of their new drugs successfully being developed and put in markets) and to maximizing shareholder value for pharma companies' investors (pharma companies now need to provide good short-term performance, show a sound midterm strategy and have conviction around your long-term strategy as the industry is being shaped by shareholder value) (Bobkoff, 2019). Pharma companies understand the potential RWD holds to show effectiveness and thereby hopefully gain faster market access and a full reimbursement approval; still pharma companies do not hold infinite budgets and they are not willing to dedicate more (financial) resources than presently.

However, pharma companies are fully aware the fastest to market will win in their competitive landscape; flexible manufacturing capabilities are essential to compete in current market (Chew, 2016). Pharma companies have solved this by focusing on delivering on their core services, implementing new technologies and relying on outsourcing. Outsourcing has allowed pharma companies to gain access to new development expertise and span any gaps in manufacturing capabilities to increase speed on go-to-market projects (Chew, 2016). So, outsourcing of data processing to a third-party data processing company (e.g. LynxCare) is for pharma companies a logical decision.

When pharma companies choose to manage risks by fostering closer relationships with strategic partners, pharma companies are able to enhance their operational agility (Chew, 2016).

c. Towards a collaboration model working with third-party LynxCare

Pharma companies and hospitals can choose instead to outsource from LynxCare their data processing and analyzing expertise and solve the issues of time consumption and allocating resources out of their core businesses.

A few hospitals suggested to LynxCare perhaps instead of the "fair-share revenue scheme" to introduce a long-term access fee for pharma companies to gain a clear overview of a processed data page (from small and easily clinical collected data); and for bigger special projects (e.g. data research for rare cancer) to be paid by a payment/ commission per project and gain sole access from pharmaceutical side to data until the end of project, this guarantees lower risks for all involved stakeholders that data will less likely be leaked out or damaged. [Figure 15: Arrows A, B, C, D — Mentality: EQUITY $\boldsymbol{\delta}$ = LynxCare sees itself as a mediator that can facilitate for better cooperation between hospitals and pharma companies, and LynxCare proposes that the value of processing and sharing data steps ($\boldsymbol{\delta}1 + \boldsymbol{\delta}2$) contributing to the development of a new drug ought to be negotiated per project and paid accordingly to negotiations $\boldsymbol{\delta}$, $\boldsymbol{\delta}1$, $\boldsymbol{\delta}2$].

This will provide for hospitals the transparency they desperately require knowing who is looking at the data [Figure 15: Arrow C]. The insights are free for hospitals to use to enhance their hospital standard of health quality operations, pharma companies will meanwhile have the option to decide upon which insights they wish to share or not with the rest of pharmaceutical industry once they finished and wrapped up a collaboration project with LynxCare and hospitals in the LynxCare tools. This will clear up at first the reluctance between pharma companies and hospitals to work or finance together on a project as partnerships would be only exclusive according to the project needs and at second clear up who will reap off the benefits of the project as the stakeholders who need and who make the effort to set it up in order to properly frame and collect RWE in the first place, they will be also the first ones to gain from the initial discovered valuable insights [Arrows A, B, C, D].

d. Involving government or other organizations

Pharma companies and hospitals suggested to LynxCare to expand the collaboration model by inviting the government (through Sciensano) and Zorgnet-Icuro to give advice in the negotiations.

d. Involving government or other organizations

Pharma companies will feel they have been given a chance to negotiate why they should not have to carry all the costs, it seems a fair point considering if they are being asked to share profits of a new drug with other stakeholders (LynxCare and hospitals) per project across the collaboration model. Hospitals will feel protected by Zorgnet-Icuro (where some members are hospital directors) who will advocate for hospitals interests to be protected during negotiations [Figure 15: Three-pointed arrow and Arrows A, B, C, D].

This would lead to a system where all systemic inequities are being addressed by pharma companies, hospitals and LynxCare together. Do not forget that today many hospitals are financially struggling, if hospitals close down, this could lead to loss of much valuable raw data, this affects as much hospitals to remain operational as indirectly the livelihood of new drug development research studies in pharma companies to take place. [Figure 15: Mentality: COMPROMISE & DEBT LIBERATION **μ** = No one is very happy, but each stakeholder gets what they want by removing together the initial challenges which means it's a good compromise. Ideally in future, money per project can be negotiated by the government (through Sciensano) and Zorgnet-Icuro to liberate hospitals from long-term debts].

In addition, pharma companies and hospitals will benefit administratively in terms of time gained and avoid employees to leave with depression/burnouts from having to manually organize all requested raw data.

5.2. Strategic recommendations for different stakeholders

Based on our research results, we give our recommendations to all stakeholders that were involved in this project. LynxCare's recommendations were based on the SWOT.

5.2.1 LynxCare

The SWOT from the viewpoint of pharmaceutical companies and hospitals has led to 4 types of strategies (Table 8) based on Figure 7.

Figure 15

Strategies for LynxCare to consider when entering the pharmaceutical industry

Strength-opportunity strategies	Strength-Threats strategies
• LynxCare's advanced technical capacity and near real-time services can be used to maximize rapid data delivery • LynxCare's broad RWD/RWE coverage and integration can be used to meet the need for a full hospital – or full healthcare sector - data infrastructure • LynxCare's good image and ethical mindset can be used to position themselves as a partner of hospitals • LynxCare's aim for a fair division of resources should be maximized to meet hospitals' need for financial resources.	• LynxCare's ethical mindset should be maximally unfolded and communicated toward hospitals to limit the threat of hospital's conservative position and suspicion of third parties. • LynxCare's legal framework can be used to minimize the threat of legal unclarities by creating clear contracts that guarantee an ownership of data to hospitals as well as maximum transparency • LynxCare's Technical capacity can be used as leverage over hospitals who believe they have the technical capacity in place to perform data aggregation and analyses of a similar level. • LynxCare's competitive advantage of solid trust-based relationships with hospitals should be maintained to beat competitors • LynxCare's combination of medical & data knowledge combined should be played off against their competitors • LynxCare's broad RWD/RWE coverage and integration of many hospitals and healthcare data providers might mitigate some hospitals' conservative position
Weakness-opportunity strategies	**Weakness-threats strategies**
• LynxCare's incapability of primary data capture can be mitigated by persuading hospitals that are in need of financial resources to improve their data input in exchange for higher remunerations and to provide primary data capture tools. • LynxCare's positioning as a hospital partner could make up for their unclear selling proposition (which was caused by their dual role as data supplier and buyer, causing hospitals to fear becoming subordinate to pharma's interests) • Capturing and integrating data from many hospitals and/or other healthcare stakeholders should make up for the limited completeness of data	• LynxCare should minimize hospitals' perception of them as to having an unclear selling proposition to avoid feeding their levels of suspicion, by guaranteeing full transparency and actively involving hospitals in the collaboration model with pharmaceutical companies • LynxCare should start building experience within the pharma industry by taking on small projects, to avoid threat from competitor startups

Based on this integrated table (Table 8) we have come to five concrete strategic recommendations for LynxCare:

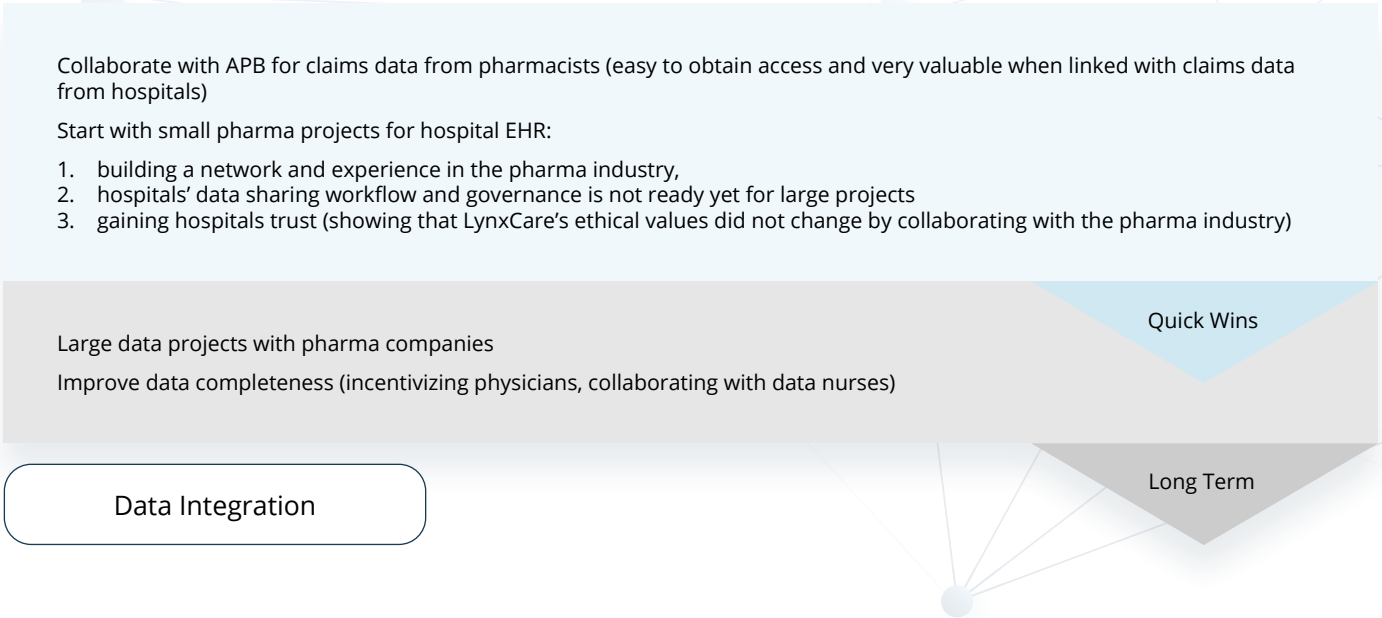
1. Focus on data integration from many hospitals and other healthcare stakeholders

LynxCare's value is focused around the opportunities and richness of data that the EHR has to offer. However, also to its limitations, such as missing data points and a difficult assessment of validity (how does one assess the correctness of inserted data by physicians). This implies that other data sources, such as P4 studies, will remain essential data sources to pharma companies for obtaining robust and causal data.

Nevertheless, LynxCare's offer can play a central role within MEAs. While P4 studies are currently perceived by the CTG as subordinate to P1/2/3, LynxCare offers unique value compared to P1/2/3: completely naturalistic data, integrated from many hospitals and other healthcare data providers. Within an MEA it might therefore be more interesting to pharma companies to opt for LynxCare rather than P4 studies. As LynxCare's unique selling proposition lies within data integration from different healthcare data providers, involving as many hospitals/healthcare data providers should, to our point of view, LynxCare's main aim in short term.

Building a solid network might persuade hospitals with a more conservative position. When hospitals see that LynxCare cooperates with their competitors and that they are benefiting from it, even the more conservative hospitals are expected to follow and allow for their MHRs to leave the building (i.e., their internal servers). Otherwise, conservative hospitals will miss out on valuable insights & financial resources and will be labeled as non-innovative.

In the long run, LynxCare can opt for a more complete model where they find a solution for missing data points. If it is possible to cancel these limitations for CRO's in P4 studies, this must also be possible for LynxCare, by offering incentives to physicians and embedding data nurses in the process. This is for the long run as first their current technological offer should be assessed in small projects with pharmaceutical companies.

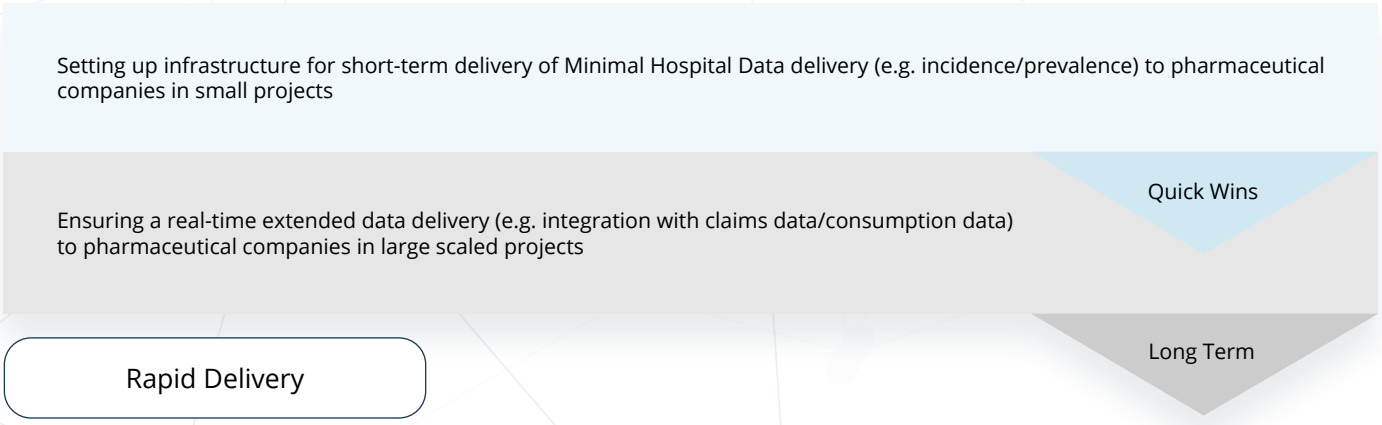


2. Seize opportunities for rapid RWD/RWE delivery

A market gap exists for RWD/RWE that can provide pharmaceutical companies with information on budget impact and disease burden during market launch, preferably before pharmaceutical companies submit their reimbursement application.

This offers an opportunity for LynxCare; 1) ensuring RWD/RWE on incidence/prevalence already during market access; 2) ensuring claims data to assess current standard of care budgets. Consequently, pharmaceutical companies might be able to prevent some cases of MEA and pharma companies immediately retain their full list price without having to give discounts in confidential contracts.

Also in post-market there is a case to be made for a rapid RWD/RWE delivery. Pharmaceutical companies have to collect RWD/RWE within +- 2 years, which is difficult with current delays of 1-2 years on IMA-data and MHD-data. In the absence of data to solve uncertainties, pharmaceutical companies end up in a spiral of temporary contracts with, often increasing, discounts. In addition, evolutions in the standard of care during waiting periods might outdate requested IMA-data and MHD-data by the time of delivery. LynxCare can address this issue with their near real-time data deliveries within 3 weeks after the request. 3 weeks versus 2 years will make a huge difference for pharmaceutical companies in revenues because the net price per package will be higher without uncertainties (i.e. discounts).



3. Strategic approach toward hospitals

A perceived transition of LynxCare's value proposition, from hospital data consultant to a dual role of serving both hospital and pharma companies might meet resistance from hospitals. However, there are good ways to deal with this and in essence, they all come down to maintaining good relationships within hospitals by means of a willingness to be transparent and honest (i.e. considering hospitals as a full partner in the collaboration model with pharma).

3. Strategic approach toward hospitals

In addition, hospitals do not want to carry the costs of setting up a data exchange structure in their hospital and want to maintain control over their data. The former can be achieved by letting pharmaceutical companies pay a basic financial contribution to set up infrastructure in hospitals. We believe this would be most convenient through a third party such as LynxCare: pharmaceutical companies pay contributions to a third party, who is then responsible to set up the infrastructure in hospitals, hence, limiting the practical/administrative burdens for hospitals and pharma companies. Letting hospitals maintain control over their data can be achieved through a platform/software (see further, paragraph C) that allows setting up projects on a pay per project basis.

A. Support hospitals' ethical values

LynxCare should be aware of the current conservative mindset in hospitals. This goes further than mere legislative unclarities but is more of an ethical matter. In addition to legal constraints, hospital directors find it contestable to commercialize patients' data without first obtaining their permission. Our recommendation is to be careful when negotiating contracts in giving the wrong impression of being 'too commercial'. Instead, indicate that the patient's interests are a priority. In pharma interviews we have heard that everything they do is in the patient's best interest at heart. This should be the starting point to lead all negotiations. A clear communication strategy should be implemented to change this impression of commercialization to an impression of enabling research and better care for patients.

B. Improve data coordinator/DPO/data director contact in all hospital engagements

Even though hospitals do not have a structural workflow in place yet for data collaborations, there is always a centrally appointed person who is responsible for data governance (e.g., clinical data coordinator, DPO).

In many hospitals, this will usually be the person that is responsible for clinical studies. LynxCare should first run data requests and permission to contact individual physicians by this central point of contact. We know LynxCare shows the willingness for a transparent and ethical approach and therefore believe that this could be extended even further within their current ethical framework.

In addition, we believe that software could play a part in this (see further; paragraph C), by communicating automatically collaboration requests by pharmaceutical companies toward hospitals, so central points of contact within hospitals (e.g. DPOs) can approve certain participation to and data analyses for projects.

C. Platform to automatize data requests and to increase transparency about hospital data use

Hospitals want an overview of what happens to their data after it leaves the hospital:

- What analyses does the third-party integrator perform with the data?
- To which pharmaceutical companies is the data/evidence resold?
- What does each pharmaceutical company need which data for?
- Is the data interpreted correctly?

LynxCare can set up a platform on pharmaceutical companies can place data requests.

Data requests are forwarded to hospitals and hospitals can confirm participation in any project by giving permission through the platform; and can see which other hospitals are participating in which projects. LynxCare then collects all relevant information from the participating hospitals, enters into personal contact with them when hospitals indicate on the platform that they wish to give extra nuances about certain variables in the EHR, and carries out aggregations, analyzes and quality checks. Finally, LynxCare publishes the results on the platform, which both participating hospitals and the requesting pharmaceutical company have access to. In this way, the process is very transparent and both pharmaceutical companies and hospitals receive a guarantee that LynxCare does not form a wall that separates them, but rather supports and facilitates the exchange of data. To emphasize this even more, a functionality could be built into the platform that the various stakeholders can also enter into direct contact with each other (e.g., one chat room per project).

D. Develop financial model in consultation with hospitals; e.g. remuneration on "a per context" basis

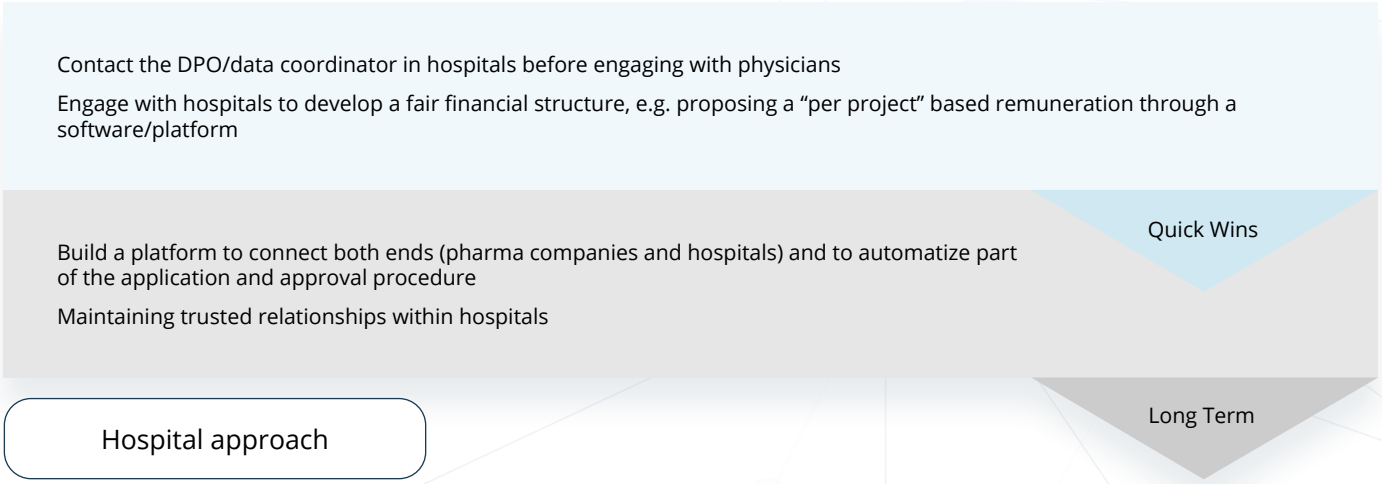
Hospitals indicated that they want their fair share of the revenue. In interviews we heard they aspired a price according to the market value of the data (e.g., one respondent mentioned €30.000).

However, it became clear that hospitals were undecided on a vast remuneration model and/or price and were open for conversation. Nonetheless, they deemed it important that they were actively involved in these negotiations, which would be allowed when implementing such "per context" approval platform/software (recommended in C).

Hospitals could approve data requests on a project basis, thus deciding "per context" whether they want to participate for a given remuneration. The feasibility of such model and related financial expectations should be further explored by LynxCare's from the hospitals' side.

D. Develop financial model in consultation with hospitals; e.g. remuneration on "a per context" basis

Another recommendation when approaching hospitals is to emphasize that LynxCare's network of hospitals increases their bargaining power when negotiating prices with pharmaceutical companies. Individual hospitals have low bargaining power because they are one of many hospitals, while there are only a handful of large pharmaceutical players active in Belgium. When pharma companies dislike the offer proposed by hospitals, they opt for another hospital to request data. Hospitals can avoid such situations by combining forces through LynxCare. This point of view is likely to appeal to all hospitals, and especially to the ones aiming for a long-term collaboration with LynxCare.



4. Take the lead for legal clarification

Our SWOT states: "LynxCare's legal framework can be used to minimize the threat of legal unclarities".

To our opinion, this is definitely the case: by showing legal awareness LynxCare could gain hospitals' trust. Nevertheless, interpretations of legal frameworks related to GDPR and exchange of EHR differ between and within different stakeholders (i.e. LynxCare and hospitals). LynxCare's legal interpretations are perceived by hospital participants as subjective – although it has been drafted by the leading healthcare GDPR law firms -, and hospitals, pharma companies and payors are requesting an objective clarification.

This presents an opportunity for LynxCare to take the lead in clarifying legal ambiguities. LynxCare could get in touch with Zorgnet-Icuro, an interest group that is occupied with formalizing data governance within hospitals. As a part of data governance formalization, they could also provide an objective legal clarification that can consequently be communicated in webinars toward hospital director, organized by LynxCare/Zorgnet-Icuro. As a result, legal constraints within hospitals for data exchange with pharmaceutical companies can be mitigated. In addition, by showing willingness to support Zorgnet-Icuro in data clarification and education, LynxCare shows to stakeholders that legal matters are important to them. This action is likely to be respected by hospital as patient data are a sensitive subject to them.

Setting up fair contracts with hospitals

Requiring legal clarification for GDPR rules from Zorgnet Icuro

Organizing webinars in collaboration with Zorgnet-Icuro to communicate legal framework toward hospitals

Quick Wins

Long Term

Legal Strategy

5. Outclass competition by hospital network, medical and IT expertise, and technical capacity

LynxCare's competition could come from other startups, from substitutes, such as CROs, and from their clients, ambitious pharma companies and hospitals who also aim to do large data-aggregation projects. LynxCare has, to our opinion, three main strengths to beat competitors:

A. LynxCare's Technical capacity can be used as leverage over hospitals who believe they have the technical capacity in place to perform data aggregation and analyses of a similar level. Hospitals are also a competitor of LynxCare because they are not yet fully aware of LynxCare's full possibilities. LynxCare can give webinars about the opportunities that their technological capacity offers and educate them about allocation of time and resources that were required to get their infrastructure in place, so that hospitals understand that setting up such projects cannot be one of their side activities.

B. LynxCares competitive advantage of solid trust-based relationships with hospitals should be maintained to beat competitors. As mentioned earlier, hospitals and pharmaceutical companies have bad experience with some competitors, which gives LynxCare a competitive advantage. In addition, they have been active within multiple Belgian hospitals for a couple of years and have had the opportunity to build a network. Such network should be valued at all costs.

C. Their combination of medical and IT expertise which they have been applying during quality checks of their analyses. A recommendation is to take it a step further and showcase excellence by not only reactively showing medical expertise but also proactively: having a witty, responsive attitude toward information in the EHR that proves medical expertise.

5.2.2 Authorities and interest groups

1. Provide clarification of laws about data ownership and anonymization

Authorities should be open to provide additional clarification about the exchange of hospital RWD/RWE when requested by any stakeholder (see earlier, Section 4.4.4(3).

Zorgnet-Icuro is an interest group that has been occupied with data governance in hospitals by setting up a template for standard GDPR data processing contracts; and could additionally support hospitals by clarifying ambiguities encountered in the legal framework.

2. RIZIV/ INAMI and other payors need to proceed with RWD/RWE upskilling programs

Pharma participants indicated that they had finished successful projects for assessing clinical uncertainties based on RWD/RWE. However, they noted that the authorities were very critical toward this data and kept finding clinical weaknesses in the data, that, to their opinion, were not weaknesses related to their product but inherent to RWD/RWE. They told that an internal upskilling had been required within their firm to correctly understand RWD/RWE and suggested that the payors should do a similar RWD/RWE upskilling. The Belgian payors (RIZIV/INAMI) have had one RWD/RWE upskilling program in December 2019, "Real World for Data" (Sharma, 2019). Upskilling programs are, however, not systematic yet. To our opinion, this upskilling program was a good start but should be followed up by other programs that can shed new light on interpreting and researching RWD/RWE.

3. Internal education on RWD/RWE Sources

Interviews showed that Belgian payors (RIZIV/INAMI) are uninformed about possibilities of RWD/RWE sources for data collection. Pharma participants indicated during their interviews that payors asked for RWD/RWE to solve uncertainties, without giving clear instructions on what metrics data should be collected, and without being aware whether these metrics were accessible in RWD/RWE sources or not. Their assumptions were confirmed during our payors interview. We found this a remarkable finding; the organization responsible for giving instructions on RWD/RWE collection was unaware about its actual possibilities. Apparently, the EMA is working on a project to research possibilities of RWD/RWE. This project should be completed asap and continued at national level. Every country has its specific health data infrastructure; hence, opportunities and hurdles will be specific to their country.

Our recommendation to the governmental payors is to indicate clearly what metrics they are looking for to solve uncertainties and have some indication on how realistic it is to gather these in current RWD/RWE sources. In practice, RWD/RWE are required for almost all innovative drugs, they shall make it explicit what they are looking for so that hospitals and pharma companies can be proactive.

4. Embrace innovation induced by RWD/RWE

RWD/RWD have potential to be the force that facilitates the way that we develop and remunerate drugs. Phases during RCT process could be optimized, such as improving hypotheses and study design, increasing speed to market. An increased speed to market aids in overcoming areas of high unmet need. Currently, regulation is designed to protect the authoritative character of RCTs and therefore mitigates innovation.

5.2.3 Hospitals

1. Awareness about need/ types of RWD/RWE

Interviews indicated little awareness from hospitals about RWD/RWE sources, and about the actual needs of pharmaceutical companies. One hospital participant stated it was interesting to see what pharmaceutical companies considered as essential RWD/RWE sources, implying lacking knowledge from their side. Practical and technical hurdles pharmaceutical companies experience should not be underestimated. Hospitals should take a more in strategic approach to this, also on the level of federated hospital data networks. Lots of hospitals are duplicating work and building up technology that is already available, whereas this energy could be put into bridging RWD/RWE gaps (e.g. EHR data exchange).

2. Designing an internal protocol for proactive RWD/RWE collection

Hospitals indicated that they were working on designing a workflow for data collection within hospitals, centered around a data coordinator/DPO. We recommend they continue streamlining workflows/protocols around data projects in hospitals.

Moreover, it is important that hospitals take a proactive attitude toward building up RWD/RWE, so requests can be accommodated quicker. Currently hospitals are reactive toward data requests from pharmaceutical companies, meaning they only start collecting RWD/RWE once a request comes in. This causes data delays, and consequently keeps patients in need for a longer time. In contrast, they must ensure data is prepared for and accessible to pharmaceutical companies.

Better designed RWD/RWE exchange protocols in hospitals to provide better routes to access data and improved use of data are essential for a faster adoption of RWD/RWE use within the Belgian healthcare landscape (Miani et al., 2014).

3. Education on legal framework of RWD/RWE

During interviews we noticed that expertise about data privacy legislation was limited in our hospital participants (e.g., privacy rules on whether patients and/or the ethics committee must give their approval prior to data exchange with third parties, e.g. pharmaceutical companies). According to general director interviewees, legal knowledge was present in other areas within their hospital; we received pointers that are better suited for questions about GDPR legislations in the form of DPOs, clinical data coordinators, and data nurses. The assumption that legal expertise was indeed present in other areas of the hospital than the general directors was confirmed during our interview with an R&D manager, who was very well informed about the legal framework but acknowledged that some legal clarifications on data exchange were necessary. Nevertheless, general directors are the decision makers in hospitals, and they recognized lacking knowledge of technical details, albeit being entitled to make the decisions about it.

We believe this knowledge is missing in decision makers because of general confusion about the legal framework, which is not uncommon as RWD/RWE exchange is a new subject. Many different interpretations of laws were given in interviews. When we confronted the payors with this, they admitted that this was an area of improvement and that it is the responsibility of interest groups (e.g. Zorgnet-Icuro) provide legal clarification and education. We advise hospitals to be open to suggestions on how to deal with data exchange. As such, they do not hamper innovation induced by RWE/RWD hence, access of new medicines to the market.

4. Embracing the value of an intermediate third-party integrator as ultimately benefiting the patients

Currently, many hospital data are unutilized, meaning many insights are going lost that could valuable for internal quality improvement. Secondary use of data could lead to additional improved hospital and patient care and this opportunity should therefore not be ignored. However, hospitals' primary goal is to take care of patients. As hospitals today are budget-restraint and do not have sufficient time and resources available, multiplying the effort of building technology themselves in each hospital is in our opinion not at the core of their activity, drains resources that are needed to treat patients and foremost do not adequately answer the needs (e.g. uniform coding and aggregation over several hospitals, access to unstructured data, liability for anonymization, third party independence) to make RWD collaborations between hospital-pharma a success. Given a fair market price, hospitals should be open to third parties that offer technology, can establish a network to provide influx of pharma projects, take the responsibility of compliance, security and privacy matters, and make this to the core of their activity.

Better input of data in EHR will improve patient care (Gores & Patel, 2018): data quality is sometimes rather poor now and ultimately data input and quality can only be improved from within the hospitals. Data input in hospitals should be as easy as possible, not to burden the clinical staff. New technologies can be implemented to provide insights in the quality of the data on a continuous basis.

5.2.4 Pharmaceutical companies

1. Develop an integrated RWD/RWE strategy, e.g. through real-world data hubs

Het gebruik van MEA steeds meer de norm wordt dan de uitzondering (zeker voor innovatieve drugs, orphan drugs, expensive drugs). In deze agreements wordt steeds achter RWD/RWE gevraagd, wat dus in belang zal stijgen in de toekomst. In het kader van value-based medicine, waarin een medicijn eerst zijn waarde moet aantonen in de praktijk vooraleer er terugbetaling kan komen , verwachten wij dan ook dat na verloop van tijd MEA's een basisonderdeel van het drug pricing en reimbursement zullen worden. Bedrijven kunnen beter beginnen met RWD/RWE te zien als een opportuniteit dan een last en een RWD/RWE strategie ontwikkelen.

We therefore recommend pharma companies to take a strategic approach to RWE and integrate RWE into the entire product lifecycle.

Already in the clinical development stage RWE can demonstrate product's practical value even before they are approved. As such, it reduces the demand and costs of post-market research (ICON, 2017).

A clear path forward - supported in the interviews with both hospitals and pharma companies – could be setting up the "real-world data hubs". Pharma companies could take a first step wherein they financially contribute (i.e. paying a standard fee) to a project for setting up the data exchange infrastructure in hospitals (see earlier, Section 5.2.1(3C). A quality infrastructure in hospitals will guarantee pharma companies a swift data access, while hospitals remain in control through a per project approval process.

2. Value reputable RWD/RWE sources over contestable sources

Pharmaceutical companies indicated that standardized market reports are an important source of information. We look with concern upon such data collection practices:

- Data are collected contestable legal circumstances, often without approval by authorized decision makers. Instead, physicians are contacted directly by market research agencies and are offered money in exchange for data and insights.
- These results are lacking quality: also the scientific validity is contested, as no one is present to control and validate data quality.

Hospitals are bothered by these practices as physicians are being contacted under the radar without their approval. Such practices contribute to a negative perception of pharmaceutical companies with regard to data collection.

We understand pharmaceutical companies' despair for data. Nonetheless, supporting such questionable practices should at all times be avoided. They could regain hospitals' trust by opting for reputable RWD/RWE sources over less ethical sources (i.e. sources that do not engage in contestable legal circumstances).

3. Give clear instructions on required criteria and data

Hospitals often have difficulties understanding the data requirements from pharmaceutical companies. Just like CROs, LynxCare aims to specialize in translating data requests to data mining protocols in hospital data. However, data requests need to be solid and clear in order for LynxCare to perform an accurate job. This is still a point of improvement from pharma's side.

5.3. Research project limitations and recommendations for future research

Our research project had two limitations:

First, due to time limitation we were unable to address all stakeholders appointed by participants. We were definitely open to participants' suggestions, e.g., during our pharmaceutical interviews we received the recommendation to interview the payors/ HTA bodies for the purpose of our study, which we consequently integrated into our research design. However, we were unable to address all recommendations (e.g., DPOs, data nurses, physicians). The scope of our study might have been too broad for some of the participants that we interviewed:

Hospital1 [hospital CEO]: "The scope of your subjects is very broad: you cover both strategic and technical subjects. For accurate technical information, you need to address a DPO. But to cover the entire the scope of your research, you need to interview a CEO, a DPO, a data nurse, a DPO, and a physician that is involved in clinical studies... You should interview the entire ecosystem."

Even though we were constrained in the number and of interviewees, we made sure most we included experienced decision makers on RWD/RWE exchange in hospitals and pharma companies. These provided sufficient confidence about the representativeness of our data and conclusions.

Second, neither of us authors had a background/ experience in RWD/RWE which made it difficult at times to understand everything during our interviews; hence, to ask more thorough questions. During the course of the ICP, we always researched subjects that were unclear to us, and we noticed our expertise had increased enormously toward the end. Interviews started proceeding more fluently and we felt more confident to go further in depth. Luckily, interviewees were very understanding of the situation and we could at all times rely on our supervisors' medical. To avoid important conceptual mistakes and to validate research results, a final draft of the paper was sent to a representative number of interviewees (cf. Section 3.4(4), to allow for feedback and checks on the validity of the paper. This leads us to believe that this limitation should not have led to biased results.

6. Conclusion

What makes LynxCare unique to the pharmaceutical industry is their ability to unlock and mine unstructured (i.e., EHR) and structured (i.e., claims) hospital data.

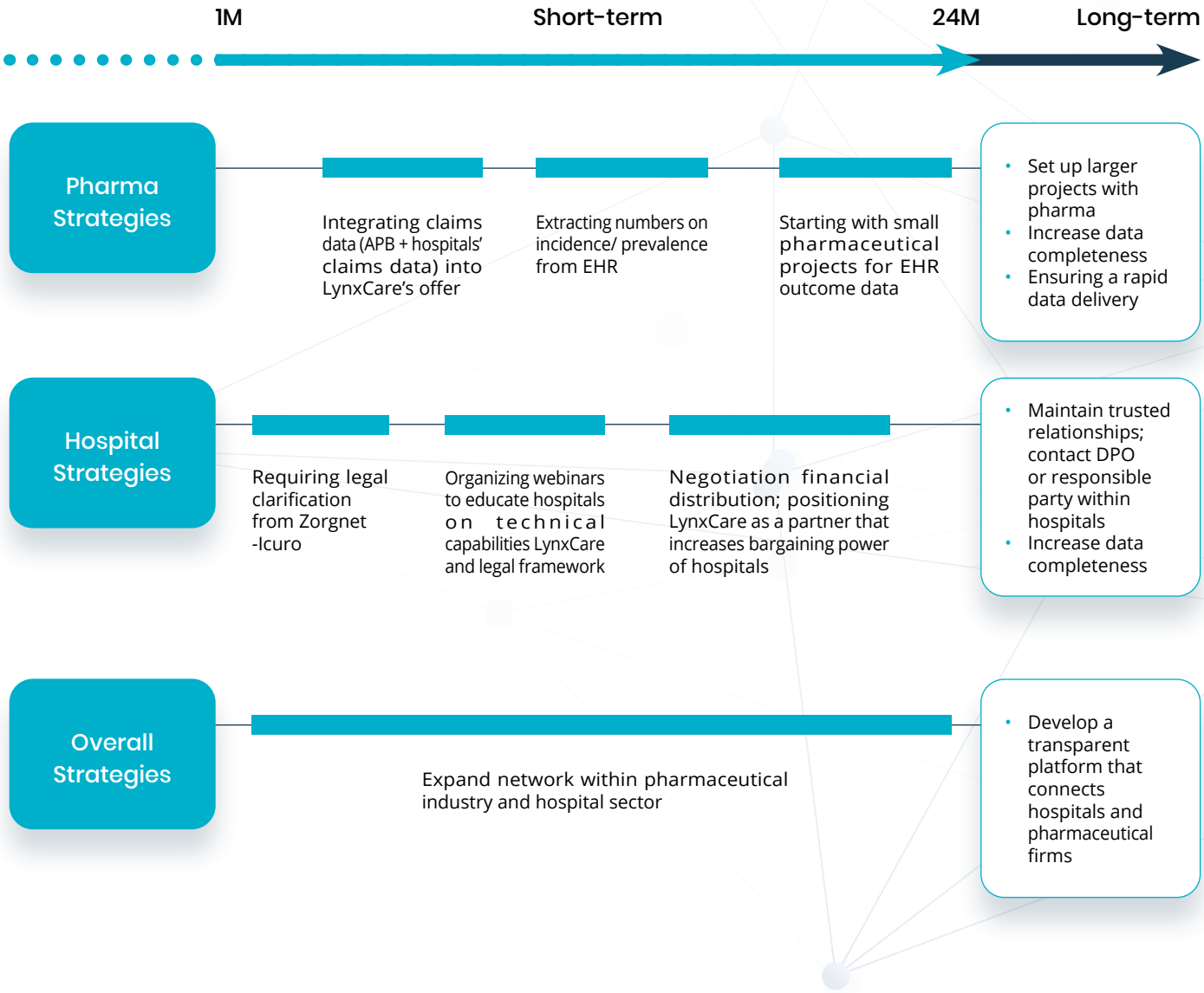
In addition, LynxCare already has a network within hospitals, while maintaining a clean image within the hospital and pharmaceutical sectors, which differentiates them from competitors. There is a major pharma industry need for aggregated hospital data, as well as aggregated data from the entire healthcare industry. Such data needs are mainly present within the framework of MEAs, to solve budgetary uncertainties (e.g., number of patients, number of responders). Solving clinical uncertainties is also becoming increasingly an application domain of RWD/RWE.

LynxCare possesses both the technological tools and the medical background to capture this market opportunity. Especially the combination of both, as well as, their agility as a private company makes them the ideal candidate for the job. In general, we advise LynxCare to make their priority to continue extending their network in both the hospital and pharmaceutical industry, while maintaining a good relationship with hospitals that are already their clients. We therefore believe LynxCare should not move too fast but take it up one project at a time and build up experience from there. Moreover, building trusted relationships within hospitals is indispensable to turn it into a success. We know LynxCare already has a solid image within hospitals they can build from but advise them to provide legal clarification first to hospitals. Internal hospital politics are a sensitive matter and losing trust in one hospital might lead to sector wide distrust. When legal clarification is obtained, LynxCare should start with smaller projects with hospitals to prove that in spite of their dual role (serving both hospitals and pharma) they are still their partners. We are convinced that both hospitals and pharmaceutical companies will be very prepared to collaborate in larger projects once they see how it is a success in smaller projects.

The most important alternative that pharmaceutical companies have for LynxCare are, to our respect, CROs as they have a similar value proposition. CROs also facilitate indirect collaboration between hospitals and pharmaceutical companies. The difference with LynxCare, is that CROs cause a large delay on data and that they have a questionable image in the hospital sector. In contrast, LynxCare has a competitive advantage of delivering data quicker thanks to their technological capacity, being RWD/RWE experts, and starting with a clean slate.

In our discussion we have given our strategic recommendations on the short term (i.e. quick wins) vs. in the long-term. In what follows we provide a timeline for strategic guidance:

Figure 16 Short-term and long-term strategies to penetrate the pharmaceutical industry



7. References

- AHRQ (2015a). Databases Used for Hospital Quality Measures. Content last reviewed June 2016. Agency for Healthcare Research and Quality, Rockville, MD. Retrieved on 25 May, 2020 via https://www.ahrq.gov/talkingquality/measures/setting/hospitals/databases.html
- AHRQ (2015b). Examples of Hospital Quality Measures for Consumers. Content last reviewed March 2016. Agency for Healthcare Research and Quality, Rockville, MD. Retrieved on 25 May, 2020 via https://www.ahrq.gov/talkingquality/measures/setting/hospitals/examples.html
- Annemans, L. (2016). Principles for using real world data throughout an innovative medicine's lifestyle [manuscript]. (Retrieved April 27, 2020), from prof. Annemans via email
- Annemans, L. (2017a, September 1). The use of real world data throughout an innovative medicine's lifecycle. (Retrieved April 27, 2020), from https://www.riziv.fgov.be/nl/themas/kost-terugbetaling/door-ziekenfonds/geneesmiddel-gezondheidsproduct/terugbetalen/innovatieve-geneesmiddelen/Paginas/innovative-medicins-lifecycle.aspx
- Annemans, L. (2017b). Outcome based pricing and reimbursement of innovative medicines with budgetary limitations. Discussion document for the multistakeholders meeting on pharmaceuticals (Meeting DG GROW 12th September 2017).
- Annemans, L. (2018). Lieven Annemans: We need to reach a common understanding about real world data. Retrieved on 30 May, 2020 from https://blogs.bmj.com/bmj/2018/03/06/lieven-annemans-we-need-to-reach-a-common-understanding-about-real-world-data/
- Arpinelli, F., & Bamfi, F. (2006). The FDA guidance for industry on PROs: the point of view of a pharmaceutical company. Health and quality of life outcomes, 4, 85. doi:10.1186/1477-7525-4-85
- Aureen, A., Paris, V., & Lopert, R. (2019). Using Routinely Collected Data to Inform Pharmaceutical Policies. (Paris; OECD Publishing, 2019).
- Bahadur, N. (2008, March 17). Overview of Drug Development [Novartis presentation]. Retrieved from https://admin.ich.org/sites/default/files/inline-files/Clinical_Dev_Plans_-_Namrata_Bahadur.pdfhttps://admin.ich.org/sites/default/files/inline-files/Clinical_Dev_Plans_-_Namrata_Bahadur.pdf
- Barrett, J. S., & Heaton, P. M. (2019). Real-World Data: An Unrealized Opportunity in Global Health? Clinical pharmacology and therapeutics, 106(1), 57–59. doi: 10.1002/cpt.1476

- Blumenthal, D.M., Goldman, D.P., & Jena A.B. (2016). Outcomes-Based Pricing as a Tool to Ensure Access to Novel but Expensive Biopharmaceuticals. Annals of Internal Medicine, 166(3). doi:10.7326/M16-1847
- Bobkoff, D. (2019, April 29). Pharma: an industry shaped by shareholder value. Retrieved June 17, 2020, from https://www.marketplace.org/2016/06/15/profit-pharma/
- Bouet, J., Floch, O., Guerrier, K., & de Neuville, B. (2019). Health Data Hub: an ambitious French initiative for tomorrow's health. OpusLine. Retrieved on 31 May, 2020 from https://www.opusline.fr/wp-content/uploads/2019/03/Note-dActualité-HEALTH-DATA-HUB.pdf
- Bowling, A. (1997). Research methods in health (1st edn). Buckingham: Open University Press.
- Brooks, K. (2017, April 4). Closing the Gap in Real-World Evidence: Parexel's Joshua Schultz discusses research challenges and the need for standards to overcome RWE limitations. Contract Pharma. Retrieved on 15 June, 2020 from https://www.contractpharma.com/contents/view_online-exclusives/2017-12-04/closing-the-gap-in-real-world-evidence/
- Burns, P.B., Rohrich, R.J., & Chung, K.C. (2011). The levels of evidence and their role in evidence-based medicine. Plastic and reconstructive surgery, 128(1), 305–310. doi:10.1097/PRS.0b013e318219c171
- Bussières, A., & Stuber, K. (2013). The Clinical Practice Guideline Initiative: A joint collaboration designed to improve the quality of care delivered by doctors of chiropractic. The Journal of the Canadian Chiropractic Association, 57(4), 279–284.
- Chatterjee, A., Chilukuri, E.F., Knepp, A., Sathore, S., Zabinski, J. (2018). Real-world evidence: Driving a new drug-development paradigm in oncology. White paper by McKinsey&Company. Retrieved June 18, 2020 via https://www.mckinsey.com/industries/pharmaceuticals-and-medical-products/our-insights/real-world-evidence-driving-a-new-drug-development-paradigm-in-oncology
- Chew, R. E. (2016, September 29). Speed-to-Market: Process and Capacity on Demand. Retrieved June 17, 2020, from https://www.americanpharmaceuticalreview.com/Featured-Articles/239808-Speed-to-Market-Process-and-Capacity-on-Demand/
- CLINICAL GYAN. (2018, December 16). Phases of Clinical Trial. Retrieved from https://www.youtube.com/watch?v=RuzoAjNyJr0&fbclid=IwAR0jc_TRPvmeBpPh2ZG4ohSnFoTFzsCXLrp3R_tpNFIUdHJy01UMoxc_fVc&app=desktop
- Comer, B. (2019). Six drug pricing models have emerged to improve product access and affordability. Health Research Institute, PwC US. Retrieved on 29 May, 2020 via https://www.pwc.com/us/en/industries/health-industries/library/6-drug-pricing-models.html
- Cook, K. (2016, October 6). 4 advantages of working with a clinical trial research organization. ContactRoom. Retrieved on 31 May, 2020 from https://blog.contractroom.com/4-advantages-of-working-with-a-clinical-trial-research-organization
- Danzon, P.M. (2018). Affordability Challenges to Value-Based Pricing: Mass Diseases, Orphan Diseases, and Cures. Value in Health, 21(3), 252-257. doi:10.1016j.jval.2017.12.018.

- Department of Health. (2009). Guidance on the routine collection of Patient Reported Outcome Measures (PROMs), (April 2008), 1–28. Retrieved from http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/documents/digitalasset/dh_092625.pdf
- Dixon, T. (2019). Clinical Pharmacy Education, Practice and Research. doi.org/10.1016/C2017-0-01328-9
- Eichler, H., Adabie, E., Breckenridge, A., Flamion, B., Gustafsson, L.L., Leufkens, H., Rowland, M., Schneider, C.K., & Bloechl-Daum, B. (2011). Bridging the efficacy–effectiveness gap: a regulator's perspective on addressing variability of drug response. Nature Reviews Drugs Discovery, 10, 495-506.
- FDA (2018). Framework for FDA's Real-World Evidence Program. U.S. Food & Drug Administration. Retrieved on 29 May, 2020 via https://www.fda.gov/media/120060/download
- FDA, O. of the C. (n.d.). FDA Step 3: Clinical Research. (Retrieved April 27, 2020), from https://www.fda.gov/patients/drug-development-process/step-3-clinical-research
- Franken (2014). Decision making in drug reimbursement. PhD Thesis. Erasmus University Rotterdam.
- Gandjour, A. (2017). Implications of Value-Based Pricing. From CDDF multi-stakeholder workshop, 7-8 September, 2017. Madrid, Spain. Retrieved on 29 May, 2020 from https://cddf.org/files/2017/09/1620-Afschin-Gandjour.pdf
- Gerecke, G., Clawson, J., & Verboven, Y. (2015). Procurement: The Unexpected Driver of Value-Based Health Care. The Boston Consultancy Group and MedTech Europe. Accessed via https://www.medtecheurope.org/resource-library/procurement-the-unexpected-driver-of-value-based-health-care/
- Gores, M., & Patel, D. (2018). RWE: From "Nice To Have" to "Must Have": Are you ready to meet healthcare stakeholders' ever-increasing evidence demands? [White Paper]. IQVIA. https://www.iqvia.com/library/white-papers/rwe-from-nice-to-have-to-must-have
- Gregson, Sparrowhawk, Mauskopf, & Paul (2005). Pricing Medicines: Theory and Practice, Challenges and Opportunities. Nature Reviews Drugs Discovery, 4, 121-130. doi:10.1038/nrd1633
- Guinn, D., Madhavan, S., & Beckman, R.A. (2012). Harnessing Real-World Data to Inform Platform Trial Design. Article from the book "Platform Trial Designs in Drug Development: Umbrella Trials and Basket Trials", Pages 55-68. Retrieved from https://books.google.be
- Haynes, B. (1999). Can it work? Does it work? Is it worth it? The testing of healthcare interventions is evolving. BMJ, 319(652). doi:10.1136/bmj.319.7211.652
- Health & Medicine Week (2018). Real Benefits of Real-World Evidence in the Healthcare Industry - A Quantzig Whitepaper. Achieved from https://search.proquest.com/docview/2016785279?accountid=17215

- Houston, J.D., & Fiore, D.C. (1998). Online Medical Surveys: Using the Internet as a Research Tool. M.D. Computing, 15(2), 116-120.
- Hughes, B., Kessler, M., & McDonell, A. (2016). Breaking New Ground with RWE: How some pharmacos are poised to realize a $1 billion opportunity. www.quintilesims.com
- IQVIA (n.d.). 7 Market Access Trends for 2027. Retrieved on 25 May, 2020 via https://www.iqvia.com/-/media/iqvia/pdfs/library/presentations/7-market-access-trends-for-2027.pdf
- Isomeri, O., & Hemmilä, P. (2018). Market access, pricing and reimbursement of medicines in Finland. Retrieved on 22 May 2020, via https://futurecarefinland.fi/en/2018/06/medicines-in-finland/
- Mägi, K., Lepaste, M., & Szkultecka-Dębek, M. (2018). Drug Policy in Estonia. Value in Health Regional Issues, 16, 1–4. Retrieved from https://www.sciencedirect.com/science/article/pii/S2212109917300936?via%3Dihub
- Makady, A., Goettsch, W., & Zorginstituut Nederland. (2017). GetReal - Project No. 115546 WP1: Deliverable D1.2 Review of current policies/perspectives. Retrieved April 27, 2020, from https://www.imi-getreal.eu/Portals/1/Documents/01 deliverables/GetReal D1.2 Current Policies and Perspectives FINAL_webversion.pdf
- Massachusetts Institute of Technology. (2020, April 16). In the Face of a Pandemic, Can Pharma Shift Gears? Retrieved June 17, 2020, from https://sloanreview.mit.edu/article/in-the-face-of-a-pandemic-can-pharma-shift-gears/
- Meltzer, M. I. (2001, September 22). Introduction to Health Economics for Physicians. Retrieved from https://pubmed.ncbi.nlm.nih.gov/11583768/
- Miani, C., Robin, E., Horvath, V., Manville, C., Cave, J., & Chataway, J. (2014). Health and Healthcare: Assessing the Real World Data Policy Landscape in Europe. Rand health quarterly, 4(2), 15.
- Nell, G. (2018, January 1). Phase IV Studies and Lifecycle Management. Retrieved June 18, 2020, from https://www.sciencedirect.com/science/article/pii/B9780128021033000250
- Nordon, C., Karcher, H., Groenwold, R.H.H., Ankarfeldt, M.Z., Pichler, F., Chevrou-Severac, H., Rossignol, M., Abbe, A., & Abenhaim, L. (2016). The “Efficacy-Effectiveness Gap”: Historical Background and Current Conceptualization. Value in Health, 19(1), 75-81. doi.org:10.1016/j.jval.2015.09.2938.
- Patsopoulos, N. A. (2011, June 1). A pragmatic view on pragmatic trials. Retrieved June 16, 2020, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3181997/
- Perkmann, M., Tartari, V., McKelvey, M., Autio, E., Broström, A., D’Este, P., … Sobrero, M. (2013). Academic engagement and commercialisation: A review of the literature on university–industry relations. Research Policy, 42(2), 423-442. doi:10.1016/j.respol.2012.09.007.
- Pinkhof, H., Everdingen, J., Eerenbeemt, A., Stafleu van Loghum, B. (2010). Compact Medisch Woordenboek

- Quirk's Staff (2018). 26 Top Medical Marketing Research Companies for 2018: A Quirk's resource guide covering medical marketing research companies for 2018. Applied Marketing Science. Retrieved on 29 May, 2020 via https://www.quirks.com/articles/26-top-medical-marketing-research-companies
- Rex, J.H., Eisenstein, B.I., Alder, J., Goldberger, M., Meyer, R., Dane, A., ... Jackson, J. (2013). A comprehensive regulatory framework to address the unmet need for new antibacterial treatments. The Lancet Infectious Diseases, 13(3), 269-275. doi:10.1016/S1473-3099(12)70293-1
- Roose, H., & Meuleman, B. (2014). Methodologie van de sociale wetenschappen. Gent: Academia Press.
- Roots Analysis (2018). Real World Evidence: Market Landscape and Competitive Insights, 2018-2030. [Report Brochure]. Full version of report available from http://www.rootsanalysis.com
- Sciensano (2017, November 29). FAIR Principles. Retrieved June 17, 2020, from https://fair.healthdata.be/fair-principles
- Sharma, V. (2019). Belgian RWE Initiative Proposes Action To Support HTA/Payer Decisions. In Pink Sheet, Informa Pharma Intelligence, 81(48), 7-8.
- Silverman, E. (2013). Effectiveness/Efficacy Difference Too Often Ignored. Managed care. Retrieved on 18 May, 2020 via
- Solnica, B., Dabrowska, M., & Sypniewska, G. (2010). Laboratory Medicine as a Profession and Clinical Science - How to Perform Both of them well? EJIFCC, 21(3), 53–55.
- Stone, K. (2019, July 24). What Are Contract Research Organizations – CRO? CROs Play a Major Role in Drug Development. The Balance Small Business. Retrieved on 31 May, 2020 from https://www.thebalancesmb.com/contract-research-organizations-cro-2663066
- Umuhire, D. (n.d.). Putting real-world healthcare data to work: Pharmacy and health insurance databases. From RWE Navigator/Get Real. Retrieved June 18, 2020 via https://rwe-navigator.eu/use-real-world-evidence/sources-of-real-world-data/pharmacy-and-health-insurance-databases/
- Wenzl, M., & Chapman, S. (2020). Performance-based managed entry agreements for new medicines in OECD countries and EU member states: How they work and possible improvements going forward. [OECD Health Working paper No. 115]. doi:10.1787/6e5e4c0f-en
- Wilkinson, M.D., Dumontier, M., Aalbersberg, I.J., Appleton, G., Axton, M., Baak, A., ... Mons, B. (2016). The FAIR Guiding Principles for scientific data management and stewardship. Scientific Data, 3(1), 1–9. Retrieved from https://www.nature.com/articles/sdata201618.pdf
- Yang, C.C., Yang, H., Jiang, L., & Zhang, M. (2012). Social Media Mining for Drug Safety Signal Detection. SHB'12: Proceedings of the 2012 international workshop on Smart health and wellbeing, pages 33-40. doi:10.1145/2389707.2389714

8. Appendices

8.1. Appendix 1: Comparison clinical of studies: RCTs, Pragmatic studies, and Observational studiesOther RWD/RWE insights

Study design type	Explanatory clinical studies (e.g. RCTs)	Pragmatic clinical studies (RCTs integrating RWD aspects)	Observational studies		RWD from data mining, collection of outcome data, RWE insights
			Cohort studies	Case-Control studies	
Clinical context	Yes	Yes	Yes	Yes	Yes
Economical insights	No	Yes	Yes	Yes	Yes
Aim description	Efficacy	Effectiveness	Efficiency	Efficiency	Effectiveness, Efficiency
Aim	What effect drug in controlled setting?	What effect drug have in real-life?	What effect drug have in real-life?	What effect drug have in real-life?	What effect drug have in real-life?
Directionality	Exposure is assigned before outcome is ascertained	Outcome is ascertained	Exposure is ascertained before outcome is ascertained	Outcome is ascertained before exposure is ascertained	Outcome is ascertained
Internal Validity	High	Low	Low	Low	Low
External Validity	Low to Moderate	High	High	High	High
Sample size	Small to Large sample	Large sample	Large sample	Large sample	Large sample to National size
Study population description	Highly selected	Diverse observed	Diverse observed	Diverse observed	Diverse observed

Study design type	Explanatory clinical studies (e.g. RCTs)	Pragmatic clinical studies (RCTs integrating RWD aspects)	Observational studies		RWD from data mining, collection of outcome data, RWE insights
			Cohort studies	Case-Control studies	
Design	Sophisticated, can be randomized, blinded, controlled design	Simple design to sophisticated design	Simple randomized, blinded design	Simple randomized, blinded design	Simple design
Environment settings	Diverse setting	Diverse setting to Real-Life setting	Real-life setting	Real-life setting	Real-life setting
Analysis	Straight-forward	Account for confounding factors	Account for confounding factors	Account for confounding factors	Account for confounding factors
Development Phases	P1, P2, P3	Mostly P4	Mostly P4	Mostly P4	Preclinical, PI, PII, PIII, PIV
Key insight	Intervention's effect is maximized, statistically credible results	Maximize applicability and generalizability	1) Gather data regarding sequence of events, assess causality 2) Investigate rare exposures 3) Examine multiple outcomes for a given exposure	1) Investigate rare exposures 2) Examine multiple outcomes for a given exposure	1) Maximize applicability and generalizability. 2) Generate hypotheses for RCTs 3) Biomarker identification, 4) Assess trial feasibility 5) New prognostic indicators & patient characteristics identification

- Carlson, M. D. A., & Morrison, R. S. (2009). Study Design, Precision, and Validity in Observational Studies. Journal of Palliative Medicine, 12(1), 77–82. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2920077/
- Institute for Work & Health (Toronto). (2016, February 1). Observational vs. experimental studies. Retrieved June 16, 2020, from https://www.iwh.on.ca/what-researchers-mean-by/observational-vs-experimental-studies
- Patsopoulos, N. A. (2011, June 1). A pragmatic view on pragmatic trials. Retrieved June 16, 2020, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3181997/
- Nordon, C., Karcher, H., Groenwold, R. H. H., Ankarfeldt, M. Z., Pichler, F., Chevrou-Severac, H., … Abenhaim, L. (2016b). The "Efficacy-Effectiveness Gap": Historical Background and Current Conceptualization. Value in Health, 19(1), 75–81. Retrieved from https://www.valueinhealthjournal.com/action/showPdf?pii=S1098-3015%2815%2905067-6

8.2. Appendix 2: Interview guide pharmaceutical companies

Theme 1: pricing models

	Method	Formula and / or example unit	Countries
Cost-plus pricing	Costs of production + profit margin	$/€	
Value-based pricing	Cost-Benefit Analysis (CBA)	Total costs ($) / Total benefits ($)	Australia, Belgium, Finland, France, Germany, Ireland, Norway, Portugal, Russia, Switzerland, Scotland, Canada
	Cost-Effectiveness Analysis (CEA) = treatment impact on life expectancy	ICER = ▲ costs / ▲ effectiveness $ / life years gained $ / QALYs gained	Australia, Belgium, Finland, France, Germany, Ireland, Norway, Portugal, Russia, Switzerland, United Kingdom, Italy, The Netherlands, Poland, Spain, Sweden
	Cost-Utility Analysis (CUA) = treatment impact on quality of life	$/QALYs gained	Australia, Belgium, Finland, France, Germany, Ireland, Norway, Portugal, Russia, Switzerland, Italy, The Netherlands, Poland, Spain, Sweden, Canada, New Zealand

1. Does your company use any of these pricing models/contracts? What is the role of RWD/RWE in each model?

Theme 2: Value of RWD/RWE in pricing and reimbursement

2. What is the importance of RWE in the value dossier?
3. What is the importance of RWE in the post-launch phase?
4. Can you give some specific examples of budgetary uncertainties that are often demanded in MEAs?

5 What are the possible consequences of an MEA on the pricing of the medicine?

A. In Belgium often we get the answer that MEAs can only reduce a price based on RWD but never increase it. The list price seldomly changes but discounts are given. Is this the same for other countries or is it typically Belgian?
B. Do other countries than Belgium also make use of MEAs and what is the impact of RWE in these agreements?

6 Which subtypes of MEA do you use (pay-for-performance,…)?

7 Are there any other types of agreements than an MEA in Belgium where RWD is considered important? What is the impact of RWE on these contracts?

8 In the literature we found that in cases of an unmet medical need alternative regulatory pathways allow drugs to be launched on the market sooner.

A. What are examples of these alternative regulatory pathways?
B. How does this process impact drug price?

9 In the literature we found that in other countries formal structures exist (e.g., NICE in the UK, G-BA in Germany, and TLV in Sweden) for an early dialogue with authorities and payers, that already start during clinical development.

A. Does Belgium also have these formal procedures? Does your company engage in early dialogue?
B. What do you believe are advantages of such early dialogue?

10 In another interview we heard that RWD/RWE is primarily relevant in a health budget discussion rather than a product pricing discussion.

A. Do you agree with this statement?
B. Which role does RWD/RWE play in negotiating discounts?

Theme 3: types of RWE and alternative data sources

11 Which types of RWE do you use and why? Which sources are more valuable? Why?

Types of RWE	+	—
Databases		
IMA-database	1. Consumption data of drugs used within the hospitals 2. Representative data 3. Affordable 4. Accessible	1. No outcome data 2. Only accessible when product is already in the market 3. Only accessible for a running dossier, when RIZIV specifically requires information 4. Labour intense request process 5. Big delay on data 6. Only hospital data, you cannot link it with external data (e.g., when patient is dismissed from hospital and continues treatment with a regular pharmacy) 7. limited diagnostic data (no clinical data)
MZG-database (hospital data)	1. Representative data	1. Big delay on data 2. Not enough detail
Registers		
Registers (e.g., cancer registers, TARDIS)	1. Representative data 2. Cancer register can be used for budget impact (#patients) 3. Tardis = comprehensive outcome data 4. Potential for longitudinal data series (e.g., Nordic countries) 5. Potential to contain lots of data (if it would be entered systematically) Samenvatting van de voordelen = er wordt op een geprotocolleerde manier nagedacht over de samenstelling van een dataset	1. Limited #registers available 2. Only indirect access (need to ask physician - Depends on willingness of physician to share their data) 3. No top-quality information, much information is not available (e.g., mutations) 4. Two years delay on data 5. Many missing data points (quality depends on willingness doctors) 6. willingness of doctors in Belgium is limited, need more incentives = hangt af van register tot register, kijk naar registerlijst
IQVIA database	7. LPD database (GP-sentinal network) 8. Hospital set (?)	1. Commercial data (perceived by hospitals as a commercial partner) 2. Hospitals don't like collaborating with IQVIA
healthdata.be (Sciensano) = op een geüniformeerde manier registers controleren	1. Epiodemiological information 2. Outcome based information 3. Facilitator, zorgen voor goedkeuring op vlak van gdpr 4. Architectuur: standaardisatie in gegevensverzameling	1. Expensive 2. Labour intense 3. Focus on MEA projects → enkel binnen legal framework

Types of RWE	+	—
Registers		
Statbel	1. Mortality and population stats	
APB = apotheek database	1. Gives access to pharmanet data 2. Easy to build a dossier, no need for a 'legal framework' (RIZIV explicitly requiring the information)	
Zorgnet Icuro = still in development	1. Not operational yet	1. Only for Flanders
PITTER	1. Information on labo tests	1. No access yet
CIVARS = database from RIZIV	1. Information on drug prescriptions in hospitals 2. Reimbursement authorization databases for Chapter 4 products (both in hospitals and retail pharmacies) 3. Contains information on patient population (#patients that are currently treated with certain criteria)	1. Accessible through IMA (same advantages) or RIZIV 2. Limited to H4 drugs
Data Generation		
P4 clinical studies	1. Observational data 2. Prospective data generation	1. Very expensive 2. No priority for CTG level

12 We would like to go over this list of RWE alternatives and complete its strengths/opportunities, as well as its weaknesses/threats.

A. We hear from professional organizations that some pharma companies prefer going directly to hospitals for MZG-data and ICD-data instead of working with an intermediary (such as IQVIA). Why would go you for the direct option?
B. Pharma companies can outsource their clinical research to CRO's (e.g., to do RCTs/P4). For some RWD a CRO is set up to collect the data in hospitals. What are the advantages/disadvantages of working with a CRO?

13 We would like to go over this list of RWE alternatives and complete their strengths/opportunities, as well as its weaknesses/threats.

Alternatives to RWE	+	—
RCTs	1. Causality (strongest level of evidence)	1. Not representative
Expert Reviews	1. Fast, high level insights in patient care trajects	1. Opinion, subjective 2. No real data
Social listening	Lots of qualitative data	Relevance perhaps not optimal
Market Research	Close to RWE	Other purposes: internal decisions

Theme 4: collaboration models pharma-hospitals

14 We have heard in other interviews that the collaboration models regarding RWE between pharma and hospitals are unstructured so far. Is this different in other countries?

A. Which countries?
B. What do these collaboration models look like?
C. Are these good examples to copy in Belgium?

15 What types of RWD/RWE do you need the most? Why? Which ones do you have difficulties accessing?

16 Today we know that the collaboration models are not very structural. What is the best collaboration model for you?

C. What would you require from this collaboration model?
- I. Data required vs. only statistics (to answer study questions)
- II. Dd hoc vs. long-term structural collaboration vs. midterm
- III. Direct collaboration vs. third intermediary party
(of combinatie met Zorgnet Icuro)
- IV. Other requirements?

16 D. How do hospitals perceive the benefits for participating with RWE centers? Arrange by order of importance

- I. Financially every time paying per project or a fee that give access to answers & all data needs over long period of time. (pot maken van alle farma bedrijven)
  1. Financially in a commission per project
  2. Financially in a structural contribution to the center
  3. Directly or through a third party
- II. Providing benchmarks about participating centers
- III. Providing disease specific dashboards to support the centers
- IV. Allow the center to use the RWD for other research projects
- V. Other benefits you would like to offer to centers in exchange for RWD access?

17 RWE data hubs are a limited number of centers per country with which pharma has a structural collaboration and continuous access to RWD that together form a representative image of the population?

A. Do you think such data hubs could meet all your RWE needs?
B. How many centers and what type of centers should be part of such a data hub network per country?
C. Do you see a role as a pharma to set up these centers?
D.Do you need a trusted third party and what should be its role in setting this up?

Theme 5: role government/hospitals

18 What role should the government (RIZIV/CTG) in the collaboration model between hospitals and pharma?

19 We are also going to interview both hospitals and RIZIV in our next steps

A. According to you, which questions should we definitely ask hospitals?
B. Which questions should we definitely ask RIZIVv?

Theme 6: Benefits and restrictions of RWD/RWE for pharmaceutical companies

20 In general, are there still other use-cases of RWE that we haven't discussed yet?

A. What role can RWD/RWE play for evaluating rare patient features?
B. E.g., optimization of logistic/operational/sales processes

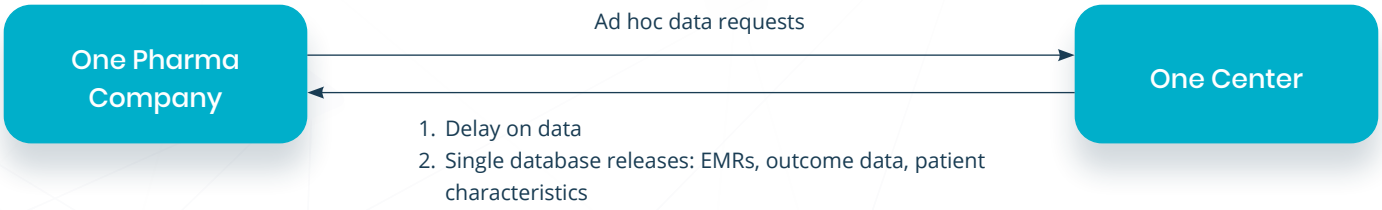
21 What are important restrictions for using RWD/RWE for pharmaceutical companies?

8.3. Appendix 3: Interview guide hospitals

1 Can you complete the following table?

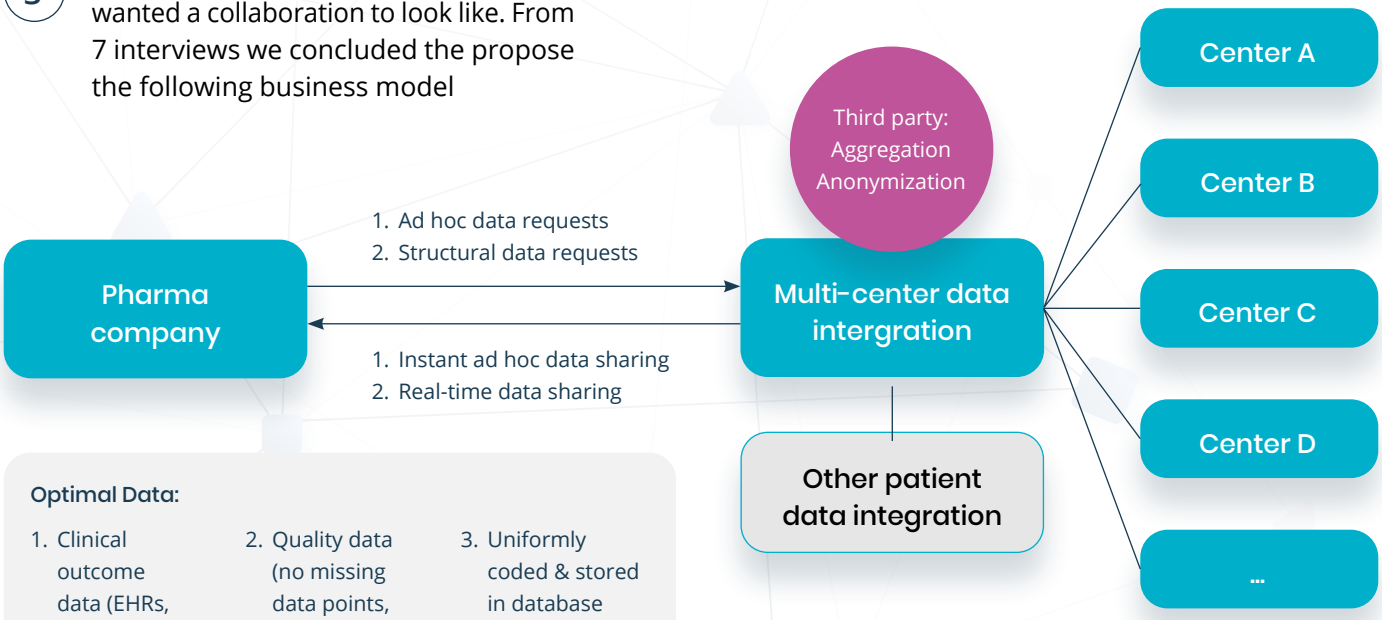
Processing		Permission patient required	Permission ethical committee required
1	**Data processing by hospital or third party (processor) for internal care quality management** Extraction and structuring of personal data of patients / study participants to evaluate and promote the quality of care within the hospital, as stipulated in an Order Statement. Incl. training of used algorithms and processing software	Yes / No	Yes / No
2	**Data processing by hospital or third party (processor) for scientific studies in continuous monitoring (purely retrospective - secondary data)** Extraction and structuring of available personal data of patients / study participants from pre-existing clinical data sources, as well as of the personal data subsequently added to these data sources for clinical purposes, for monitoring and study purposes, as determined in an Assignment Statement. Incl. training of used algorithms and processing software	Yes / No	Yes / No
3	**Questionnaires by hospital or third-party processor for scientific studies (prospective - primary data, possibly supplemented with secondary data)** Collection of new personal data of patients / study participants via questionnaires (PROMS / PREMS), as well as extraction and structuring of these new personal data for study purposes, as stipulated in an Assignment Statement. Incl. training of used algorithms and processing software	Yes / No	Yes / No
4	**Anonymization by hospital or third-party processor in the context of data valorization.** Anonymization of extracted or structured personal data of patients / study participants for internal use and / or transfer to third parties, as stipulated in an Order Statement. Incl. training of used algorithms and processing software → pseudo-anonymization / coding	Yes / No	Yes / No

2 We hear from pharma companies that at the moment, collaboration models (pharma-hospitals) aren't very structured for data exchange. What is your perspective on the collaboration between hospitals and pharma on the following issues?



- Who DOES the work to generate and aggregate the data? The departments (e.g., data nurses) or the hospital (e.g., IT department)?
- What technical means ARE currently used?
- DO you receive financial contribution for the data or only for the work performed?
- Who IS responsible for the anonymization of the data?

3 We asked pharma companies what they wanted a collaboration to look like. From 7 interviews we concluded the propose the following business model



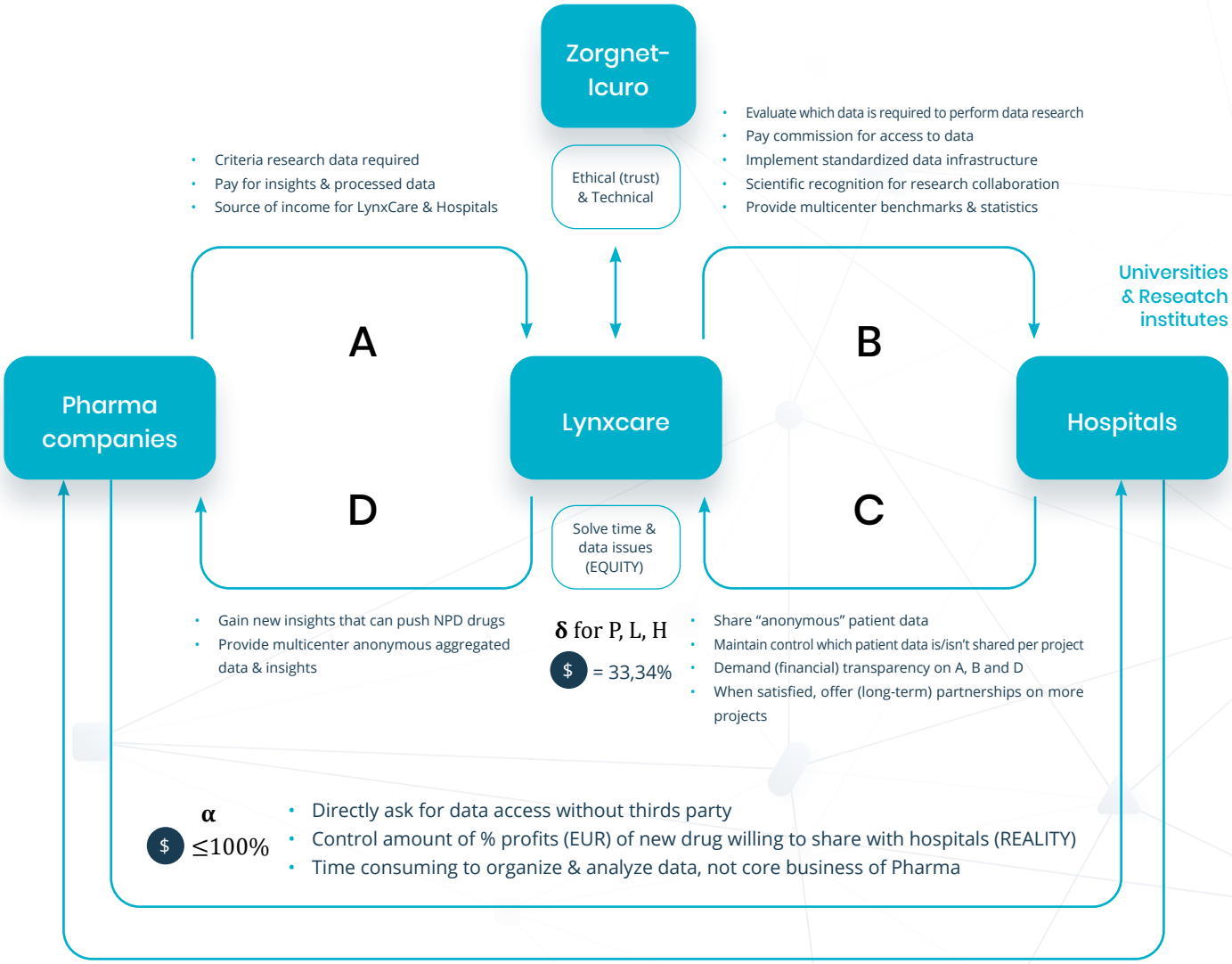
Optimal Data:

1. Clinical outcome data (EHRs, pharmacy data, claims data, laboratory data)
2. Quality data (no missing data points, traceability)
3. Uniformly coded & stored in database over all centers

What do you see as the main challenges and opportunities for you as a hospital to answer to such business model. Imagine we would be working out the proposed business model. What do you think about the following:

- Who SHOULD do the work to generate and aggregate the data? The departments (data nurses)/the hospital (IT departments)/a third party.
- What technology WOULD be required to answer these RWD needs? ?
- Who SHOULD receive financial rewards for delivering the data? Or should this only be for the work performed?
- Who SHOULD be responsible for the anonymization/ aggregation?

4 Pharma companies indicated they prefer to rely on a third party to set up the data infrastructure in a consistent way, LynxCare would like to help hospitals in there. The following could be a proposed business model:



Can you give feedback on A, B, C, D and fill in anything missing?

A = Pharma companies → LynxCare
B = LynxCare → Hospitals
C = Hospitals → LynxCare
D = LynxCare → Pharma companies

5 Do you know what RWD/RWE means? What is it used for?

6 We are also going to interview both hospitals and RIZIV in our next steps

A. Do you have examples of specific projects with these data sources?
B. What hurdles do you encounter?

Medical data sources	Are you involved in exchanging this data? In which projects?	What hurdles?
Minimale Ziekenhuis Gegevens (MZG) Some hospitals directly collaborate with pharma, providing anonymized reimbursement data.		
InterMutualistisch Agentschap (IMA) =Reimbursement data that the hospital submits is gathered and provided by IMA to pharma Agency that has multiple objectives, such as collecting, consolidating and aggregating data of the 7 Belgian Mutualities before giving this data to the RIZIV and pharma companies. • Permanent sample (EPS) • Health concerns from hospitals • Medicines "Farmanet.be" • Data population from National Registry • Patient files and contacts		
CIVARS = internet platform offered by IMA / RIZIV to pharma. Contains reimbursement authorzation data: doctor completes reimbursement request for specific patient (fills in criteria for patient), platform automatically indicates whether a patient will receive a refund. Commercial 3rd party databases E.g., IQVIA		

Medical data sources	Are you involved in exchanging this data? In which projects?	What hurdles?
Zorgnet-Icuro =Initiative from hospitals. Umbrella organization of Flemish hospitals, initiatives from mental health care and elderly care. Zorgnet wants to set up a network to collect and centralize hospital data.		
Clinical registries (e.g., cancer registry) =Many departments in the hospital provide data to Sciensano (government registry) or private registries, who provide data to pharma. E.g., cancer registers, TARDIS.		
P4 clinical studies (e.g. with CROs) =As little clinical RWD is available, in exceptional cases studies with a CRO are set up where the CRO comes to the hospital to gather the data. They control the quality of the data.		
RCTs =Highly controlled environments to perform P1/P2/P3 studies to test a medicine's efficacy and safety in a small population.		

7 Here you the advantages and disadvantages of MZG-data that were mentioned in our pharma interviews:

Types of RWE	+	–
MZG-database (Hospitals data)	1. Representative data	1. Big delay on data 2. Not enough detail

A. What is your opinion on this?
B. Can pharma companies get an easy access to the data?
C. Is a legal framework obligatory to get access?

Can you rank these in order of importance? Are there any missing?

8 What role, what solution can RWE data hubs provide for you?
Pharma companies are interested to have long term collaboration with limited number of medical centers per country to provide RWD/RWE (= RWE datahubs). In return, these are several advantages they can offer:

I. Financial incentives
II. Providing benchmarks over all participating centers
III. Gaining disease-specific insights from these datahubs
IV. Allow the center to use the RWD for other research projects
V. Allow the center to use the RWD for internal operations & quality measurements
VI. Provide technological means to help hospitals building up RWD databases
VII. Other benefits you would like to offer to centers in exchange for RWD access?

9 Financial incentives: What should these look like?

1. Financially in a commission per project
2. Financially in a structural contribution to the center
3. Directly or through a third party
4.→ "revenue sharing" model (% from pharma revenues willing to be paid for the processed data)

10 Pharma companies feel that current governmental initiatives (CTG/RIZIV) aren't sufficiently fulfilling their RWD/RWE needs.
How should the government support private and hospital initiatives to answer these RWD/RWE needs?

8.4. Appendix 4: Assessing the understanding of the legal framework. Responses from hospitals interviews

	Permission required of patient?	Permission required of ethical committee?
Areas: assess whether permission patient/ethical committee is required in the following domains (for full assignment see legal table in Appendix 2)	1. Internal operation 2. Retrospective studies 3. Prospective studies 4. Anonymization	5. Internal operation 6. Retrospective studies 7. Prospective studies 8. Anonymization
Correct answers (interpretation legal consultant LynxCare)	1. NO 2. NO 3. NO (only scientific, YES legally required) 4. NO	1. NO 2. NO 3. NO (only scientific, YES legally required) 4. NO
Hospital 1: CEO	1. NO (psychologically subjects, then YES) 2. YES 3. YES 4. YES	1. NO (psychologically, then YES) 2. YES 3. YES 4. YES
Hospital 2: Head of Innovation and Research Institute	1. NO 2. YES (except registers) 3. YES 4. YES	1. NO 2. YES (except registers) 3. YES 4. YES, if hospitals are following an accreditation system, then CME approval is required
Hospital 3: Chairman of the Board of Directors	1. YES 2. YES 3. YES 4. YES	1. YES 2. YES 3. YES 4. YES (but unsure)
Hospital 4: Respondent 1: Head of R&D/ Coordinator Clinical Research Center Respondent 2: Valorization Health Manager	1. NO 2. NO (YES, we ask it in practice) 3. YES 4. Do not know	1. NO 2. NO (YES, we ask it in practice) 3. YES 4. Do not know

Interpretation

1. It seems most hospitals are aware that patient's permission and ethical comity permission are not required to perform internal health care quality management (except when dealing with psychologically affected patients).

2. It seems hospitals are not aware that patient's permission and ethical comity permission are not required to perform purely retrospective - secondary data scientific studies . (e.g. registers).

3. It seems hospitals are aware that patient's permission and ethical comity permission are required to perform purely prospective - primary data scientific studies as this fits within being legally required to participate.

4. It seems most hospitals are not aware or can't answer if patients permission and ethical comity permission are not required to perform anonymization procedure. (except ethical committee permission is required when hospitals are following CI (Joint Commission International) and AAHRPP (Association for the Accreditation of Human Research Protection Programs) guidelines/standards.)

8.5. Appendix 5: Interview guide LynxCare

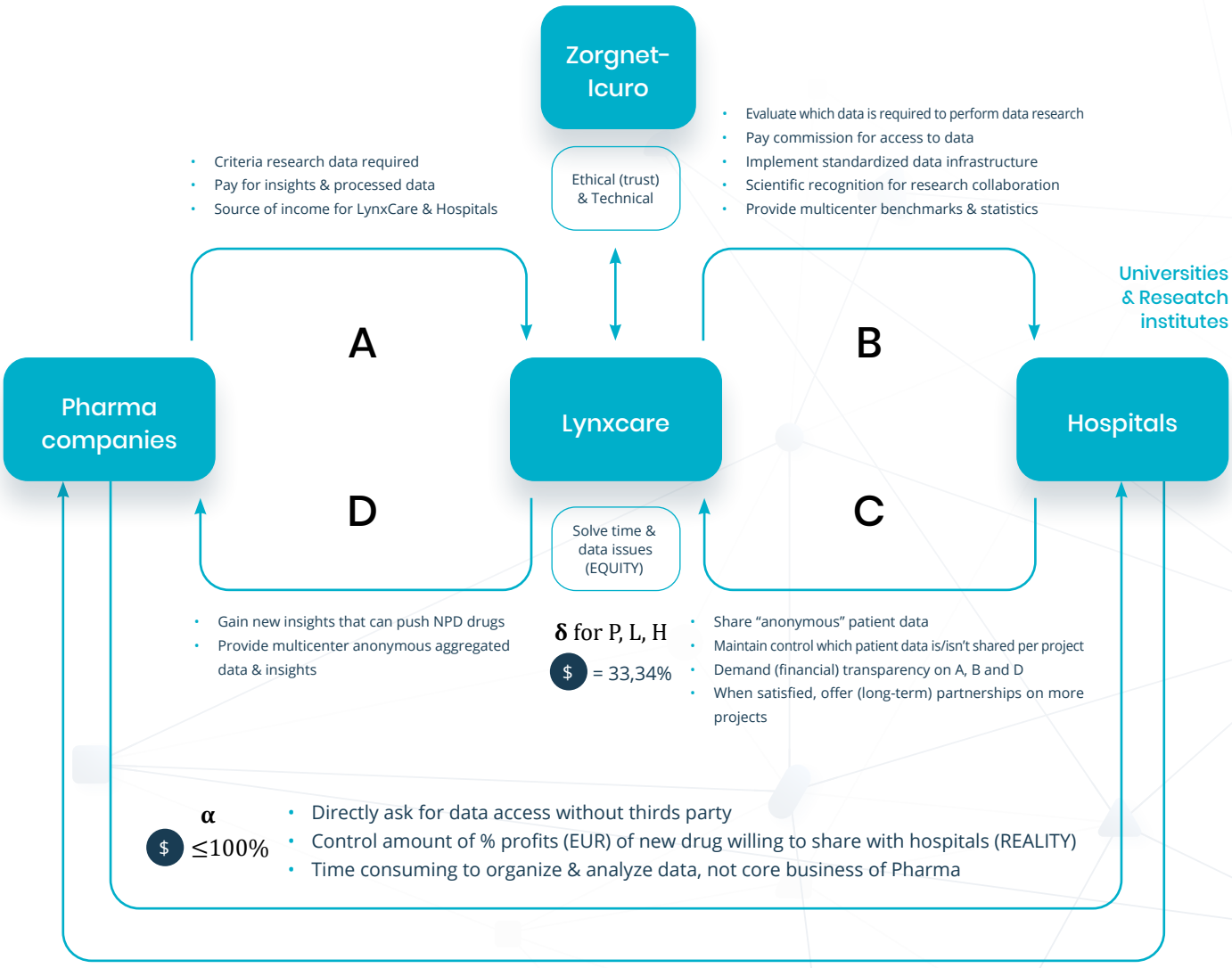
1. Clinical patient-related outcome data is most needed from the pharma. But they are not allowed to view EPD themselves?

   A. Can LynxCare have access to the EPD in certain hospitals or which are the hurdles?
   B. In which hospitals do you encounter resistance the most?
   C. Will LynxCare also expand to other types of RWD / RWE or focus only on the EPD? Eg. integration with pharmacy data.

2. What is your value proposition?

   A. RWD / RWE is mainly relevant today to reduce uncertainties in the context of an MEA. How can you reduce those uncertainties (clinical, budgetary) for pharmaceutical companies?

3 Pharma companies indicated they prefer to rely on a third party to set up the data infrastructure in a consistent way, LynxCare would like to help hospitals in there. The following could be a proposed business model:



→ What is your opinion on the following comments?

A. Pharma: "As a pharma, we do not have to go through LynxCare, we can also go directly to hospitals and do our own analysis."

B. Hospitals: "As hospitals, we do not have to go through LynxCare, we can also immediately go to pharma and set up cooperation ourselves."

C. Hospitals often feel excluded and feel that the government and third parties' side with the pharma and do not hear their interests. How do you want to avoid this perception for LynxCare?

D. We notice that hospitals are very conservative to share their data with anyone, but even more so when they feel that they are "marketing data".

a. Is it difficult to conclude contracts with hospitals?
b. What resistance are there when concluding contracts (eg ethics committee)?
c. Will hospitals show even more resistance when they know that LynxCare will also collaborate with pharmaceutical companies?
e. How do you proceed when collecting data in hospitals? Do you conclude contracts with the management, or do you go directly to individual doctors? (what about contacting in terms of ethics committee, do you do this before or after you have spoken to management or doctors?)
f. Raw data is the property of patients and hospitals have a moral duty to protect it.

"The raw data of patients should not leave the hospitals" - Within hospitals they work with servers and they don't want that data to leave the building. Can LynxCare still work on-premises servers?

- If you don't have a compatibility problem, how do you convince hospitals to use a cloud?
- Or how do you adjust your LynxCare tools to work with hospital servers and avoid that raw does not leak from hospital?

G. Anything missing in A, B, C, D areas of collaboration model?

4 How can LynxCare tools differentiate from CROs?

5 LynxCare has several competitors: IQVIA, Pharmo.nl, DHD, Performation, MRDM, Optum, Aetion, TriNetX, Telemis, OntoForce?

a. Which are your main competitors?
b. How does LynxCare differentiate? What makes LynxCare tools & service the best? (Is it the speed of data analysis)? (e.g. How much time does it take to translate / place unstructured & structured in your tools, and time to do the analysis?
c. Have you ever measured the time of LynxCare service (first contact to end of project), the speed of LynxCare tools for processing & quality for analyzing data? Have you compared this to time, speed, quality of your competitors like IQVIA ?
d. IQVIA has given a bad impression within the sector. How do you proceed to avoid this kind of reputation ("too commercial")?

8.6. Appendix 6: Interview guide government payor (RIZIV/INAMI)

1. What different mechanisms exist to impose individual or class revisions on firms? When does an individual / class revision of medicines take place? How often?

2. In an interview we heard that RWD is currently being evaluated too much from the perspective of RCTs: “and then they find other weaknesses that are not even weaknesses, but properties of RWD”. But RWD needs to be looked at differently and better valued. Are you upskilling for this?

3. What types of MEAs exist and what role does RWE play for them? (e.g., pay-for-performance)?

   a. According to pharmaceutical companies, MEAs are drawn up by the government to arrange discounts behind the scenes. Do you think this is ethical?
   b. At which uncertainties do you most often propose an MEA?
   c. Is MEA more of a budget discussion than a price discussion in practice?

4. At COVID we see that this process of those clinical trials can be accelerated enormously (vaccine already on the market within a year). How is that otherwise not possible?

5. Could P3 of the clinical trials be replaced / abandoned in exchange for the guarantee that an extensive RWD report will be published? (Is now done for example for orphan drugs).

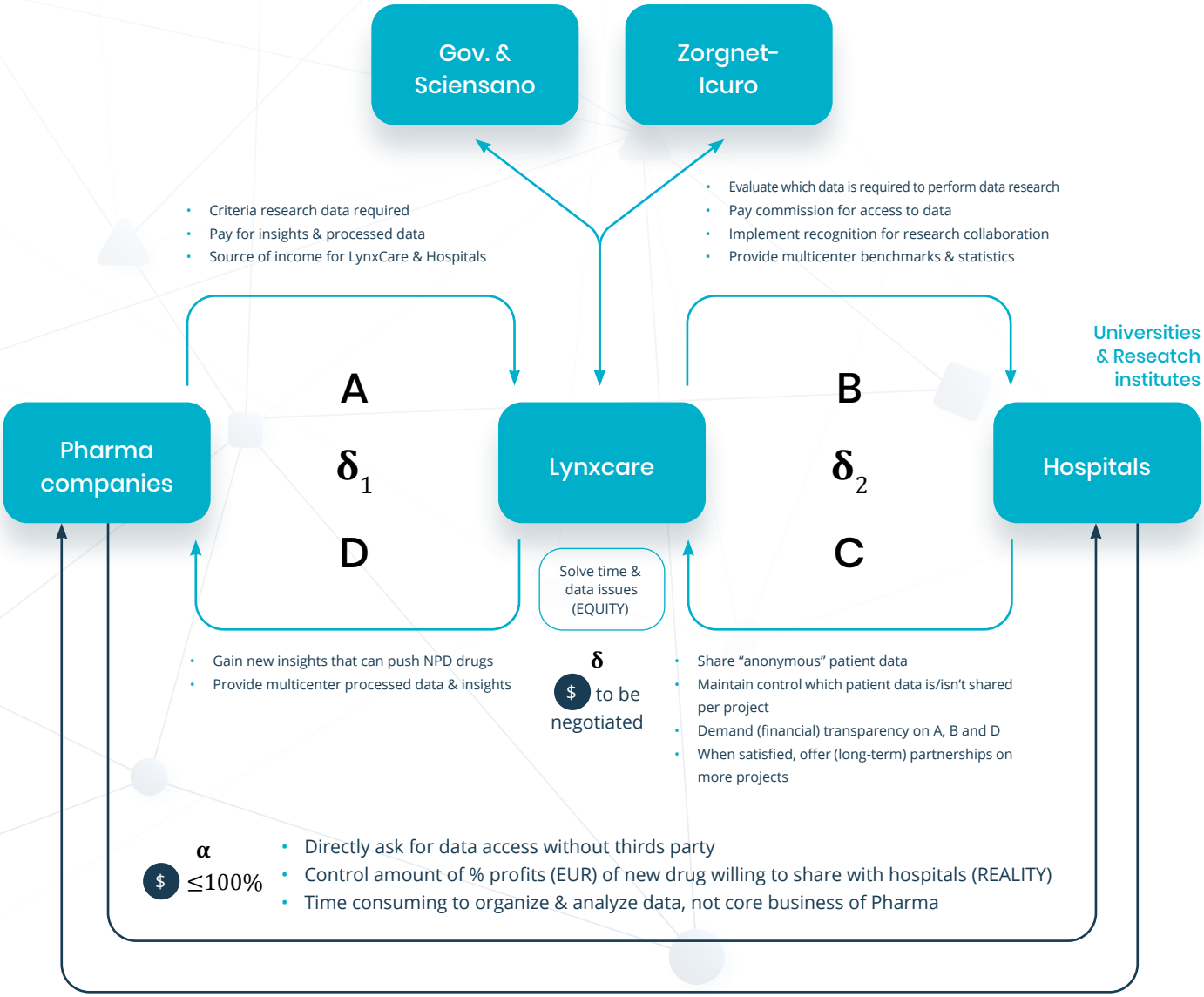
6. What are the options for an early dialogue? And what role does RWD / RWE play in early dialogue?

7. Below you will find examples of a possible collaboration model (ideal from the pharmacy point of view). What do you think is the role of government in the cooperation between pharmaceutical companies and hospitals?

8.7. Appendix 7: Value of LynxCare in the collaboration between hospitals and pharmaceutical companies. Extended explanation of Figure 15

- Solve the cause of inequity by reinvesting (DEBT) — Compromise & Debt Liberation
- Solve time & data issues

μ
$ = advice in the negotiations



β
$ ≥100%

- Directly ask for data access without thirds party
- Control amount of data willing/allowed to share with pharma companies (still fee per project)
- Not gain (or never get) the % profits (EUR) of new drug, hospitals remain financially troubled (EQUALITY)
- Time consuming to analyze data, not core business of (general) hospitals

1 The pharma companies have opted in the past and still today for a direct contact with hospitals. In this direct relationship, the pharma companies do not have to deal with a third intermediary party (e.g. CRO) and pharma companies have the advantage in the negotiations with hospitals to control what percentage of profits of a new drug (developed based on the hospitals processed data) pharma companies are willing to share with hospitals [Mentality: REALITY α = Pharma companies viewpoint is that the one providing the money for processed data has the last say]. Pharma companies choose to delegate the processing of raw data to the hospitals or to send their own pharmaceutical data staff at hospital locations to process and analyze data. However, this is quite time consuming and may hurt their pharma company for allocating its resources to a project outside its core business. [Black arrow going to the right].

2 In this direct relationship, the hospitals do not have to deal with a third intermediary party (e.g. CRO) and hospitals believe they have the advantage in the negotiations with pharma companies to expect a certain percentage of profits of a new drug (developed based on their hospitals processed data) pharma companies have to share with hospitals. [Mentality: EQUALITY β = Hospitals viewpoint is that the one providing the raw data to proceed further to processed data has the last say and advocating towards a 'revenues-fair share' model]. However, hospitals that have started the processing of raw data themselves will soon experience this is quite time consuming, they do not always have the expertise and may hurt their (general) hospital for allocating its resources to a project outside its core business while being already financially troubled. [Black arrow going to the left].

3 Pharma companies and hospitals can choose instead to outsource from LynxCare their data processing and analyzing expertise and solve the issues of time consumption and allocating resources out of their core businesses. Profits percentages between all stakeholders will have to be negotiated per project [Mentality: EQUITY δ = LynxCare sees itself as a mediator that can facilitate for better cooperation between hospitals and pharma companies, and LynxCare proposes that the value of processing and sharing data steps ($\delta 1 + \delta 2$) contributing to the development of a new drug ought to be negotiated per project and paid accordingly to negotiations δ, $\delta 1$, $\delta 2$].

3.1 At first, this creates a situation in which pharma companies share their required criteria for research data, pay commission to receive insights & processed data to LynxCare [Arrow A]. This creates a revenue source for LynxCare.?

3.2 At second, LynxCare can go to hospitals, (universities and research institutes) [Arrow B] where LynxCare can ask permission at hospitals management and ethical committees to gain access to raw data. Once access granted, LynxCare can evaluate which raw data is required to perform pharma data requirements, to a pay commission for data access (this creates a revenue source for hospitals), to implement a standardized data infrastructure (help hospitals in data management), to share scientific recognition for research collaboration with hospitals and to provide multicenter benchmarks & statistics.

3.3 At third, hospitals feel more comfortable to share 'anonymous' patient data to LynxCare. This is due to the fact that hospitals will maintain control which raw patient data is to shared or is not to be shared per project. Hospitals will be able demand (financial) transparency on the collaboration model steps [Arrows A, B and D]. When their trust has increased in working side by side with LynxCare and pharma companies following this collaboration model, hospitals may choose to offer long-term partnerships for more specialized and complex projects.

At fourth, LynxCare closes the entire cycle by providing the initial pharma required multicenter processed data. Pharma companies will gain new improved focused insights that bring value and improve new product development of drugs. [Arrow D].

However, pharma companies and hospitals may feel more comfortable if LynxCare would also invite the government (through Sciensano) and Zorgnet-Icuro to give advice in the negotiations.

Pharma companies will feel they have been given a chance to negotiate why they should not have to carry all the costs, it seems a fair point considering if they are being asked to share profits of a new drug with other stakeholders (LynxCare and hospitals) per project across the collaboration model. Hospitals will feel protected by Zorgnet-Icuro (where some members are hospital directors) who will advocate for hospitals interests to be protected during negotiations [Three-pointed arrow]. This would lead to a system where all systemic inequities are being addressed by pharma companies, hospitals and LynxCare together. Do not forget that today many hospitals are financially struggling, if hospitals close down, this could lead to loss of much valuable raw data, this affects as much hospitals to remain operational as indirectly the livelihood of new drug development research studies in pharma companies to take place. (Mentality: COMPROMISE & DEBT LIBERATION μ = No one is very happy, but each stakeholder gets what they want by removing together the initial challenges which means it's a good compromise. Ideally in future, money per project can be negotiated by the government (through Sciensano) and Zorgnet-Icuro to liberate hospitals from long-term debts.)