INTERNSHIP REPORT

# Personalized Therapies in an Institutionalized Healthcare System

## Stakeholder Perspectives on Regulatory and Reimbursement Challenges

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# Summary

**Introduction** The rapid development of personalized medicine (PM) as a healthcare model and its associated innovations, including personalized therapies (PTs) such as gene therapies and biomarker-guided treatments, is challenging existing regulatory and reimbursement systems. While these systems were largely designed around traditional population-based medicines and evidence-based medicine (EBM), PTs are often developed for small or highly stratified patient populations. This creates challenges related to evidence generation, affordability, and patient access, particularly within European healthcare systems such as the Netherlands.

**Objective** This study investigates how key stakeholders perceive the fit between emerging personalized therapies and existing regulatory and reimbursement requirements, and how they interpret and respond to these institutional influences.

**Theory & Concepts** This study uses Scott's institutional theory (regulative, normative, cultural-cognitive pillars) combined with EBM as an institutionalized framework. PM and PTs are understood as emerging innovations within this system: PM as a healthcare model and PTs as its therapeutic applications, which are not yet a separate institutional paradigm but challenge existing assumptions in the current institutional framework. Because PTs often involve small or individualized populations, they increase clinical and financial uncertainty and expose limits in current evidence and reimbursement structures. This is complemented by Oliver's theory on strategic responses, which explains how PT developers actively respond to institutional processes through strategies ranging from acquiescence and compromise to avoidance.

**Methods** A qualitative research design was used, based on 14 semi-structured interviews with stakeholders from pharmaceutical companies (small and medium-sized enterprises and large firms), academic developers, semi-public organizations, and Zorginstituut Nederland. All participants were directly involved in PT development or assessment. Participants were selected through purposive and snowball sampling. Data were analyzed using thematic analysis following Braun and Clarke's six-step approach, combining deductive coding based on institutional theory with inductive coding.

**Results** Four main themes emerged. First, stakeholders held diverging interpretations of personalized medicine, which was generally viewed not as a new healthcare model but as a continuum ranging from stratified therapies to highly individualized N=1 treatments. Second, regulatory systems (EMA/FDA) were perceived as primarily evaluating therapies based on evidentiary requirements, which stakeholders considered more difficult to meet for PTs. The FDA was generally viewed as more flexible than the EMA in accommodating these challenges. Third, reimbursement systems, particularly in the Netherlands, were perceived as introducing additional financial and evidentiary requirements, leading many companies to perceive a misalignment between regulatory approval and reimbursement. As PTs are often high-cost interventions, a broader innovation–affordability tension was identified, in which companies emphasized the importance of rewarding innovations like PTs, while public stakeholders and academics stressed the importance of affordability and the long-term sustainability of the healthcare system. Fourth, interstakeholder relationships surrounding the development and reimbursement of PTs were characterized by differing perceptions of fairness, transparency, and trust, while emphasizing the need for closer collaboration.

**Discussion and Conclusion** This study shows that PTs are perceived as only partially aligned with existing regulatory and reimbursement systems. Using institutional theory, this misfit can be explained by tensions between EBM-driven and reimbursement expectations and the characteristics of PTs, which increase both evidentiary and financial uncertainty. Developers respond to these institutional requirements through strategic adaptations in evidence generation and market-entry decisions, reflecting attempts to meet the requirements of different regulatory and reimbursement systems. In parallel, differences in stakeholder perspectives regarding value, responsibility, and acceptable uncertainty contribute to tensions around roles, trust, and collaboration within the system. In conclusion, PTs challenge current healthcare institutions due to increased uncertainty, leading to partial misalignment, strategic responses by developers, and interstakeholder tensions that complicate alignment across PT development and implementation.

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# Chapter 1: Introduction

In recent years, advances in biotechnology, genomics and data science have accelerated the development of personalized medicine (PM). PM is a healthcare approach that aims to tailor medical treatment, diagnosis, and prevention to individual patients based on characteristics such as genetic, biomarker, and epigenetic profiles [1]. By integrating these biological characteristics, healthcare specialists can better predict disease susceptibility and determine which treatments are most likely to be effective for a specific individual. The PM model aims to move beyond the traditional "one-size-fits-all" model of medicine, in which treatments are evaluated and prescribed primarily based on average effects observed in large patient populations [2]. While this traditional approach is effective for many patients, it can result in treatments that are ineffective or cause adverse effects for others, often leading to a trial-and-error process of medication selection [1]. By tailoring prevention, diagnosis, and treatment to the characteristics of individual patients, PM has the potential to improve treatment effectiveness, reduce adverse effects, enable earlier disease detection, and ultimately contribute to better patient outcomes [1,2].

Advances in genomics, biotechnology, and data science have enabled the development of a growing number of personalized therapies (PTs), including gene therapies, advanced therapy medicinal products (ATMPs), and biomarker-guided treatments [3,4]. While these therapies illustrate the potential of the personalized medicine model, their integration into existing regulatory and reimbursement systems remains challenging. Regulatory authorities such as the Food and Drug Administration (FDA) in the United States and the European Medicines Agency (EMA) traditionally evaluate medicines using evidence standards based on evidence-based medicine (EBM). EBM relies on large, randomized clinical trials (RCTs) conducted in relatively large patient populations. PTs, however, often target small and biologically stratified patient populations, making it more difficult for pharmaceutical companies to generate evidence that conforms to traditional regulatory standards [2,5].

In addition to regulatory challenges, PTs may face national reimbursement challenges. In Europe, obtaining market authorization from the EMA does not automatically result in patient access. Reimbursement decisions are made by individual EU member states and are often based on health technology assessments (HTA) that evaluate comparative effectiveness, cost-effectiveness, and budget impact [6]. In the Netherlands, for example, therapies may be additionally evaluated by Zorginstituut Nederland (ZIN), and manufacturers may face price negotiations with the Ministry of Health, Welfare, and Sport (MoH). PTs are often associated with high costs due to complex development and manufacturing processes and their relatively small target population. Consequently, personalized therapies may face not only evidentiary challenges but also tensions related to affordability, pricing, and the sustainability of healthcare systems. These challenges can delay patient access to innovative treatments despite their potential clinical value [7,8].

Although adaptations to regulatory and reimbursement for PTs are increasingly discussed, limited empirical research exists on how companies, academic developers, and policy actors navigate and respond to tensions between traditional evidence and reimbursement requirements and the characteristics of PTs [9].

Therefore, this study investigates how regulatory and reimbursement institutions shape the development and market access of PTs in the Netherlands and internationally. To address this objective, semi-structured interviews were conducted with stakeholders involved in the development and assessment of PTs, including academic developers, small and medium-sized enterprises (SMEs), large pharmaceutical companies, and Zorginstituut Nederland. The study explores how these stakeholders respond to and experience existing institutional requirements by answering the question: *How do key stakeholders perceive the fit between emerging personalized therapies and existing regulatory and reimbursement requirements, and how do they interpret and respond to these influences?* By comparing perspectives across different actors and stages of the medicine development pathway, the study aims to provide insight into how current institutions support or constrain the implementation of personalized therapies and to identify potential areas for future policy development.

# Chapter 2: Contextual Background

## 2.1: Evidence-Based Medicine

Evidence-Based Medicine (EBM) is the current dominant paradigm guiding modern medical research, clinical decision-making, and health policy. Its development reflects a gradual shift from reliance on individual clinical expertise of physicians toward the systematic use of scientific evidence in healthcare [10,11]. EBM was defined by Sackett (1997) as "*the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients,*" highlighting the integration of scientific research evidence with clinical expertise [12]. In practice, EBM follows a structured process of formulating clinical questions, systematically reviewing evidence to answer these questions, critically evaluating available evidence, and applying findings to patient care [13].

In EBM, a study's position in the evidence hierarchy is determined by its methodological rigor and its vulnerability to bias [14,15]. At the top of this hierarchy are systematic reviews and meta-analyses, which combine and evaluate the results of multiple studies to assess treatment effectiveness [15]. These are followed by randomized controlled trials (RCTs), which are widely considered the gold standard for generating clinical evidence, as they establish causal relationships between interventions and outcomes with minimal bias [16]. Observational studies, case series and reports, and expert opinion are considered lower levels of evidence [14]. This EBM paradigm has shaped regulatory approval, clinical guidelines, and reimbursement decisions globally, with a strong emphasis on population-level evidence generated under placebo-controlled conditions [15,17].

Despite its integration in society and contributions to improving medical practice, EBM has also faced criticism. Scholars have argued that its emphasis on standardized protocols may transform medical practice into "cookbook medicine", in which clinicians follow standardized treatment protocols rather than applying clinical judgement [18]. Others highlight that the strong emphasis placed on RCTs may limit applicability to real-world settings, where patient populations are more heterogeneous and complex [14]. In addition, alternative forms of knowledge including observational research and clinical expertise are often undervalued within the evidence hierarchy [19]. These critiques have become increasingly relevant in the context of emerging medical innovations, such as PTs, which often target small and biologically diverse patient populations and may not align with traditional evidence hierarchies [2,5].

## 2.2: Personalized Medicine and Personalized Therapies

### 2.2.1: Defining personalized medicine

Personalized Medicine (PM), also referred to as precision medicine, is an emerging healthcare paradigm that aims to tailor disease prevention, diagnosis, and treatment of the characteristics of individual patients. It is based on the idea that genetic variation, biomarker characteristics, environmental exposures, and lifestyle factors influence disease risk and treatment response. By taking these differences into account, the PM approach aims to identify the most suitable treatment for specific patient subgroups while reducing adverse drug reactions [1,2].

Personalized medicine has been defined by several institutions. The National Human Genome Research Institute defines personalized medicine as "*an emerging practice of medicine that uses an individual's genetic profile to guide decisions made in regard to the prevention, diagnosis, and treatment of disease*" [20]. Similarly, the FDA describes precision medicine as an innovative approach that considers differences in genes, environments, and lifestyles to deliver the right treatment to the right patient at the right time [21]. The European Commission defines personalized medicine as "*A medical model using characterization of individuals' phenotypes and genotypes (e.g. molecular profiling, medical imaging, lifestyle data) for tailoring the right therapeutic strategy for the right person at the right time, and/or to determine the predisposition to disease and/or to deliver timely and targeted prevention*" [22].

Notably, this study makes a clear distinction between personalized medicine as a *paradigm or approach*, and personalized therapies as the *specific medicinal products or interventions* developed and used within this paradigm. This distinction is important because regulatory and reimbursement systems act primarily on therapies, while PM emerges from these developments as a broader conceptual framework.

### 2.2.2: Technological drivers

The emergence of PTs and the personalized medicine model have been linked to recent advances in biotechnology and genomics, as well as the finding that patients can respond differently to the same medication. A milestone was the Human Genome Project in 2003, which enabled large-scale mapping of genetic variation and supported the identification of disease-associated mutations [23]. Moreover, genome sequencing technologies have since allowed faster and more affordable genetic analysis, enabling the identification of biologically distinct patient subgroups [24,25]. Furthermore, advances in biomarker and pharmacogenomics research allow for the prediction of treatment responses and selective use of therapies based on individual patient characteristics [26]. In clinical practice, such approaches have already been applied, for example in oncology, where targeted therapies are developed for patients, whose tumors contain specific genetic mutations [27]. More recently, gene editing innovations such as CRISPR-Cas have enabled innovations regarding the development of targeted and individualized therapies [28]. Together, these developments have led to the development of PTs that target specific molecular or genetic characteristics of patients and their diseases.

### 2.2.3: Personalized therapies

Many of the current personalized therapies fall under the category of Advanced Therapy Medicinal Products (ATMPs), which are medicines created by using genes, tissues, or cells. ATMPs are subdivided into three groups by the EMA: gene therapy medicinal products, somatic cell therapy medicinal products, and tissue-engineered products. Gene therapy medicines are developed to treat disease by altering genetic material in a patient’s cell, while somatic cell therapies aim to treat disease by manipulating a patient’s own cells [29]. Cell-based cancer treatments such as Chimeric Antigen Receptor T-cell (CAR-T) therapies and Tumor-Infiltrating Lymphocyte (TIL) therapies fall within this category and involve the extraction, modification, and reintroduction of a patient’s own immune cells [30]. Finally, tissue-engineered products are modified cells or tissues that aim to repair human tissue [29]. Many PTs therapies are developed for rare diseases or small patient populations and therefore qualify as orphan drugs. Orphan drugs are pharmaceutical agents developed for the treatment of rare medical conditions affecting no more than five in 10.000 people [31].

At the most individualized end of the spectrum are N=1 or N=few therapies, which refer to treatments developed for a single patient or a very small number of patients based on highly specific genetic or molecular characteristics. These therapies are increasingly emerging, with a possible key role for artificial intelligence (AI) [32]. An example of such a therapy is the use of patient-specific antisense oligonucleotides (ASOs). ASOs are short strands of nucleic acids designed complementary bind to a target mRNA transcript, which can prevent or modify the production of specific proteins involved in disease [33]. These N=1 therapies represent a new form of personalization that challenges existing regulatory and reimbursement frameworks.

### 2.2.4: Evidence challenges

Personalized therapies are inherently developed for small and specific patient populations. As a result, the limited number of available patients makes it difficult to conduct large RCTs, reducing statistical power and creating challenges in achieving traditional EBM standards [2,5,12]. Consequently, generating reliable evidence on treatment effects is often more difficult, leading to greater uncertainty regarding clinical effectiveness [2,5]. This uncertainty is further intensified by limited evidence on long-term effectiveness and safety, particularly for one-time treatments where it is unclear whether short-term benefits last over time [34]. To address these challenges, developers may rely on biomarker-based and surrogate endpoints to evaluate treatment efficacy. However, these endpoints provide only indirect evidence of clinical benefit and do not directly capture a treatment’s long-term effects [35,36].

## 2.3: Regulatory Pathways for Personalized Therapies

Personalized therapies are developed by a diverse group of manufacturers, including academic developers, who may receive national subsidies to support treatment development, small and medium-sized enterprises (SMEs), which employ fewer than 250 people, and large pharmaceutical companies, which exceed this threshold [37,38].

### 2.3.1: Food and Drug Administration (FDA)

The United States (U.S.) FDA approval is designed to ensure that new therapies are safe, effective, and manufactured to high quality standards before receiving market access and reaching patients. To obtain approval, manufacturers submit evidence from clinical studies demonstrating that a medicine's benefits outweigh its risks. The emergence of personalized medicine has led to changes in FDA's assessment of evidence, though traditional RCTs remain the standard [39]. For example, the FDA has shown increasing willingness to accept surrogate and biomarker-based endpoints for conditions where traditional clinical endpoints may be difficult to measure, particularly through programs such as Accelerated Approval [40]. Once a medicine receives FDA approval, pharmaceutical companies are permitted to market the product in the Unites States for the approved indication. Market access then depends on pricing and coverage negotiations with public and private payers in the United States [41].

### 2.3.2: European Medicines Agency (EMA)

In the European Union (EU), it is the main role of EMA to approve whether medicines are safe, effective, and of high quality. The EMA has several scientific committees with roles specialized for PTs that formulate draft opinions about a drug's safety and effectiveness. For example, the Committee for Advanced Therapies (CAT) evaluates ATMPs, while the Committee for Orphan Medicinal Products (COMP) focuses on medicines for rare diseases and determines whether a medicine qualifies as an orphan drug. These committees send their draft opinions to the Committee for Medicinal Products for Human Use (CHMP), which formulates a final opinion on market authorization to send to the European Commission for the final decision [42]. Furthermore, the ongoing reform of the EU pharmaceutical legislation aims to improve access to innovative and affordable medicine by creating a more efficient regulatory framework that supports innovation and competitiveness by 2028 [43].

## 2.4: From Regulatory Approval to Reimbursement

Obtaining market authorization from the EMA for a specific medicine does not automatically guarantee patient access to that medicine within European healthcare systems, as reimbursement decisions are taken by individual EU member states. As a result, pharmaceutical companies must apply for reimbursement separately in each country after receiving market authorization. The reimbursement evaluation process often involves Health Technology Assessments (HTAs), although the scope and methodology of HTA systems vary considerably between European countries. HTA is used in several countries, including France, Sweden, the United Kingdom and the Netherlands, to determine whether a new treatment offers sufficient added value compared with existing standards of care. Depending on the country, assessments may consider factors such as at relative effectiveness, cost-effectiveness, budget impact, and societal value. However, the degree in which these factors influence reimbursement decisions vary; for example, some countries place greater emphasis on clinical benefit and therapeutic added value, whereas others incorporate cost-effectiveness analyses [44].

To enhance efficiency and increase consistency in the assessment of clinical evidence in Europe, the EU introduced the Joint Clinical Assessment (JCA), which will be applied to all centrally authorized medicines from 2030 onwards. The JCA is a joint evaluation of a medicine's relative clinical effectiveness and safety compared with relevant alternatives and is conducted collaboratively by EU member states. While the JCA is intended to support national HTA processes by harmonizing the clinical assessment, member states do remain responsible for assessing cost-effectiveness, budget impact, and affordability within their own healthcare systems. Therefore, reimbursement outcomes and patient access can still vary considerably between European countries [45].

## 2.5: The Dutch Reimbursement System

### 2.5.1: Institutional structure and assessment process

Following market authorization, reimbursement decisions for medicines in the Netherlands assessed by Zorginstituut Nederland (ZIN), with help of HTA. ZIN advises the Ministry of Health, Welfare and Sport (MoH) on whether medicines should be included in the basic health insurance package, either through the outpatient reimbursement system or hospital reimbursement pathways [46].

During this HTA, ZIN evaluates whether a medicine meets the criteria of the state of science and practice (Stand van de Wetenschap en Praktijk; SWP), which is the Dutch legal standard for demonstrating effectiveness. Clinical effectiveness is assessed relative to the existing standard of care by using the PICO framework to define the patient population, intervention, comparator, and relevant outcomes. In addition to relative effectiveness, ZIN assesses the clinical relevance of treatment effects by considering the Minimal Clinically Important Difference (MCID), thereby determining whether observed benefits are meaningful for patients. Furthermore, ZIN considers cost-effectiveness by using measures such as cost per quality-adjusted life year (QALY), budget impact, necessity, and feasibility. Based on this assessment, ZIN provides advice to the MoH, which ultimately decides whether a medicine will be included in the basic health insurance package. Once included in the basic insurance package, healthcare insurers are responsible for financing the covered care within the Dutch healthcare system [46].

### 2.5.2: Personalized therapies and price negotiations

Ultimately, a medicine can only become available in a sustainable way to patients once an agreement on pricing and reimbursement is reached. Pharmaceutical companies set initial list prices that are influenced by multiple factors, including research and development costs, expected market size, therapeutic value, and strategic pricing considerations [47]. As PTs are developed for small patient populations, they often have high per-patient costs and higher list prices [48].

At the same time, the Dutch healthcare system operates within a publicly financed framework in which total spending is controlled through agreements between the government, health insurers, and healthcare providers [49]. As a result, reimbursement decisions require prioritization, as paying for high-cost medicines may reduce the budget available for other healthcare domains, including hospital care, long-term care, and subsidies that support academic developers in the translation and development of new medical innovations [38,50].

For certain high-cost intramural (hospital) medicines, reimbursement may be temporarily delayed through the lock-procedure (Dutch: “sluis”). During this period, the medicine is not yet reimbursed while ZIN conducts an HTA. ZIN may then recommend reimbursement only under conditions such as price reductions, managed entry agreement, or appropriate-use agreements. Following reimbursement advice, the MoH negotiates pricing and reimbursement conditions with the manufacturer during the lock-procedure. After successful assessment and agreement on pricing conditions between company and the MoH, the medicine can enter in the basic health insurance package and patients in the Netherlands gain access to the therapy [46].

# Chapter 3: Theoretical Background and Conceptual Framework

## 3.1: Institutional Theory as Analytical Lens

Institutional theory is used as a lens to understand how organizations and companies adapt to the social, regulatory, and cultural environment in which they operate. This study draws on the institutional perspective developed by W. Richard Scott, who defines institutions as comprising of "regulative, normative, and cultural-cognitive elements that, together with associated activities and resources, provide stability and meaning to social life." [51]. According to Scott, the regulative, normative, and cultural-cognitive pillar interact together to establish institutional structures that steer actions, promote stability, and demonstrate resilience to change, although they are not entirely resistant to transformation. Together, they form the environment in which organizations and companies operate. To gain legitimacy within this environment, organizations and companies act according to the expectations of the regulative, normative, and cultural-cognitive pillars [51].

The regulative pillar refers to formal rules, laws, and policies that shape behavior through monitoring, incentives, and sanctions [51]. Within healthcare and pharmaceutical sectors, this pillar is represented by the activities of regulatory agencies, including the FDA and the EMA, and national bodies such as the MoH and HTA organizations such as Zorginstituut Nederland. These institutions establish the requirements that pharmaceutical companies must meet for the approval and reimbursement of medicines, thereby shaping the evidence required to achieve legitimacy [42,52]. Scott (2013) argues that actors create and maintain these laws and rules to safeguard certain interests, while organizations and companies comply with these rules to secure benefits or avoid sanctions. He further suggests that the regulative pillar tends to play a more prevalent role in market and business environments where competing interests are prominent and formal rules are necessary to maintain order.

The normative pillar refers to values, norms, and roles that define appropriate goals and appropriate means in pursuit of these goals [51]. Unlike the regulative pillar, which relies on formal rules and sanctions, the normative pillar influences behavior through shared values, norms, professional standards, and social expectations. In the medicine development pathway, this pillar is reflected in the ethical principles, professional standards, and shared norms about clinical best practices that influence decision-making among pharmaceutical companies and regulators. Examples include ensuring patient safety, transparency in clinical research, and the expectation that medicines should address unmet medical needs and provide meaningful therapeutic value [53]. While standards such as Good Clinical Practice originated from professional and ethical norms, they have also become embedded in regulatory requirements and therefore contain both normative and regulative elements. Researchers, interest groups, patient advocacy groups, and healthcare professionals play an important role in shaping these norms by establishing standards regarding appropriate and legitimate behavior. Organizations adapt to these expectations to maintain credibility and reputation, while also regarding such practices as morally appropriate. Consequently, the normative pillar influences how evidence is generated, how clinical trials are designed, and how stakeholders assess the value and acceptability of evidence of new medicines during the development process.

The cultural-cognitive pillar refers to the shared beliefs, assumptions, and taken-for-granted understandings that shape how institutions and organizations move and perceive their environment [51]. The cultural-cognitive pillar influences behavior through common ways of thinking that are often accepted without question. In the medicine development pathway, this pillar is reflected in the assumption that RCTs are the gold standard for providing the most reliable evidence and demonstrating the safety and efficacy of new medicines [16]. Furthermore, this pillar is seen in the global acceptance of the evidence-based medicine paradigm as the standard [54]. Although these approaches also have normative dimensions, as they prescribe what is considered good scientific and clinical practice, they are discussed here as cultural-cognitive elements because they have become deeply embedded and are often taken for granted by pharmaceutical companies, regulators, clinicians, and HTA bodies. As a result, organizations tend to design development programs and evidence-generation strategies in line with these shared understandings. Because such beliefs become taken for granted over time, they could influence decision-making and persist even when alternative approaches to evidence-generation emerge. Consequently, the cultural-cognitive pillar may play an important role in determining how innovation is evaluated and how legitimacy is achieved throughout the medicine development process.

Although institutions create stability by providing a stable backbone in which PT developers operate, Scott emphasizes that they are not static and continuously evolve over time. Institutional change can occur either gradually via incremental adaptations of rules, norms, and shared beliefs or more rapidly through fundamental transformations of existing institutional frameworks. Institutionalization refers to the process through which ideas or ways of working become widely accepted, taken for granted, and integrated within the regulative, normative, and cultural-cognitive pillars of an institution. While these pillars are analytically distinct, they are closely interconnected in practice and may overlap. Ideas may originate as shared assumptions within the cultural-cognitive pillar, become reinforced as professional norms within the normative pillar, and eventually be codified into formal rules and regulations within the regulative pillar. However, Scott does not assume a fixed sequence, as change may emerge from any pillar and subsequently influence the others. Conversely, deinstitutionalization occurs when practices or beliefs that were established lose their legitimacy and are gradually abandoned or replaced. According to institutional scholars, such processes are often driven by functional, social, or political pressures. As a result, institutions can also be understood as dynamic systems that can adapt when existing rules, norms, and assumptions are increasingly challenged [51].

## 3.2: Evidence-Based Medicine as an Institutionalized Framework and Personalized Medicine as an Emerging Challenge

EBM has become the dominant framework guiding clinical research, regulatory decision-making, and reimbursement assessments in healthcare [51]. From an institutional perspective, EBM hierarchies reflect shared assumptions about what constitutes credible and legitimate evidence. Over time, these assumptions have become embedded within regulatory frameworks, reimbursement procedures, professional standards, and clinical practice. In Scott's terms, EBM can be understood as an institutionalized framework supported by all three institutional pillars. The regulative pillar is reflected in regulatory and reimbursement requirements that have historically prioritized evidence generated through RCTs. The normative pillar is visible in professional standards regarding methodological rigor and appropriate evidence generation. The cultural-cognitive pillar is reflected in the shared assumption that RCTs represent the gold standard for demonstrating the safety and effectiveness of new treatments. Consequently, evidence is not merely a neutral or objective concept but is shaped by institutional understandings of methodological rigor, credibility, and acceptable uncertainty. These institutionalized understandings influence how new therapies are evaluated and what forms of evidence are considered sufficient to achieve regulatory approval and reimbursement [51].

At the same time, more pluralistic approaches to evidence have emerged that challenge traditional hierarchical thinking. These perspectives argue that different research questions may require different methodological approaches and that the suitability of evidence depends on the context in which it is generated and applied [55]. This has led to a growing interest in complementary forms of evidence, such as real-world evidence (RWE), observational studies, electronic health records, and biomarker-based endpoints [56,57]. From an institutional perspective, these developments illustrate that understandings of what type of evidence counts as legitimate evidence are not fixed but can evolve over time. While traditional evidence hierarchies remain to shape decision-making, alternative forms of evidence are increasingly gaining legitimacy within regulatory and reimbursement discussions [56,58]. Rather than replacing EBM, these developments broaden the range of evidence considered relevant for healthcare decision-making and contribute to ongoing adaptations within existing institutional frameworks.

These developments are particularly relevant in the context of PM. PTs often target relatively small patient populations defined by specific genetic, molecular, or biomarker characteristics. Consequently, generating evidence through large randomized controlled trials may be difficult, impractical, or ethically challenging and developers may rely on alternative forms of evidence [9]. This creates tensions within an institutional environment that has historically been shaped by population-based evidence standards [12]. PTs reveal limits of cultural-cognitive assumptions about what constitutes robust evidence, particularly the expectation that treatment effectiveness should be demonstrated through RCTs. They may also create normative tensions regarding appropriate standards of evidence and acceptable levels of uncertainty. Furthermore, developers may encounter regulative challenges when existing regulatory and reimbursement frameworks continue to rely on evidence requirements that were originally designed for larger patient populations and conventional medicines.

Rather than representing a paradigm that is separate from EBM, personalized *medicine* can be understood as an innovation that operates within an institutional environment shaped by EBM while simultaneously challenging some of its underlying assumptions. Personalized *therapies* remain dependent on existing regulatory and reimbursement institutions for legitimacy and market access, while their characteristics increasingly test the suitability of established evidence standards.

## 3.3: Uncertainty in Evidence and Thresholds of Acceptability

In healthcare decision-making, evidence is rarely fully certain. As clinical research produces knowledge based on probability rather than absolute truths, decisions about approval, reimbursement, and use of medicinal innovations must be made under conditions of uncertainty [59]. For this study, uncertainty is conceptualized along two dimensions that are particularly relevant to the development and assessment of PTs.

The first type concerns evidentiary uncertainty, which includes uncertainty regarding the clinical evidence of a therapy, including its effectiveness, safety, and long-term outcomes. Evidentiary uncertainty is particularly relevant when evidence is derived from small trials, surrogate endpoints, or short follow-up periods, as is often the case in emerging therapies. Regulatory agencies such as the EMA and FDA primarily focus on managing this type of uncertainty by assessing whether the available clinical evidence is sufficient to support a positive benefit–risk balance [39,42].

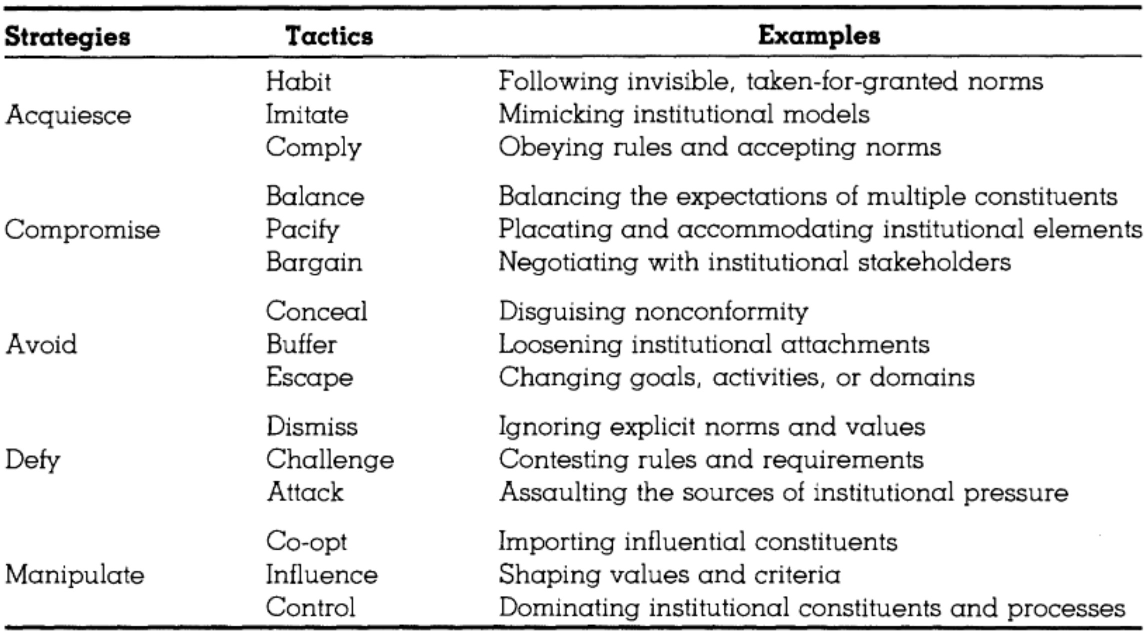
The second type concerns financial uncertainty, which includes uncertainty regarding the economic consequences of a therapy, including its cost-effectiveness, budget impact, affordability, and reimbursement implications. In contrast to evidentiary uncertainty, which focuses on whether a treatment works, economic uncertainty is about whether it provides sufficient value relative to its costs and whether it is financially sustainable to offer this treatment in a publicly funded healthcare system. This type of uncertainty is particularly relevant for HTA bodies such as ZIN, where considerations of cost-effectiveness and budget impact play a central role in reimbursement decisions [52].

Importantly, uncertainty is not assessed in the same way by all institutions. Instead, different organizations have different thresholds for how much uncertainty they are willing to accept when making decisions about new medicines. These uncertainty thresholds refer to the amount of uncertainty that decision-makers consider acceptable before granting approval or reimbursement. Regulatory agencies such as the EMA and FDA may be willing to tolerate higher levels of uncertainty than traditionally accepted, for example when addressing unmet medical needs [40,60]. Reimbursement bodies, however, may apply different thresholds because their assessments consider both clinical benefits and factors as cost-effectiveness and budget impact [52].

These uncertainty dynamics are particularly relevant in the context of personalized medicine. Because PTs often target small patient populations and are associated with high costs per patient, both clinical and economic uncertainty may be greater at the time of assessment [61,62]. Developers must therefore not only generate evidence under conditions of uncertainty but also ensure that this evidence meets the uncertainty thresholds applied by regulatory and reimbursement bodies.

## 3.4: Strategic Responses to Institutional Processes

Developers of PTs, including pharmaceutical companies and academic developers, can strategically respond to institutional rules and norms. To understand how these organizations respond to institutions, Oliver (1991) defined five strategic responses that they can adopt in response to institutional pressures. The first one is acquiescence, meaning that organizations accept institutional pressures and follow the rules. Tactics include habit (following taken-for-granted norms), imitation (imitating institutional models), or compliance (following rules and norms). The second strategic response includes compromise: organizations partially conform but try to balance different demands. Tactics include balancing (satisfying multiple stakeholders), pacifying (complying superficially with some demands), and bargaining (negotiating with regulators or stakeholders). The third strategic response is avoidance: organizations try to avoid having to comply fully. Tactics include concealment (pretending to comply), buffering (isolating core activities from scrutiny), and escape (changing activities or domains to avoid rules). Fourth, defiance reflects a more explicit rejection of institutional demands. Tactics include dismiss (ignoring rules), challenge (questioning their legitimacy), attack (criticizing or opposing institutional actors). The last strategic response is manipulation: the most active strategy where organizations try to change the institutional environment itself. Tactics include co-opt (bringing influential stakeholders into the organization), influence (lobbying or shaping norms), control (dominating the sources of institutional pressure) (Figure 1) [63].



| Strategies | Tactics | Examples |
|---|---|---|
| Acquiesce | Habit | Following invisible, taken-for-granted norms |
| | Imitate | Mimicking institutional models |
| | Comply | Obeying rules and accepting norms |
| Compromise | Balance | Balancing the expectations of multiple constituents |
| | Pacify | Placating and accommodating institutional elements |
| | Bargain | Negotiating with institutional stakeholders |
| Avoid | Conceal | Disguising nonconformity |
| | Buffer | Loosening institutional attachments |
| | Escape | Changing goals, activities, or domains |
| Defy | Dismiss | Ignoring explicit norms and values |
| | Challenge | Contesting rules and requirements |
| | Attack | Assaulting the sources of institutional pressure |
| Manipulate | Co-opt | Importing influential constituents |
| | Influence | Shaping values and criteria |
| | Control | Dominating institutional constituents and processes |

*Figure 1. Strategic responses to institutional processes, according to Oliver (1991) [63].*

In the context of PM, these strategic responses help explain how PT developers navigate regulatory and reimbursement systems that define legitimate forms of evidence and acceptable levels of uncertainty. Rather than responding uniformly, PT developers may combine strategies such as adapting clinical trial designs to meet regulatory expectations (acquiescence or compromise), engaging in dialogue and negotiation with regulators and HTA bodies (bargaining), or using real-world evidence and scientific discourse to broaden accepted standards of evidence (influence or manipulation). In doing so, they operate within an institutional environment shaped by established evidence hierarchies, while simultaneously attempting to secure legitimacy.

## 3.5: Theoretical Framework and Sub Questions

Altogether, the concepts discussed in this chapter provide a framework for understanding how evidentiary and financial requirements for PTs are shaped by institutional processes. Institutional theory serves as analytical lens by explaining how pharmaceutical companies operate within an environment structured by regulative, normative, and cultural-cognitive pillars. Within this environment, EBM has become institutionalized as the dominant framework for defining what constitutes legitimate and credible evidence. Through regulations, professional standards, and shared assumptions about methodological quality, EBM has shaped the evidence standards used in medicine development, approval, and reimbursement. Consequently, decisions about evidence are not only technical or scientific but are influenced by institutional expectations on methodological rigor, acceptable standards, and levels of uncertainty.

PTs challenge these established institutional frameworks, as their characteristics often make the generation of conventional evidence more difficult. This increases evidentiary uncertainty, which encompasses the safety, effectiveness, and long-term outcomes of therapies. It may also increase financial uncertainty, which concerns the cost-effectiveness, budget impact, and affordability of PTs within healthcare systems. These uncertainties are assessed differently by regulatory and reimbursement institutions, which apply distinct thresholds of acceptability based on their responsibilities. As a result, developers of PTs must navigate multiple and sometimes differing institutional demands to achieve market access. In response, pharmaceutical companies can adopt different strategic responses, including acquiescence, compromise, avoidance, defiance, and manipulation.

The interaction between institutional pressures, institutionalized evidence standards, clinical and financial uncertainty, uncertainty thresholds, and organizational strategies therefore forms the central conceptual framework of this study. This framework enables an analysis of how developers of PTs navigate institutional expectations regarding evidence and uncertainty, and how these interactions shape both organizational strategies and gradual institutional adaptations. Based on this framework, the following sub questions can be formulated:

1. How do different stakeholder groups conceptualize personalized medicine?
2. How do regulatory evidence requirements under existing institutional frameworks influence the development and approval of personalized therapies?
3. How do reimbursement systems (particularly in the Netherlands) evaluate personalized therapies, and how do they manage financial and evidentiary uncertainty?
4. How do developers and other stakeholders strategically respond to regulatory and reimbursement institutional pressure, and how do these interactions shape system dynamics in personalized medicine?

# Chapter 4: Methodology

## 4.1: Study Design and Data Collection

This study adopted a qualitative research design using semi-structured interviews to explore how stakeholders involved in the development, regulation, and reimbursement of PTs perceive the fit between emerging PTs and existing regulatory and reimbursement requirements, and how they interpret and respond to these influences.

A qualitative approach was chosen because the study aims to understand interpretations, experiences, and perceptions of key stakeholders. Semi-structured interviews are suitable for this, as they generate contextual and explanatory data on how actors perceive regulatory and reimbursement systems. The findings will therefore reflect the stakeholder perspectives and perceptions, rather than objective descriptions of regulatory or reimbursement processes themselves. Other methods, such as surveys, could have produced less nuanced insights, while document analysis would not have captured the interpretations of frameworks and reasoning behind stakeholder decisions [64].

Interviews of approximately one hour were conducted using an interview guide based on the theoretical framework (see Appendix) The guide covered topics such as the respondent's involvement in personalized medicine, and experiences with regulatory and reimbursement systems. A funnel structure was used to ensure consistency, starting with broad questions about background and role, and gradually moving toward more specific topics, including strategic decision-making and the interpretation of regulatory and reimbursement frameworks. This design supported comparability across interviews while leaving room for unexpected insights.

All interviews were audio-recorded and transcribed verbatim with informed consent. Transcription enhances data reliability by ensuring that analysis is based on an accurate representation of the respondent's perceptions rather than selective notetaking. Identifying information was removed, and data were securely stored in accordance with institutional data protection guidelines.

## 4.2: Study Population

Participants were selected using purposive sampling, supplemented by snowball sampling. This approach was appropriate because the study focused on specialized expert perspectives from stakeholders directly involved in personalized therapy development or assessment. The sample included 14 representatives from SMEs, large pharmaceutical companies, academic developers, semi-public organizations, and Zorginstituut Nederland (Table 1). Importantly, this study did not aim for statistical representativeness, but for analytically rich insights into institutional perspectives across stakeholder groups.

A potential limitation of purposive and snowball sampling is the risk of selection bias, as participants may share similar perspectives or come from overlapping networks

[65]. To minimize this risk, the sampling procedure focused on including stakeholders from diverse organizational backgrounds with different perspectives. Data collection continued until thematic saturation was reached, meaning that no new insights emerge from additional interviews. However, it is important to note that despite continuous comparison of emerging themes during the data collection process, saturation was ultimately determined based on the researcher's judgement, thereby introducing a degree of interpretive subjectivity [66].

*Table 1. Overview of respondents and organizational background.*

| Type of organization | Number of respondents | Description |
|---|---|---|
| **Semi-public biotech company** | 1 | Publicly affiliated organization in biotechnological development |
| **Semi-public health innovation organization** | 1 | Publicly funded collaborative organization in the health innovation sector |
| **Academic developers** | 2 | Academic developers within academic medical centers involved in the development and clinical translation of advanced therapies |
| **SME pharmaceutical** | 4 | Small to medium-sized private companies in the pharmaceutical sector |
| **Large pharmaceutical** | 4 | Multinational private companies in the pharmaceutical sector |
| **Zorginstituut Nederland** | 2 | Dutch public healthcare institute responsible assessing and advising on the quality, effectiveness, and cost-effectiveness of healthcare in the Netherlands. |
| **Total** | 14 | |

## 4.3: Data Analysis

Interview transcripts were analyzed using thematic analysis in Atlas.ti to identify common themes and patterns, shared meanings, and differences across stakeholder perspectives. A combined approach of both deductive and inductive reasoning was applied. Deductive coding was guided by institutional theory and the theoretical framework, while inductive coding allowed for new insights or unexpected themes that emerged from the interviews. This combination was suitable for this study because it kept the analysis linked to existing theory, while still leaving room for emerging or unexpected patterns in how stakeholder experience and respond to regulatory and reimbursement requirements for PTs.

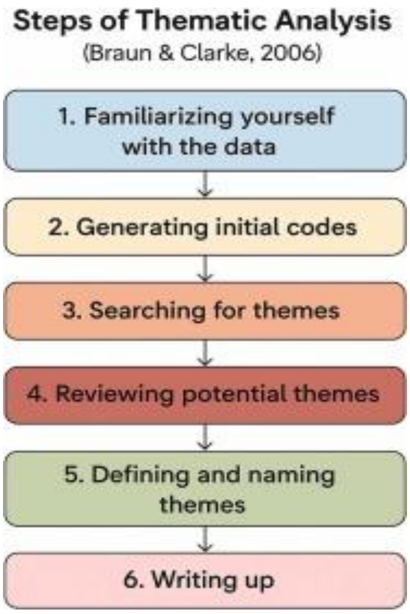


*Figure 2. Six-step framework of data analysis, Braun & Clarke (2006) [67].*

The analysis followed the six-step framework developed by Braun & Clarke [67] (Figure 2). First, the data was familiarized through transcribing audio and reading the transcripts. Second, initial codes were generated by labeling segments of text. Third, these codes were examined to identify broader themes in the interviews. Fourth, identified themes were reviewed and refined to ensure they accurately represent the data and are coherent. Fifth, themes were clearly defined and named. Finally, the findings were interpreted and linked to the research question and theoretical framework. The process was iterative, allowing for continuous refinement of codes and themes throughout the analysis.

## 4.4: Validity and Reliability of the Study

The validity of this study refers to the extent to which the research design and interview questions adequately capture the concepts under investigation [68]. To enhance validity, the semi-structured interview guide was designed to reflect the central concepts derived from the theoretical framework, such as evidence standards, regulatory constraints, reimbursement criteria, uncertainty management, and strategic responses of developers of PTs. The use of open-ended questions allowed participants to elaborate on their experiences and interpretations, ensuring that the complexity of institutional and strategic reasoning was covered. To further enhance the credibility of the findings, member checking was conducted to allow participants so participants could confirm the accuracy of interpretations and clarify potential misunderstandings, which helped improve the validity of the analysis.

It is also important to note that interviewing high-level stakeholders in regulatory and pharmaceutical settings may introduce response or social desirability bias [69]. Participants may frame their answers in a more strategic or goal-oriented way that reflects their organization’s interests and position, which can reduce the level of nuance in their responses. This challenges the validity of the findings, as response bias may cause the participants' answers to not fully reflect their real reasoning and experiences. While this cannot be completely avoided, using anonymity and open-ended questions were used to mitigate this risk.

Reliability refers to the transparency and consistency of the research process rather than the replication of exact results [68]. To enhance reliability, all interviews followed the same general topic guide, ensuring comparability across respondents. Interviews were audio-recorded, transcribed verbatim, and coded following a procedure based on Braun and Clarke's thematic analysis framework. Together, these measures contributed to the credibility, consistency, and trustworthiness of the study's findings.

## 4.5: Ethical Considerations

To ensure this study was in accordance with ethical principles, participation in this study was entirely voluntary and respondents had the right to withdraw at any time without providing a reason and without any negative consequences. Prior to participation, all respondents received information regarding the purpose of the study, the use of the collected data, and their rights as participants. Written informed consent was obtained before conducting the interviews.

To protect confidentiality, interview transcripts were anonymized and identifying information was removed. Data was securely stored according to a data management plan (see Appendix) and accessible only to the researcher. All procedures were conducted in accordance with institutional ethical guidelines and applicable data protection regulations.

# Chapter 5: Results

This chapter presents the findings from the stakeholder interviews. The results are organized into four themes. First, stakeholders' interpretations of personalized medicine are explored, showing differences in how the concept is understood. Second, perceptions of regulatory requirements and market-entry strategies are discussed, with a focus to differences between the U.S. and Europe. Third, experiences of stakeholders with the Dutch reimbursement system are elaborated on, including evidence requirements, affordability considerations, responses of stakeholders to these requirements, and proposed adaptations. Finally, the chapter explores interstakeholder relationships, focusing on perceptions of fairness, transparency, trust, and opportunities for improved collaboration.

## 5.1: Diverging Interpretations of Personalized Medicine as a Concept

When respondents were asked what they understood by the term personalized medicine, no single definition emerged. While all stakeholders associated personalized medicine with tailoring treatment to individual patients, their interpretations regarding the degree of individualization differed considerably. Most pharmaceutical companies described personalized medicine primarily as a therapeutic approach that targets stratified patient subgroups defined by for example biomarker-guided therapies or specific genetic mutations. This perception viewed personalized medicine mostly as the development of increasingly targeted therapies within the existing healthcare system. Academic respondents predominantly had a more individualized interpretation of PM, explaining it as therapies specifically designed for individual patients, such as patient-specific cell and gene therapies. Respondents from ZIN noted that, from a reimbursement perspective, whether a therapy is considered “personalized” is often less relevant than the context in which it is assessed, as evaluations focus primarily on the available evidence and clinical value. Overall, respondents viewed personalized medicine as a continuum ranging from treatments developed to relatively larger stratified patient groups to highly individualized N=1 therapies, rather than as a broader healthcare approach.

Respondents generally viewed personalized medicine as an important development in healthcare, but only few considered it a complete paradigm shift. Instead, discussions focused predominantly on PTs, which were viewed as an extension to the existing healthcare approach rather than a replacement of the current system. At the same time, many interviewees argued that increasingly individualized therapies challenge traditional regulatory and reimbursement assessment for therapies targeting very small patient populations. Several respondents noted that these challenges are likely to become more evident as PTs continue to become increasingly individualized, including N=1 therapies. Consequently, respondents from both industry and academia emphasized that adaptations to either existing regulatory or reimbursement systems will be necessary to accommodate current and future generations of PTs.

## 5.2: Regulatory Preferences and Sequencing of Market Entry

The interviews indicated that companies generally prefer to launch personalized therapies such as orphan drugs and ATMPs in the United States before entering the European market. Respondents described the U.S. market as more commercially attractive due to higher medicine prices and more direct market access, which grant the opportunity to recover medicine development costs. This was particularly highlighted by SMEs, which noted that early access to the U.S market provides revenue streams that support ongoing development of medicine and allows for later expansion into other markets. One respondent summarized this perspective by stating that "*for market approval, the United States is always the top priority because it is the largest market, offers relatively high prices, and had fairly easy access*." In contrast, respondents described the European market less attractive commercially because EMA approval does not automatically result in patient access. Companies must still obtain reimbursement separately in all 27 EU member states, a process described as complex and time-consuming, delaying commercialization and revenue generation.

Besides these commercial considerations, respondents also stated that differences in regulatory requirements between the FDA and EMA contribute to a preference for the U.S. market. While RCTs remain the dominant evidentiary standard, companies argued that this model is often difficult to apply to PTs because of small patient populations and the need for long-term follow-up. Across both SMEs and larger companies, the FDA was generally perceived as more flexible in accepting uncertainty, whereas the EMA was viewed as requiring more extensive and longer-term clinical data. As companies typically conduct a single global clinical trial rather than separate studies for different markets, they stated that "*clinical studies are primarily designed to satisfy FDA* requirements." Several respondents noted that evidence sufficient for FDA approval may not always meet EMA expectations, leading some companies to seek FDA approval and U.S. revenue generation first before investing in additional data collection for European market authorization.

Academic developers similarly reported that obtaining EMA market authorization reported that obtaining market authorization for PTs often requires more effort than anticipated. They argued that EMA's regulatory framework fits conventional therapies does not always accommodate the characteristics of emerging PTs. Some respondents felt that the EMA prioritizes adherence to regulatory rules over patient interests and felt that academic organizations may not always be taken as seriously as commercial developers during interactions with regulators. As one respondent noted, regulators "*adhere closely to existing rules, even when those rules do not always fit a new type of product*." However, not all experiences were negative. Another respondent emphasized that EMA and CBG were supportive and willing to engage in discussions about available regulatory pathways and potential options.

Almost all respondents, both from companies and academia, highlighted the need for a shift in evidence-generation standards, stating that PTs no longer fit the traditional "*gold standard*" of clinical evidence generation. Notably, respondents did have the impression that both EMA and FDA are aware of these challenges and adapting their regulatory frameworks in response. As one respondent noted, EMA and FDA have "*increasingly started asking companies how to respond to the next generation of personalized therapies*." For example, EMA's conditional approval pathways, its emphasis on ethical considerations, and the upcoming reform of EU pharmaceutical legislation were highlighted as signs of increasing flexibility and adaptation to innovative therapies. Even so, the FDA was perceived as adapting more quickly than the EMA to emerging innovative and personalized therapies.

## 5.3: The Reimbursement Procedure in the Netherlands

### 5.3.1: Evidence requirements for personalized therapies: EMA–ZIN alignment

Companies generally generate evidence with global clinical studies that fit market access requirements across multiple jurisdictions. Following EMA market authorization, companies can start separate reimbursement procedures for the 27 EU member states, each with its own requirements and evaluation criteria. Respondents from industry reported that evidence accepted by the EMA is not always sufficient for reimbursement in the Netherlands. While the EMA primarily evaluates safety, efficacy, and the overall benefit-risk balance, companies perceived ZIN as placing greater emphasis on cost-effectiveness, clinical relevance, and reducing evidentiary uncertainty. As a result, ZIN may request additional evidence, including comparative or longer-term data, which can be difficult to generate for PTs due to small patient populations and ethical constraints surrounding traditional trial designs. In contrast, an academic developer noted the reimbursement process could proceed "*quite successfully, as long as you provide the necessary evidence and argumentation*."

Several companies described this difference as a misalignment between regulatory approval and reimbursement requirements. One respondent described a case in which the EMA considered it unethical to continue placebo-controlled studies because a personalized therapy appeared very effective. Therefore, the treatment received market authorization from EMA, and the company could apply for reimbursement in different EU states. Nevertheless, ZIN did still require placebo-controlled evidence for reimbursement and ultimately denied reimbursement for the subgroup lacking such data. Respondent argued that such cases illustrate the EMA's greater willingness to accept more uncertainty in evidence compared with reimbursement authorities. Companies also noted that it is not feasible to adapt their entire evidence-generation strategy specifically to the Netherlands in advance, as the Dutch market represents only a small part of the global pharmaceutical industry.

ZIN, however, did not characterize these differences as a misalignment. According to ZIN respondents, the EMA and ZIN assess different questions. Whereas the EMA evaluates whether a medicine had a positive benefit-risk balance, ZIN assesses its relative effectiveness and added value compared with already reimbursed treatments in Dutch context. Consequently, additional evidence may be requested to support reimbursement decisions and reduce uncertainty regarding a therapy's effectiveness, for example by requesting comparisons with existing therapies to determine whether a new treatment offers added value. ZIN argued that this can also benefit companies by potentially enabling less conservative pricing and reimbursement advice. Additionally, ZIN emphasized that RCTs are not a strict requirement for demonstrating established SWP and are in fact becoming increasingly uncommon, particularly for highly PTs. Instead, the broader clinical and societal context of these PTs are considered during the assessment. As a result, therapies supported by limited evidence can still meet the SWP criteria and receive a positive reimbursement advice, sometimes accompanied by conditions to ensure appropriate use and justify reimbursement despite remaining uncertainty. Overall, ZIN argued that its current framework is sufficiently flexible to evaluate personalized therapies.

### 5.3.2: Innovation-affordability tension

Besides evidentiary requirements, companies experienced a broader tension between innovation and affordability within the Dutch reimbursement system. Respondents argued that reimbursement decisions are disproportionally driven by affordability and are "*based on costs rather than potential added value.*" According to companies, ZIN and the MoH primarily assess high-cost medicines through the lens of cost containment and budget impact, whereas the added value of innovation for patients and society is not focused on. This focus is reflected in reimbursement instruments such as the lock, cost-effectiveness analyses, cost-per-QALY analyses, clinical relevance thresholds (e.g., MCIDs), and price negotiations. Respondents argued that these mechanisms are difficult to apply to PTs, which are characterized by small patient populations, high per-patient costs, and greater evidentiary uncertainty. As a result, companies often receive positive reimbursement advice only after agreeing to substantial price discounts.

Companies further argued that this affordability focus does not sufficiently align with how innovation in personalized medicine occurs. They explain that drug development is high-risk and that revenues from successful therapies are needed to compensate for failed projects and fund future innovation. Strict cost-effectiveness requirements and high discount demands from ZIN and the MoH are often difficult to meet, as companies need to recover R&D investments. As one respondent stated: "*If the entire world paid the prices that the Netherlands pays, there would be no further innovation in pharmaceutical development.*" Companies also addressed the growing misalignment between the Dutch standard of care and that of other European countries, as delayed or restricted reimbursement limits the availability of new medicines in the Netherlands. This has two consequences: (1) the Netherlands is less often included in clinical trials, reducing Dutch patient participation in RCT, and (2) companies are sometimes required to generate additional evidence for ZIN when applying for reimbursement, as Dutch standard-of-care comparators are different from those used in international trials.

ZIN on the other hand emphasizes that the reimbursement system is designed to ensure both high-quality care and affordability of medicines within the Dutch healthcare system. ZIN highlights that its primary task is to assess whether a medicine complies with the SWP and to evaluate its cost-effectiveness, after which it provides advice to the MoH. According to ZIN, its assessment framework is applicable to various types of indications, including innovative medicines, and allows for a reliable determination of whether a treatment meets SWP criteria. ZIN further argues that unrestricted access to all new medicines is not feasible and not necessarily desirable, as this could create false hope if treatments ultimately do not deliver the expected benefits. Furthermore, ZIN explains that rising drug prices and the increasing development of innovative therapies have made instruments such as the lock necessary to maintain affordability of medicinal healthcare and ensure that only effective medicines are reimbursed.

Semi-public healthcare innovation and biotech organizations viewed the tension between innovation and affordability as a shared responsibility rather than a problem that can be attributed solely to reimbursement policies. Respondents argued that companies often focus on reimbursement discussions on making reimbursement requirements less strict, while paying insufficient attention to the affordability of the prices they set. One semi-public organization emphasized that the growing number of innovative and PTs makes affordability an unavoidable societal issue for which governments have a responsibility to consider sustainable healthcare spending. Respondents also pointed to venture capital-driven incentives and high expected returns as factors contributing to high list prices, particularly for PTs. Some respondents therefore argued that alternative financing models or new revenue mechanisms may be needed to balance innovation with long-term affordability. While smaller companies were perceived as relatively open to discussing such alternatives, larger pharmaceutical companies were viewed as less willing to reconsider existing business models. Even so, semi-public organizations stressed that addressing the innovation-affordability tension will require changes from both reimbursement systems and pharmaceutical business models.

Academic developers generally understood the rationale behind ZINs reimbursement assessments for high-cost PTs. Respondents recognized the difficult societal dilemma involved with these therapies, noting that treatments can cost up to millions of euros per patient and that it is not always possible to fund every therapy without careful evaluation. Overall, academics understood the limits that ZIN and the MoH face, recognizing they cannot approve reimbursement for all PTs without price conditions.

### 5.3.3: Strategic market entry decisions in response to Dutch reimbursement requirements

Both SMEs and large pharmaceutical companies reported that the Netherlands has become a less attractive market for early reimbursement submissions over the past decade. While the Netherlands was previously considered a priority country, respondents explained that it is now viewed as a medium-raking market due to increasingly strict reimbursement requirements, higher evidentiary demands, and longer waiting times before reimbursement decisions. As a result, some companies developing PTs reported delaying reimbursement applications or "*choosing to bypass the Netherlands entirely"* because they expect rejection under the current Dutch assessment criteria and evidentiary standards. In particular, SMEs described being selective in the order in which they initiate reimbursement procedures across EU member states. Due to limited organizational capacity compared large pharmaceutical companies and the complexity of preparing reimbursement submissions for multiple jurisdictions simultaneously, SMEs tend to prioritize countries where reimbursement approval is considered more likely, such as Germany, Italy, Spain, and France. Several respondents from companies also noted that they attempt to influence reimbursement policies collectively through industry and interest groups.

In response, ZIN stated that it understands why some companies may be hesitant to submit reimbursement applications or may expect a negative reimbursement outcome in advance. However, ZIN argued that its assessment framework is well suited to PTs and sought to reassure companies that the specific context of each submission is considered. According to ZIN, this enables them to conclude that a therapy meets the criteria of SWP in most cases, even when the available evidence differs from that typically generated for conventional therapies.

Besides concerns about meeting Dutch reimbursement requirements, some company respondents explained that international reference pricing can also influence decisions about when and whether to enter the Dutch market. As one respondent from a company noted, "*the Netherlands is a reference country for many other countries, and lower prices in a reference country directly reduce revenues in other countries*." Companies therefore may be reluctant to enter the Dutch market if reimbursement is expected to require a substantial price discount, as this could affect prices and revenue elsewhere in Europe. ZIN similarly suggested that this may partly explain why some companies submit reimbursement applications later in the Netherlands than in other countries. However, ZIN emphasized that this is only a possible explanation and that it cannot speak on behalf of manufacturers regarding their actual motivations.

### 5.3.4: Stakeholder proposals for adaptive reimbursement frameworks

Across stakeholder groups, several alternative reimbursement approaches were proposed to enable better suitability for PTs. Companies advocated outcome-based reimbursement, risk-sharing agreements, pay-for-performance approaches, and more flexible pricing models that would allow earlier patient access while managing uncertainty after market entry. These approaches were perceived as particularly relevant to rare diseases and high-cost PTs, where evidence generation before reimbursement is often more restricted due to small patient populations and ethical constraints. When asked whether ZIN is open to such changes, on respondent noted, "*I think there are certainly people within ZIN who would support that as well, but they are ultimately constrained by political agreements, which makes it difficult to change the* system."

A semi-public healthcare innovation organization further emphasized the importance of testing pilot-based reimbursement models in collaboration with smaller companies and exploring alternative financing and payment structures that differ from venture capital-driven incentives to improve affordability and sustainability. Thus, stakeholders addressed the need for more dynamic and experimental reimbursement approaches for the growing number of PTs to better align innovation, access, and affordability.

In contrast, ZIN respondents did not perceive a broad need for fundamental changes to the reimbursement system. They argued that the current framework is suitable for most medicines and that challenges primarily arise for specific categories, such as ultra orphan drugs.

## 5.4: Interstakeholder Relationships and System Dynamics in Dutch Reimbursement

### 5.4.1: Perceptions of an uneven playing field between stakeholders

When discussing whether the reimbursement system provides an equal playing field for pharmaceutical companies and academic developers, several differences emerged. Pharmaceutical companies frequently argued that academic developers of personalized medicine received more support mechanisms, such as subsidies, hospital exemption pathways, and more intensive guidance during the reimbursement process. Academic developers, however, did not recognize this perceived advantage. They were generally satisfied with their interaction with reimbursement bodies and stated that their PTs often focus on ultra-small patient populations that are not directly comparable to industry pipelines. In their view, academic and commercial development pathways are complementary rather than competing, as they focus on PTs that are not commercially attractive to pharmaceutical companies.

Academic respondents generally viewed public funding as important for supporting innovation, although some questioned whether available funds had always been spent tactically and suggested that stricter external review mechanisms could have improved their use. ZIN similarly emphasized that all developers are assessed under the same criteria, regardless of origin. They stated that additional support provided to academic groups is primarily focused on guiding the groups through the reimbursement process, for example by offering early scientific advice and additional consultations.

### 5.4.2: Transparency and trust in pharmaceutical pricing

Both public and private stakeholders addressed a lack of transparency and trust regarding medicine pricing. Academic developers and public stakeholders, including ZIN, argued that greater transparency into pharmaceutical development costs could contribute to more informed and balanced discussions about pricing and reimbursement decisions. One academic developer suggested that "*companies often assess, even before development has properly started, how severe a condition is and how many patients there are, and from that already determine what they will charge* *for a treatment,"* noting that this is not closely related to the actual R&D costs involved. In contrast, pharmaceutical companies argued that the level of transparency they can provide is limited, as successful medicines also must cover the costs of failed projects, long development timelines, and future innovative projects. Furthermore, several companies stated that development costs are difficult to attribute to individual medicines because they are often shared across multiple products, making it difficult to determine the exact cost of a single medicine.

These differing perspectives regarding pricing and transparency contribute to broader tensions in trust between stakeholders. Companies often reported feeling that they were perceived by public actors as primarily profit-driven organizations, stating being labeled as "*greedy profiteers"* (Dutch: "*geldwolven*" or "*graaiers"*)." In the companies' view, these labels limit their involvement in broader discussions on healthcare system design regarding PTs, despite their expertise in HTA and market access. An academic developer stated thinking that pharmaceutical companies "*are much more driven by ultimately generating as much revenue as possible, whereas we (academics) are primarily focused on bringing new, innovative therapies to patients in an affordable way."* At the same time, ZIN reported sometimes being perceived by companies as "*difficult*" and "*strict*", while emphasizing that such perceptions of reimbursement bodies are not unique to the Netherlands. Indeed, pharmaceutical companies often described ZIN and the MoH as strict and disproportionally focused on cost control, as one respondent noted, "*The MoH just wants to spend as little as possible."* A semi-public healthcare innovation organization added that companies often focus dialogue with public actors on reimbursement outcomes rather than broader discussions on affordability and system sustainability, contributing to a dynamic in which stakeholders increasingly view each other as opponents rather than collaborators.

### 5.4.3: Towards improved collaboration in reimbursement processes

Despite these differences, all stakeholder groups expressed a desire to strengthen collaboration and open communication. Respondents indicated that current interactions are often shaped by assumptions and limited mutual understanding, and that more structured and early collaboration could improve alignment across the development and reimbursement pathways. A recurring proposal from companies was to introduce earlier and more parallel decision-making for PTs, where uncertainty is relatively high. Instead of separate steps for approval, assessment, and pricing, companies suggested agreeing together with ZIN on evidence requirements, target groups, and acceptable uncertainty at an early stage. This type of collaboration was seen as a way to improve predictability and alignment in decision-making for PTs.

# Chapter 6: Discussion and Conclusion

This study aimed to answer the following research question: *How do key stakeholders perceive the fit between emerging personalized therapies and existing regulatory and reimbursement requirements, and how do they interpret and respond to these influences?* To address this question, Scott's institutional theory was used as an analytical lens, complemented by concepts from evidence-based medicine, clinical and financial uncertainty, uncertainty thresholds, and organizational strategic responses. Together, these concepts provided a framework for examining how institutional expectations regarding evidence and uncertainty shape the development, assessment, and market access of personalized therapies, as well as the perceptions, behaviors, and strategic responses of key stakeholders.

Based on this framework, semi-structured interviews were conducted with stakeholders involved in the evaluation, development, regulation, and market access of PTs. Stakeholders included academic developers, SMEs, large pharmaceutical companies, semi-public organizations, and Zorginstituut Nederland. Based on the sub questions derived from the theoretical framework (see section 3.5) and the findings, four key themes were revealed: system change and personalized medicine conceptualization; regulatory requirements and strategic responses; reimbursement requirements and strategic responses; and interstakeholder relationships. This chapter interprets these findings through an institutional lens, relates them to existing literature, discusses the scientific and societal relevance of the study, reflects on its strengths and limitations, and provides recommendations for future research and practice.

## 6.1: Interpretations of Findings

### 6.1.1: Personalized medicine as incremental adaptation within evidence-based medicine

One finding of this study is that stakeholders did not share a single definition of personalized medicine. Most respondents conceptualized PM primarily through the lens of PTs, ranging from biomarker-guided treatments to highly individualized N=1 therapies. This contrasts with definitions proposed by institutions such as the European Commission, which define PM as a healthcare model that includes prevention, diagnosis, and treatment customized to an individual's specific characteristics [22].

From an institutional perspective, this finding suggests that PM had not yet become institutionalized as a distinct healthcare paradigm. Instead, respondents described it as a technological and therapeutic extension of the existing healthcare system. Scott's institutional theory helps explain this observation: stakeholders continue to interpret PM through deeply embedded cultural-cognitive assumptions about how healthcare, evidence generation, and medicine development should be organized [51]. Although PTs introduce new technological possibilities, respondents generally understood them within existing ways of thinking about treatment development and evaluation. As a result, PM was rarely framed as a fundamentally new healthcare model, but rather as an extension of established practices.

At the same time, respondents described an increasing tension between emerging PTs and existing institutional frameworks. Respondents stated that this tension became more apparent as therapies became more personalized, particularly for highly individualized cell and gene therapies and N=1 treatments. These findings are consistent with literature suggesting that PTs challenges traditional evidence generation standards because small patient populations often make large RCTs difficult to conduct [2,5]. Within Scott's framework, these tensions can be seen as placing pressure on institutionalized assumptions about what counts as legitimate evidence [51]. There central role of RCTs within EBM shows not only methodological preferences but also deeper cultural-cognitive beliefs about what is considered scientifically rigorous and acceptable uncertainty.

Interestingly, although respondents frequently argued that regulatory and reimbursement systems require adaptation to facilitate the implementation of PTs, few described PM as a possible new system to transform the healthcare system. Instead, stakeholders generally proposed incremental adjustments to existing institutions. This finding aligns with institutional theory, which suggests that institutional change is often gradual rather than revolutionary due to institutional resilience [51]. Rather than observing deinstitutionalization of the current EBM framework and institutionalization of the PM model, this study suggests a process of incremental institutional adaptation in which PTs slowly challenge existing frameworks while still relying on them for acceptance and legitimacy.

### 6.1.2: Institutional logics shaping diverging uncertainty thresholds in market access

Another finding is that PT developers perceive regulatory and reimbursement institutions as applying different thresholds for acceptable uncertainty. Regulatory agencies such as the EMA and FDA were primarily described as focusing on evidentiary uncertainty by assessing whether the available evidence demonstrates a sufficiently positive benefit–risk balance. Respondents generally perceived the FDA as more willing to accept uncertainty than the EMA, although both agencies were seen as increasingly willing to accept alternative forms of evidence when RCTs are difficult or unethical to conduct. Existing literature similarly points to the growing use of surrogate endpoints, real-world evidence, and adaptive regulatory pathways for innovative therapies [70,71]. From an institutional perspective, this suggests a gradual adaptation of regulatory frameworks and the regulative pillar in response to the evidentiary challenges associated with PTs.

In contrast, respondents described reimbursement bodies such as ZIN as applying a broader set of evaluative criteria that focus on both clinical and financial uncertainty. In addition to assessing relative clinical effectiveness, ZIN evaluates cost-effectiveness and budget impact to determine whether a therapy can be sustainably integrated into the Dutch healthcare system. This may create situations in which a therapy can be clinically acceptable according to regulators but economically or societally not justifiable for reimbursement. These findings support the concept of uncertainty thresholds introduced in the theoretical framework. Regulatory and reimbursement institutions perform different functions within the healthcare system and therefore tolerate different levels and types of uncertainty. While companies often interpreted these differences as evidence of misalignment between institutions, ZIN explained them as a consequence of distinct institutional responsibilities.

The findings further suggest that market approval and reimbursement are guided by two distinct institutional logics. The first is an evidentiary logic, focused on demonstrating safety and effectiveness through acceptable forms of clinical evidence. The second is financial logic, focused on affordability, cost-effectiveness, and the sustainability of healthcare spending. This connects to Thornton and Ocasio's institutional logics perspective, which explains how these logics shape how actors interpret problems and make decisions within the same institutional environment [72]. Although the theoretical framework acknowledged financial uncertainty as a relevant concept, it primarily emphasized evidence generation and evidentiary uncertainty because the literature used to develop the framework mainly focused on evidentiary challenges [2,26]. The findings indicate, however, that financial factors are not just a secondary consequence of evidence generation, but are an equally important institutional logic shaping market access decisions for PTs. This is consistent with broader literature showing that PTs often involve high development and implementation costs, creating challenges for reimbursement and the long-term sustainability of healthcare systems [73,74]. This suggests that the original theoretical framework underestimated the extent to which financial considerations structure stakeholder perceptions and decision-making.

This logics distinction helps explain why stakeholders interpreted differences between EMA approval and Dutch reimbursement decisions differently. Companies often viewed additional evidence requests and pricing negotiations as signs of institutional misalignment, whereas ZIN regarded them as a necessary part of evaluating the broader societal implications of reimbursement. Rather than reflecting institutional inconsistency, the findings suggest that PTs move through multiple decision-making bodies characterized by different institutional logics and uncertainty thresholds. These differences not only influence how therapies are assessed, but also how developers design evidence-generation strategies and make market-entry decisions. Understanding these differences is therefore important for explaining both the market access challenges associated with PTs and the ways in which developers anticipate and respond to institutional requirements during development and market entry.

### 6.1.3: Developers adapt strategically to institutional pressures through evidence-generation and market-entry decisions

Building on the differing institutional logics identified above, the findings support Oliver's (1991) argument that organizations do not passively comply with institutional pressures but respond strategically to them [63]. Developers of PTs were found to adapt both evidence-generation strategies and market-entry decisions to navigate regulatory and reimbursement requirements.

A first example concerns evidence generation. Companies explained that they often design clinical development programs with the requirements of major regulatory authorities in mind, particularly the FDA. Since running separate development programs for different regions is often not realistic, they try to generate evidence that will be acceptable in the largest and most commercially attractive markets. This reflects a combination of acquiescence and compromise: companies accept that evidence is required, but at the same time prioritize the expectations of certain regulators over others when shaping the drug development strategy. However, literature suggests that drug development is usually global. Companies generally design trials so the same results can be used for multiple countries and submitted to different regulators simultaneously [75]. From this perspective, the prioritization described by respondents may reflect the fact that global trial designs are influenced by the relative importance of different markets, within which the U.S. is particularly important due to its commercial size.

Strategic responses were also observed in market-entry decisions. Many respondents, particularly those from SMEs, described prioritizing the U.S. over Europe because they perceived the U.S. as offering a larger commercial market and a faster route to market. This can be interpreted as a form of compromise, whereby companies adapt to institutional requirements while selectively prioritizing jurisdictions perceived to offer more favorable conditions. This interpretation is supported by previous research on pharmaceutical launch sequencing, which shows that companies make strategic decisions regarding the timing and location of product launches [76].

The strategic response of avoidance was also reported by respondents. Several companies reported delaying or avoiding reimbursement submissions in the Netherlands, either within their own organizations or based on observations of other firms. They stated this was a consequence of the challenging reimbursement requirements and pricing negotiations. However, this pattern is not reflected in the existing literature on pharmaceutical market access in the Netherlands. This raises the question of whether this represents a new development in practice or whether it may be overstated by respondents. Furthermore, it raises the question of how to classify this behavior: whether this behavior should be understood as true avoidance or rather as a form of compromise. As suggested by both ZIN and several companies, considerations such as international reference pricing may play a role in these decisions by creating a price ceiling that influences pharmaceutical pricing and market access decisions [77]. Therefore, firms may strategically enter other markets first and return to the Netherlands at a later stage, suggesting a strategic response of compromise.

Overall, companies also demonstrated acquiescence by accepting and complying with the evidence standards set by regulatory authorities. Importantly, these strategic responses appeared to be shaped by both evidentiary and financial uncertainty. Evidence-generation strategies mainly focused on dealing with evidentiary uncertainty, while decisions around market access and reimbursement were more influenced by financial uncertainty related to pricing, reimbursement outcomes, and revenue generation. This suggests that companies respond to institutional pressures strategically to achieve both evidentiary legitimacy and financial legitimacy across different healthcare systems.

### 6.1.4: Diverging stakeholder values and the challenges of institutional adaptation

A final finding of this study is that stakeholders generally agreed that existing institutions need to adapt to accommodate the growing number of PTs. However, there was a variation in how this adaptation should be shaped and which values should guide it. This theme arose during inductive coding, highlighting the importance of stakeholder values and perceptions regarding PTs in addition to the application of formal institutional structures.

These differences could be explained with Scott's institutional perspective, as they may reflect diverging normative orientations across stakeholder groups [51]. Pharmaceutical companies emphasized innovation, investment recovery, and the financial risks associated with pharmaceutical development of PTs. In contrast, ZIN and the Ministry of Health were perceived as prioritizing affordability, solidarity, and the sustainability of publicly funded healthcare systems. Academic stakeholders emphasized transparency, openness, and scientific integrity. These differing normative perspectives help explain why similar issues regarding pricing or reimbursement decisions are interpreted in fundamentally different ways across stakeholder groups.

An area where these differences became visible was the innovation-affordability tension. Most stakeholders recognized that PTs are often high-cost interventions. However, they differed in how responsibility for managing these costs should be distributed. Pharmaceutical companies emphasized that high prices reflect the risks of research and development, including high failure rates and long-time development, which must be compensated for by products that are successful. This aligns with literature describing how pharmaceutical innovation systems spread risk across different development projects [78]. Public stakeholders such as ZIN and the MoH were often perceived by companies as prioritizing affordability and sustainability of the healthcare system. This perception is consistent with policy descriptions from the Dutch government, which emphasize the importance of keeping medicines affordable and ensuring the sustainability of the healthcare system within a publicly funded system [79]. Semi-public and academic stakeholders positioned themselves between these perspectives, acknowledging the importance of innovation while also recognizing the need to ensure affordability and system sustainability. Overall, the findings suggest that the innovation–affordability tension is not only economic but also reflects different views on how the costs and benefits of new medicines should be shared across society.

Another way in which these differing perspectives became visible is in how stakeholders perceived each other's roles and motivations. Stakeholders differed in their expectations of transparency in areas such as pricing and decision-making and described each other in ways that showed limited mutual understanding. These findings suggested that tensions between stakeholders are not only driven by differences in evidence or policy but also shaped by limited transparency and understanding between actors operating within the same system. This suggests a limitation in institutional theory in fully capturing relational dynamics between actors, as this theory is less capable of implementing how trust and interstakeholder dynamics influence the institution [51]. An addition to the theoretical framework could therefore be the inclusion of institutional trust as a relational mechanism, helping to explain how stakeholders interpret each other's actions and how these interpretations influence the functioning of institutions in practice [80].

Taken together, these findings suggest that the future development of PM and implementation of PTs does not only depend on adapting regulatory and reimbursement mechanisms, but also on improving trust, transparency, and mutual understanding between stakeholders. Institutional change in this context is therefore likely to involve not only technical changes, but also shifts in how actors perceive each other's roles, responsibilities, and contributions within the healthcare system. Although stakeholders widely acknowledged the need for improved collaboration and earlier dialogue, they simultaneously described a system characterized by limited trust and interstakeholder tensions. This indicates that while institutional adaptation is recognized as necessary, differences in values and perceptions of responsibility complicate the alignment in the PM landscape.

## 6.2: Scientific and Societal Relevance

This study contributes to the scientific literature on PM and PTs by integrating institutional theory with EBM and HTA to explain how market access is shaped across different institutions [51]. It shows that regulatory and reimbursement systems operate according to different but interacting institutional logics, where regulators primarily focus on clinical safety and efficacy, while reimbursement bodies additionally apply financial logics related to cost-effectiveness and affordability. Rather than looking at these domains as separate silos, the study demonstrates that evidentiary and financial considerations both structure what is considered acceptable evidence and uncertainty in decision-making. In addition, the findings show that developers actively interpret and respond to these institutional processes by adapting evidence-generation strategies, prioritizing certain markets, and engaging in strategies proposed by Oliver (1991) [63]. Overall, the study contributes to institutional theory by showing how organizations act strategically within an environment with diverging institutions. It also contributes to the PM literature by showing that access to PTs is shaped by the interaction of evidence requirements, financial constraints, and relationships between stakeholders.

From a societal perspective, the findings are relevant to policy debates on how to balance innovation, affordability, and access in healthcare systems. The results show that tensions around access to PTs are not only technical or economic, but also reflect different interpretations of value, responsibility, and acceptable uncertainty across stakeholder groups. This is particularly relevant in the context of ongoing reforms in European pharmaceutical legislation and the Joint Clinical Assessment [43,45]. Importantly, these dynamics ultimately also have consequences for patients, as reimbursement delays, differing institutional requirements, and strategic market-entry decisions can affect the availability and timing of access to PTs.

## 6.3: Strengths and Limitations

This study has several strengths. By including stakeholders from industry, academia, semi-public organizations, and Zorginstituut Nederland, it provides a multifaceted perspective on the development and market access of PTs. The combination of deductive and inductive analysis allowed existing institutional theory to be applied while also identifying themes that emerged directly from the data. In addition, the use of semi-structured interviews generated rich qualitative insights into stakeholder experiences and perceptions.

Several limitations of this study should be acknowledged. First, although a range of stakeholder groups was included, important stakeholders such as the Medicines Evaluation Board (CBG), the Ministry of Health, Welfare and Sport, healthcare insurers, and patient organizations were not represented, resulting in a less comprehensive view of the institutional landscape. In addition, industry respondents were more strongly represented than academic stakeholders and public actors, which may have contributed to a greater emphasis on market-access challenges and an overrepresentation of industry perspectives. The use of purposive and snowball sampling may also have introduced selection bias, as participants were partly recruited through overlapping professional networks. Furthermore, the study focused predominantly on the Dutch context, limiting the broader generalizability of the findings to other healthcare systems. In addition, the results reflect stakeholder perceptions and experiences rather than actual decision-making behavior and may therefore differ from institutional practice. Finally, as with all qualitative research, the interpretation of the findings may have been influenced by the researcher’s positionality, despite efforts to maintain a systematic and transparent research process.

## 6.4: Recommendations

### 6.4.1: Future research

Several suggestions for future research emerge from this study. First, future studies could include a broader range of stakeholders, such as the Ministry of Health, the Medicines Evaluation Board, healthcare insurers, clinicians, and patient organizations, to develop a more complete understanding of the institutional environment surrounding PTs and to prevent an overrepresentation of a specific stakeholder group. Second, comparative cross-country research could provide insight into how different reimbursement systems shape innovation, affordability, and patient access of PTs. The United States and China may be particularly interesting cases for comparative research, as both countries have invested a lot in precision medicine and biotechnology and are seen as global leaders in the development of personalized therapies [81,82]. Third, future research could further explore how personalized medicine and personalized therapies are defined across stakeholder groups, as the findings show variation in this definition ranging from biomarker-guided treatments and orphan drugs to highly individualized N=1 approaches. Improving conceptual clarity in this area may strengthen both academic debate and policy development. Finally, given the emergence of increasingly individualized therapies, future studies could examine whether and how existing regulatory and reimbursement institutions are adapting to these therapies. This can include processes of institutional change and potential deinstitutionalization, particularly in relation to the evaluation and implementation of N=1 therapies [83].

### 6.4.2: Practical recommendations

The findings of this study suggest several practical recommendations for stakeholders involved in the development, regulation, and reimbursement of PTs. First, greater alignment between regulatory and reimbursement processes is needed. Although regulators and reimbursement bodies fulfilled different institutional roles, stakeholders frequently reported uncertainty regarding evidence requirements following market authorization. Strengthening early and parallel dialogue between developers, regulators, and reimbursement bodies could improve clarity regarding evidence expectations, acceptable uncertainty, and post-market evidence generation, particularly for PTs where traditional evidence generation is challenging. One way to facilitate this would be via a formal multi-stakeholder platform in which developers, regulators, reimbursement bodies, academic experts, and patient representatives can discuss evidence requirements and potential reimbursement challenges at an early stage of development.

Second, efforts should be made to improve transparency and mutual understanding regarding innovation costs and medicine pricing. The findings showed that disagreements about affordability are not only the result of conflicting interests but also reflect different understandings of how pharmaceutical innovation is financed. While companies emphasized the costs, risks, and long development timelines associated with drug development, public stakeholders mainly questioned how development costs relate to the prices ultimately charged for medicines. Greater transparency by developers about how medicines are developed, how prices are determined, and how pharmaceutical innovation is financed could help create more constructive discussions and increase trust between industry and public stakeholders. At the same time, full financial transparency by developers is not always possible because of commercial considerations and the difficulty of linking costs to individual medicines. In such cases, developers should communicate more openly about these limitations and the reasons behind them. Such communicative transparency may help build greater mutual understanding and trust, even when complete transparency is not possible.

Third, affordability should be approached as a shared responsibility rather than as a problem that can be solved by a single stakeholder group. The findings suggest that tensions between innovation and affordability cannot be addressed solely through stricter reimbursement requirements or lower list prices. Policymakers, reimbursement bodies, industry, and other involved stakeholders should therefore continue exploring alternative approaches. Examples include outcome-based agreements, risk-sharing arrangements, and innovative financing mechanisms. This could ensure both sustainable healthcare spending and continued incentives for innovation.

Finally, stakeholders, in particular regulatory and reimbursement bodies, should be open to the possibility that future generations of PTs may require more fundamental institutional adaptation rather than continuous adjustments to existing frameworks. An interesting finding of this study was that stakeholders generally viewed personalized medicine not as a new healthcare paradigm, but primarily through the lens of personalized therapies. As a result, discussions about implementation focused mainly on adapting existing regulatory and reimbursement systems rather than reconsidering the underlying assumptions of those systems. However, the increasing emergence of highly individualized therapies, including N=1 treatments, may increasingly challenge the feasibility of regulatory and reimbursement models that are built around population-based evidence generation and standardized assessment procedures [83]. Therefore, policymakers, regulators, and reimbursement bodies should also explore whether elements of the broader personalized medicine paradigm itself offer alternative ways of organizing evaluation, reimbursement, and access, rather than only making incremental adjustments to existing institutions. This may become increasingly relevant as PTs continue to move beyond traditional patient populations and towards truly individualized treatment approaches.

## 6.5: Conclusion

Overall, this study showed that key stakeholders perceived PTs as only partially fitting within existing regulatory and reimbursement frameworks, as they challenge the limits of the current system. Both industry and academic actors emphasized that evidentiary requirements under current regulatory frameworks are increasingly difficult to meet for PTs due to small patient populations, reliance on surrogate endpoints, and limited long-term data. Furthermore, Dutch reimbursement requirements were perceived by companies as difficult to meet, as cost-effectiveness analyses are often challenging to satisfy due to the high per-patient costs of PTs. In contrast, public and semi-public stakeholders and academics generally viewed these requirements as necessary to ensure affordability and the long-term sustainability of the healthcare system. Overall, most stakeholders called for incremental adaptations within existing regulatory and reimbursement structures, rather than advocating for a fundamental shift toward a new healthcare approach such as PM.

In terms of stakeholder responses to these requirements, pharmaceutical companies actively adjust their evidence-generation and market entry strategies to meet expectations of regulatory authorities, while also prioritizing markets perceived as more predictable or commercially attractive. Furthermore, multiple stakeholders highlighted tensions between stakeholder groups, particularly regarding transparency and pricing of PTs. Therefore, stakeholders recognized that earlier dialogue and greater alignment between regulators, reimbursement bodies, and developers could improve PT access. Taken together, these findings directly answer the research question by showing that stakeholders perceive PTs as only partially fitting within the current system due to evidentiary and financial challenges, and that they respond through a combination of strategic adaptation and calls for improved interstakeholder cooperation.

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# AI-statement

While writing this thesis, AI tools were used to help in finding relevant literature sources, suggesting synonyms, and improving grammar and sentence clarity. All ideas, analyses, interpretations, and conclusions presented in this thesis are the original work of the author, and AI tools were used solely to assist in the writing process.

# Appendixes

## Interview Guide

Interview guide developers

**Background and Current Evidence-Making**

Let’s start with some broader questions about the current system first. And then in the end we will talk about personalized medicine.

1) Can you describe your current role and organization?

We all want to see evidence that a product or medicine works in practice. How is this evidence currently established in the drug development pathway?

2) Can you tell me something about the development of specific medicine: which specific population was chosen and why? Do you see potential for other diseases/are you working on something else right now?
3) How did regulatory requirements influence your clinical trial design and your development strategy for targeted therapeutic approaches?
    a. Were there specific challenges in meeting these requirements (RCTs)?
    b. Have you ever modified study design, endpoints, or target populations due to regulatory expectations, or set up an additional study due to these requirements?
    c. What role do evidence(making) and uncertainty play here?
        i. How would you define “evidence” in the drug development pathway?
        ii. How would you define “uncertainty” in the drug development pathway?
    d. What makes evidence or a development approaching “credible” or “legitimate” in your field?
    e. Do you feel that the regulatory system applies equally to all developers, or are there differences in flexibility depending on the type of organization? Can you give an example of this inequality?

4) How do reimbursement or HTA requirements in the Netherlands influence your evidence generation and development decisions?
    a. Are there specific challenges in meeting these requirements?
    b. Have you ever modified study design, endpoints, or target populations due to HTA expectations, or set up an additional study due to these requirements?
    c. What role do evidence and uncertainty play here?
        i. How would you define “evidence” in the drug development pathway?
        ii. How would you define “uncertainty” in the drug development pathway?
    d. What makes evidence or a development approaching “credible” or “legitimate” in your field?
    f. Do you feel that HTA system applies equally to all developers, or are there differences in flexibility depending on the type of organization? Can you give an example of this inequality?
5) Do you experience alignment or tensions between regulatory requirements of the EMA and reimbursement requirements of ZIN? And if so, how?

**International context**

6) What differences have you experienced between the EMA and FDA in approving these therapies?
    a. How do these differences influence your development strategy?
    b. Do you prioritize one system over another, why?
7) What differences have you experienced between the reimbursement authorities between different countries (USA vs Netherlands, more countries) in approving these therapies?
    a. How do these differences influence your development strategy?
    b. Do you prioritize one system over another, why?

**Future approaches**

8) In your opinion, to what extent does the current system support the development of personalized/patient-specific therapies in practice?
    a. Can you explain how you see the current system/paradigm of medicine development?
9) Are you familiar with the paradigm personalized medicine?

    a. In your experience, how does the personalized medicine paradigm differ from the current dominant paradigm for medicine development?
    b. Evidence generation and uncertainty management

10) What changes in regulatory or reimbursement systems would, in your view, better support the development and implementation of these therapies?

11) Are you aware of any promising initiatives or pilots in this area?

12) If you could design an ideal framework for medicine development in the context of personalized medicine/therapies, what would it look like?
    a. How would evidence be generated?
    b. How would uncertainty be handled?
    c. When would evidence be legitimate?

13) Is there something I haven't asked that you would still like to talk about?

Interview guide regulators/reimbursement bodies

**Background and Current Evidence-Assessment**

1) Can you describe your current role and organization?

We all want to see evidence that a product or medicine works in practice.

2) How do you currently assess medicine, what criteria do you look at?
3) From your institutions' view, what makes evidence sufficient or "legitimate" in your field?
4) How do you manage "uncertainty" in your evaluations? When is something uncertain?

5) Do different stakeholders (EMA, ZIN, FDA) interpret or tolerate uncertainty differently?
6) Can you reflect on the alignment or tensions between regulatory requirements and reimbursement requirements? (evidence & uncertainty)
7) How do you help academic developers, SMEs, and large pharmaceutical companies navigate these requirements? And how do you balance equality and equity in this balancing act? → show image here

**International context**

8) In your experience, what are the key differences between the EMA and FDA in approving?

    a. Is there alignment between these regulators? How?

9) In your experience, what are the key differences between the HTA of the Netherlands and different countries in allowing for reimbursement?

    a. Is there alignment between these institutions? How?

10) Are you aware of products being launched elsewhere that aren't introduced in Europe/Netherlands? And if so, do you have any idea what drives this?

**Innovation in medicine development**

11) What is your view on the rise of more personalized or targeted therapeutic approaches, such as….?

12) Do these personalized or targeted therapeutic approaches challenge the current system and your assessment frameworks, and if so, how?

13) How do you manage these challenges? (EMA → conditional approval), (ZIN → evaluation VT and differences with ODAP)

14) How do developers of personalized or targeted therapeutic approaches respond to these challenges?

    a. Have you seen adaptations in study design, endpoints, or target populations?

    b. Have you seen developers abandoning a product because of these challenges

15) In your opinion, to what extent does the current system support the development of personalized/patient-specific therapies in practice?

    a. Can you explain how you see the current system/paradigm of medicine development? (Evidence, uncertainty)

    b. Are you familiar with the paradigm personalized medicine?

**Future approaches**

16) Are you aware of any promising initiatives or pilots (policies) in this area?

17) If you could design an ideal framework for medicine development in the context of personalized medicine/therapies, what would it look like?

    a. How would evidence be generated?

    b. How would uncertainty be handled?

    c. When would evidence be legitimate?

18) How can you help academic developers, SMEs, and large pharmaceutical companies navigate these changes? And how do you balance equality and equity in this balancing act?

19) Is there something I haven't asked that you would still like to talk about?

## Data Management Plan

Semi-structured interviews are the source of data for this report. Before conducting the interview, informed consent will be obtained from participants. The interviews will be recorded. The audio files will be stored, and the interviews will be transcribed verbatim into raw data. The raw data will be pseudonymized and analyzed using Atlas.ti, using deductive coding first. After deductive coding, inductive coding will be applied, and the data will be processed and ready to be analyzed. The table below demonstrates the type, format, sensitivity, storage and archiving strategies for the obtained data.

| **Description** | **Type** | **Format** | **Sensitivity** | **Storage** | **Archiving** |
|---|---|---|---|---|---|
| Interview recordings | Audio | mp3 | High | Spraakrecorder app | Deleted after transcribed |
| Interview guide | Text | txt | Low | Map name: Thesis Regulations Personalized Medicine | Not archived |
| Interview notes | Text | txt | Medium | In notebook | Disposed of after internship |
| Interview transcripts | Text | txt | High | Password-protected on Hollandbio drive. Map name: Interview_data | 5 years in protected drive |
| Key file | Text | txt | High | Password-protected on Hollandbio drive separate from other files. Map name: Key_file_interviews | In "Key files interviews" map for 5 years in protected drive. |
| Data analysis documents | Text | txt | Medium | Password-protected on Hollandbio drive. | 5 years in protected drive |

| | | | | | |
|---|---|---|---|---|---|
| | | | | Map name: Interview_data | |
| Metadata | Text | txt | Medium | Password-protected on Hollandbio drive. Map name: Interview_data | 5 years in protected drive |
| Informed consent forms | Text | txt | High | Password-protected on Hollandbio drive separate from other files. Map name: Informed_Consent_files | 5 years in protected drive |
| Data visualization | Visualization | png | Low | Map name: Thesis Regulations Personalized Medicine | Not archived |
| Draft version | Tekst | txt | Low | Map name: Thesis Regulations Personalized Medicine | Not archived |
| Final version | Text | txt | Low | Map name: Thesis Regulations Personalized Medicine | Submitted on Onstage |
| Presentation | ppt | .pptx | Low | Map name: Thesis Regulations Personalized Medicine | Not archived |

The data was stored on a secured drive of Hollandbio. The researcher and the on-site supervisor only had access to draft versions and final versions of the data. The maps used for the data were password protected. After completion of the internship, the researcher's on-site supervisor is responsible for storing, managing, and archiving the data. The data will be archived for five years in the protected drive of Hollandbio.

## Codebook and Operationalization Table

| Theme | Construct / Subtheme | Definition / Description |
|---|---|---|
| **Institutional Pressures** | Regulative pillar | Formal rules, laws, procedures, and requirements imposed by regulatory and reimbursement institutions (e.g., FDA, EMA, ZIN, VWS). |
|  | Normative pillar | Professional standards, values, and expectations regarding appropriate evidence generation, patient benefit, and good clinical practice. |
|  | Cultural-cognitive pillar | Shared beliefs and taken-for-granted assumptions regarding legitimate evidence and medicine development (RCTs as gold standard). |
|  | Regulatory constraints | Perceived barriers resulting from regulatory or reimbursement requirements. |
|  | Institutional differences | Differences between institutional environments (e.g., FDA versus EMA, EMA versus ZIN). |
|  | Cultural-cognitive mismatch | Perceived mismatch between personalized therapies and existing evidence standards or institutional expectations. |
| **Evidence & Uncertainty** | Quality of evidence | Perceptions regarding robustness, validity, and acceptability of evidence used for regulatory approval or reimbursement. |
|  | Clinical/evidentiary uncertainty | Uncertainty regarding safety, efficacy, long-term outcomes, and |

| **Theme** | **Construct / Subtheme** | **Definition / Description** |
|---|---|---|
| | | generalizability of clinical evidence. |
| | Financial uncertainty | Uncertainty regarding cost-effectiveness, budget impact, pricing, and long-term healthcare expenditures. |
| **Strategic Responses to Institutional Processes** | Acquiescence | Acceptance of institutional requirements through habit, imitation, or compliance. |
| | Compromise | Partial conformity through balancing competing demands, pacifying stakeholders, or bargaining with institutions. |
| | Avoidance | Attempts to circumvent institutional requirements through buffering, concealment, or strategic market sequencing. |
| | Defiance | Explicit rejection or criticism of institutional demands through dismissal, challenge, or attack. |
| | Manipulation | Attempts to influence institutional rules, norms, or decision-making through lobbying, collaboration, or advocacy. |
| **Interstakeholder Dynamics** | Distrust | Lack of confidence in the intentions, expertise, or decisions of other stakeholders. |
| | Communication barriers | Difficulties in information exchange, mutual understanding, or collaboration between stakeholders. |

| Theme | Construct / Subtheme | Definition / Description |
|---|---|---|
| | Misaligned interests | Differences in priorities, objectives, or incentives between stakeholders. |
| | Transparency | Perceptions regarding openness about pricing, development costs, evidence generation, and decision-making processes. |
| | Equal playing field | Perceptions regarding fairness of institutional support, assessment procedures, and opportunities for different stakeholders. |
| **Innovation & Affordability Tensions** | Cost risks | Financial risks associated with development, reimbursement, and adoption of personalized therapies. |
| | Innovation incentives | Factors that stimulate or discourage investment in pharmaceutical innovation. |
| | R&D investments | Discussions regarding development costs, failed projects, return on investment, and innovation financing. |
| | Affordability pressures | Concerns regarding healthcare budgets, cost containment, and sustainability of healthcare systems. |
| | Dynamic payment models | Outcome-based reimbursement, risk-sharing agreements, pay-for-performance, and other adaptive financing mechanisms. |
| **Institutional Change & Future Adaptation** | Personalized medicine paradigm shift | Perceptions regarding whether PM represents incremental |

| **Theme** | **Construct / Subtheme** | **Definition / Description** |
|---|---|---|
| | | change or a fundamental transformation of healthcare. |
| | Institutional adaptation | Changes in regulatory or reimbursement frameworks to accommodate personalized therapies. |
| | Shared-risk models | Collaborative approaches for managing uncertainty and financial risk between stakeholders. |
| | Future recommendations | Stakeholder proposals for improving regulation, reimbursement, evidence generation, or collaboration. |