Shaping the changing landscape of clinical evidence

A multi-stakeholder perspective on the feasibility of a pay-for-proof pricing model for improved access to innovative drugs in the Netherlands

Internship at Roche Nederland B.V.

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List of abbreviations

AA	Accelerated assessment
ACP	Adviescommissie Pakket
ADME	Absorption, distribution, metabolism, and excretion
AEC	Approval under exceptional circumstances
CED	Coverage with evidence development
CF	Conditional financing
CHMP	Committee for Medicinal Products for Human Use
cieBOM	Commissie ter Beoordeling van Oncologische Middelen
CMA	Conditional market authorization
CR	Complete response
DAP	Drug access protocol
DoR	Duration of response
DRUP	Drug rediscovery protocol
EBM	Evidence-based medicine
EC	European Commission
EMA	European Medicines Agency
GCP	Good clinical practice
GVS	Geneesmiddelenvergoedingssysteem
HTA	Health Technology Assessment
ICER	Incremental cost-effectiveness ratio
MA	Market authorization
MEA	Managed entry agreement
MSI	Microsatellite-instable
NME	New molecular entity
OECD	Organization for Economic Co-operation and Development
ORR	Overall response rate
OS	Overall survival
PFS	Progression-free survival
PR	Partial response
RCT	Randomized controlled trial
RWD	Real-world data
RWE	Real-world evidence
SD	Stable disease
SoC	Standard of care
SvWP	Stand van de wetenschap en praktijk
VT	Voorwaardelijke toelating
VWS	Ministerie van Volksgezondheid, Welzijn en Sport
WAR	Wetenschappelijke adviesraad
WHO	World Health Organization
ZIN	Zorginstituut Nederland

Abstract

Background: Innovative payment models have the potential to ameliorate the impact of uncertainty and provide a flexible framework that facilitates patient access and additional evidence generation over time. This is becoming increasingly important as healthcare expenditures are continuously rising, while simultaneously a growing number of drugs are developed based on less comprehensive evidence.

Objective: To assess the feasibility of a pay-for-proof (PFP) payment model for line extensions within solid oncology of Roche Nederland B.V.

Methods: First, a scoping review was performed to explore current trends around EMA approval, reimbursement and access pathways in the Netherlands, as well as innovative pricing models. Further, a contribution was made to the development of the PFP model, and its feasibility and ecosystem readiness were assessed through a multi-stakeholder analysis.

Results: The PFP model is a performance-based, personalized reimbursement scheme that links payment to a discount scheme based on regulatory milestones. Overall, stakeholders were supportive of the data-driven nature of the scheme, structured way of addressing uncertainties, and ability to reflect real-world value. Main challenges include the need for a uniform data-infrastructure, complex real-world data methodologies, and potential resistance due to perceived unfairness regarding differential pricing.

Conclusion: For successful implementation of the proposed PFP model, we advise Roche Nederland B.V. to *(1)* ensure the scheme is easy executable for medical specialists, and *(2)* make use of an existing data-infrastructure instead of developing a new platform. Further, *(3)* propagate the highest price as reference price and link discounts to specific conditions to justify differential pricing, and *(4)* predefine which uncertainties remain and ensure a link between uncertainties to address and conditions of the scheme. Last, *(5)* actively involve relevant stakeholders during implementation of the PFP model.

Layman's summary

After a novel drug has obtained market authorization in the EU, decisions must be made on a national level regarding the reimbursement of the treatment. This process is often informed by Health Technology Assessment (HTA) agencies, who are responsible for assessing the effects of the treatment in the context of a specific healthcare system. In these assessments, HTA agencies aim to shed light on the *relative* effectiveness of the drug in comparison to the therapy that is generally applied to quantify its added therapeutic value. Due to tight healthcare budgets and increasing expenditures, making well-informed reimbursement decisions is becoming increasingly important.

The *randomized controlled trial* (RCT) is a study design that is often considered the gold standard, as directly comparing the effects of a newly proposed therapy against an existing treatment in one single study provides the highest level of evidence. However, several trends are ongoing that result in a growing number of drugs being developed through study types that deviate from the traditional RCT design. The lack of strong comparative evidence in these study designs hampers an adequate assessment on the relative effectiveness of treatments. Ultimately, this results in significantly delayed patient access or even no access at all.

Payment models have the potential to manage uncertainties that are associated with a drug through flexible agreements regarding its reimbursement. The objective of this study was to assess the feasibility of an innovative pay-for-proof (PFP) payment model and contribute to its development, ultimately advising Roche Nederland B.V. whether the Dutch healthcare system is ready for the implementation of payment models that aim at improving access to drugs associated with new types of evidence. In the PFP model, the price of a drug is based on data obtained through clinical trials as well as the growing data from real-world practice, in which higher levels of evidence are rewarded by declining discounts, thereby reflecting the real-world value of innovations.

Interviews were conducted with internal and external stakeholders of Roche. Results indicated that stakeholders believe current reimbursement procedures are not sustainable, whereas the PFP model was perceived as a fair and robust alternative that enhances flexible reimbursement and enables reflection of the real-world value of innovations. Main challenges include complex methodologies associated with real-world data and the need for a solid data-infrastructure. Further, the differential pricing used in the PFP scheme may possibly result in resistance due to perceived unfairness.

For successful implementation of the PFP scheme in the Netherlands, several recommendations were made. First, *(1)* ensure the scheme is easy executable for medical specialists. Further, *(2)* make use of an existing data-infrastructure instead of developing a new platform. Next, *(3)* propagate the highest price as reference price and clearly link discounts to specific conditions to justify differential pricing. More, *(4)* before engaging in the scheme, define which uncertainties remain and always ensure a link between these uncertainties and the conditions applied in the scheme. Last, *(5)* ensure active involvement of relevant stakeholders during implementation of the PFP model. Hence, the PFP model contributes to Roche's Pharma Vision 2030 to achieve 3-5 times more patient benefits for 50% less costs to society.

1. Introduction

The Dutch healthcare system primarily relies on the principles of evidence-based medicine (EBM) regarding the evaluation and reimbursement of novel innovations. EBM is defined as *"the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients"* (1). In practice, this means that decision-makers regarding drug reimbursement strive to base their conclusions on the most robust type of clinical evidence that is associated with the least uncertainty, with the ultimate goal of increasing the chance that a therapy is both effective and safe while simultaneously limiting unjustified healthcare expenditures. According to the EBM approach, phase III randomized controlled trials (RCTs) provide one of the most reliable types of clinical evidence and are thereby widely recognized as the gold standard for evaluating the (relative) effectiveness of interventions (2–4). Correspondingly, many assessment frameworks applied by reimbursement agencies demand the inclusion of an RCT to allow an adequate evaluation of the submitted evidence.

However, a growing number of drugs receive market approval based on less comprehensive evidence obtained through non-randomized phase I/II trials (4,5). This is in particular the case for drugs intended for rare indications, for which RCT studies are often not feasible due to small numbers of eligible patients. Moreover, advances in healthcare technologies result in increased development of precision medicine or personalized healthcare – care that is tailored to fit the individual needs of a patient by taking one's genetic profile, lifestyle, and environment into account (6,7). Personalized healthcare contradicts most traditional medical treatments based on a 'one-size-fits-all' approach designed for the average patient, as depicted in Figure 1 (8). Indeed, personalized healthcare generally shows promising results through higher overall response rates (ORR) in comparison to more traditional chemotherapies indicated for broader patient populations (5,9).

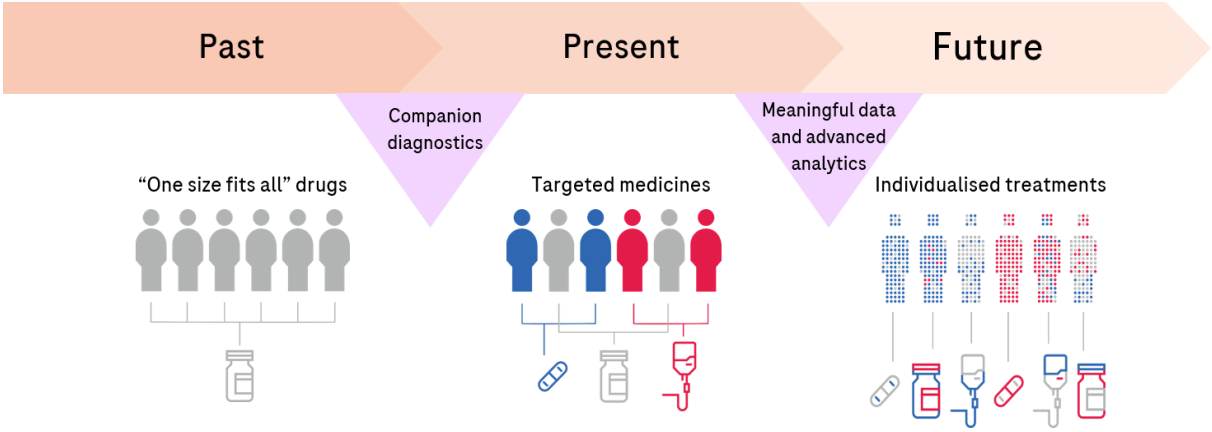

Figure 1: Paradigm shift from 'one-size-fits-all' drugs to personalized healthcare (10).

As these highly innovative technologies are often expected to fulfill an unmet clinical need, the corresponding study designs and primary outcomes are accepted by the European Medicines Agency (EMA) through expedited pathways, in which active control comparisons through RCTs are generally not required (11–14). Contrarily, Health Technology Assessment (HTA) agencies struggle with this lack of comparative evidence as it does not fit in the traditional EBM pyramid that is applied in reimbursement processes all over the world, including in the Netherlands (3,4,15). As a result, HTA agencies are having difficulties with adequately assessing the strength of the submitted clinical evidence and the relative effectiveness of novel drugs in comparison to the current standard of care (SoC) (14,15). Ultimately, this hampers many reimbursement processes of innovative drugs, resulting in significantly delayed patient access or even no access at all.

Besides evaluating the (relative) effectiveness of novel drugs, HTA agencies also assess the costs of a new intervention in relation to its effectiveness. However, as long-term clinical data and real-world experience are often not yet available at market launch, this evaluation is often subject to clinical uncertainty. Hence, our system obliges an immediate price determination and assessment at the point in time that is associated with the most clinical uncertainty, inherently hampering the assessment itself. Alternatively, a price could be set initially low and increase over time as confirmatory evidence becomes available (assuming it will) (14,16). Hence, there is a growing demand for a flexible system in which agreements between payer and manufacturer allow a balance between the price of a drug and the declining uncertainties that are associated with the available clinical evidence over time. This is in particular important for the growing number of innovative drugs that are developed through non-randomized phase I/II studies, as these are inevitably associated with a higher degree of uncertainty as long as evaluation frameworks focus on more traditional study designs and corresponding outcomes.

A possible solution to increase access to innovative drugs could be to let go of these rigid one-off assessments and switch to a learning loop system in which the value of innovations is based on both the strength of clinical studies as well as the growing real-world data (RWD) over time. In a certain learning healthcare system, a cycle of collecting, analyzing, and interpreting data, followed by bringing it back into practice, stimulates continuous learning and allows a proper balance between drug prices and the value that a product delivers (17–19). A step in the direction of a learning healthcare system can be taken through an innovative pricing model that consists of a discount scheme based on growing evidence over time, or in other words, decreasing uncertainty. A certain pay-for-proof (PFP) model could offer a solution to products associated with less comprehensive evidence that does not fit in the current framework of

reimbursement agencies, thereby creating a context that allows controlled reimbursement of innovations that may be rejected otherwise.

Ultimately, regulatory policies should aim at balancing evidence generation with patient access – high demands for strong clinical evidence lead to longer development times, higher costs, and delayed access. Approving drugs too early, on the other hand, may potentially cause harm to patients and add to unjustified healthcare costs as the risks and benefits are not yet sufficiently reviewed (14). Especially in an era in which healthcare systems are dealing with increasing budgetary distress due to an ageing population and a growing number of innovative but costly drugs, pricing models have the potential to ameliorate the impact of uncertainty and provide a flexible framework that contributes to earlier patient access and simultaneously allows additional evidence generation (4,13,20,21).

1.1 Study objectives

The main objective of this study was to assess the feasibility of a PFP pricing model in which innovations are rewarded based on the changing level of evidence over time. The study primarily focused on drugs for solid oncology within Roche Nederland B.V., but the results may provide a structural solution to improve access to the growing number of drugs that are being developed based on non-randomized trials in the Netherlands. In summary, this study consisted of four key objectives:

i. Perform desk research to investigate trends around a) EMA regulatory approval, b) reimbursement and access pathways in the Netherlands, and c) innovative pricing and reimbursement models;
ii. Contribute to the development of the PFP model in which innovations are rewarded based on growing evidence (i.e. less uncertainty);
iii. Assess views and ecosystem readiness by pitching the model with internal and external stakeholders of Roche;
iv. Advise Roche Nederland B.V. whether the Dutch healthcare system is ready for the implementation of new models to reward innovation based on new types of evidence.

2. Methods

2.1 Internship company

This study was conducted as part of a 6-month internship at Roche Nederland B.V. The Roche Group was founded in 1896 in Basel and has become a global pioneer in pharmaceuticals and diagnostics that is currently active in more than 150 countries. Roche strives to be a frontrunner in personalized healthcare by tailoring patient care based on one's individual circumstances (22). By having pharmaceuticals and diagnostics in one company, the two divisions share expertise and collaborate to identify better drug targets at an early stage as well as the patient groups that will benefit most from the treatments. In 2021, there were 32 Roche medicines on the World Health Organization (WHO) Model List of Essential Medicines, 27 billion tests conducted with Roche Diagnostic products, and 16.4 million patients treated with Roche medicines (23). The purpose of Roche is to deliver medical solutions right now to transform patients' lives in the future – *doing now what patients need next*.

2.2 Research design

2.2.1 Literature review

The first part of the study was performed through a scoping review to get insight into current trends regarding: a) EMA regulatory approval, b) reimbursement and access pathways in the Netherlands, and c) innovative pricing and reimbursement models. A scoping review is considered an ideal tool for identifying and mapping available evidence and information without the need of answering a detailed research question, thereby "*summarizing a range of evidence in order to convey the breadth and depth of a field*" (24,25). Hence, a scoping review is an appropriate approach to shed light on current and emerging trends and identify knowledge gaps relevant to this study.

For information on EMA regulatory approval, the main source included the official website of the EMA as well as scientific publications. Information on access pathways was retrieved via official websites of ZIN, trade associations (e.g. HollandBio), and scientific publications. Last, trends around innovative pricing models were primarily explored through scientific publications. Table 1 shows an overview of the web-based search strategy of scientific literature using PubMed and Google Scholar. In addition to this targeted search strategy, relevant articles were also identified through (reverse) snowballing. The obtained information was summarized to clearly illustrate key concepts and themes relevant to the objectives of this study.

Table 1: Search terms used for the scoping review. Combinations of the listed keywords were made using Boolean operators.

Topic	Search terms
EMA regulatory approval	EMA, European Medicines Agency, evidence, market authorization, market approval, cancer, oncology, accelerated approval, early access, conditional approval, accelerated approval, adaptive pathways, regulatory affairs, pharmaceutical regulation, non-randomized trials
Reimbursement and access pathways	HTA, Health Technology Assessment, reimbursement, cancer, oncology, access, DRUP, Drug Rediscovery Protocol, DAP, Drug Access Protocol, the Netherlands, evidence, evidence development, comparative evidence, comparative effectiveness, value-based, EBM, evidence-based medicine, RWD, RWE, real-world data, real-world evidence, nonrandomized trials
Innovative pricing and reimbursement models	MEA, managed entry agreement, reimbursement, payment, pricing, model, scheme, value-based pricing, HTA, health technology assessment, outcome-based, performance-based, pay-for-performance, coverage with evidence development, conditional reimbursement, cancer, oncology, risk sharing, the Netherlands

2.2.2 Stakeholder analysis

Next, interviews were conducted with internal and external stakeholders of Roche. Interviews with internal stakeholders had an exploratory intent to assess views around the current reimbursement and healthcare system in the Netherlands, as well as alternative access routes (with a focus on the PFP model). External interviews aimed at verifying results and assessing feasibility as well as ecosystem readiness of the PFP model. In short, interviews aimed at gaining insights in:

- Views on the current healthcare system and proposed changes (*internal*)
- Thoughts on a learning healthcare system (*internal*)
- Overall impression of the proposed PFP model (*internal and external*)
    - Conditions that should be considered (*internal and external*)
    - Challenges and/or limitations (*internal and external*)
    - Approach for successful implementation (*internal and external*)
    - Suggestions or remarks regarding the design of the model (*external*)

Internal interviewees within Roche were selected on their expertise in relevant areas while ensuring a diverse cohort. External stakeholders included employees from other pharmaceutical companies, trade associations, academia, and the National Health Care Institute (*Zorginstituut Nederland*, ZIN). An in-depth, semi-structured interview protocol was developed for interviews with internal stakeholders (Annex 1), whereas a few guiding core questions were prepared for external interviews (Annex 2). All interviews were transcribed or summarized and subsequently analyzed using inductive thematic coding based on the six-phase model of Clarke and Braun (2006) (26,27):

i. **Familiarize the data**: Analytically and critically (re)read the transcripts to become familiar with the data and allow recognition of patterns, relationships or other striking outcomes.

ii. **Generate initial codes**: Label the data with codes that shape broader themes across the data. Codes can evolve throughout the coding process but should be relevant to answering the research question.

iii. **Search for themes**: During this phase, initial codes are translated to themes, in which similar codes are grouped into a broader theme. The aim is to explore underlying patterns and relationships between themes and explore how well the data is represented.

iv. **Review themes**: Phase IV consists of an iterative process of reviewing and modifying the themes generated in the previous phase to check if they are appropriate in relation to the data collected. Themes should be coherent and distinct from one another. Possibly, this phase could lead to the deletion or merging of several themes to end up with the themes most relevant to the research question.

v. **Define themes**: This phase consists of a refinement of the included themes to check if all themes have a clear focus and to what extent they relate to each other.

vi. **Writing-up**: The final phase involves producing written results of the thematic analysis.

In this study, phase six of the thematic analysis consisted of two parts – first, a detailed overview of all obtained findings was developed (see Annex 5 and 6). Next, key statements were identified to develop a concise overview of the most relevant findings regarding: 1) existing alternative access routes, 2) benefits of the PFP model, 3) challenges and limitations of the PFP model, and 4) conditions or suggestions of the PFP model. Identification of key statements was performed by assessing which findings were confirmed by multiple interviewees (N>1). Data saturation of internal interviews was checked by assessing if novel insights were obtained during the last two interviews performed. As certain important external stakeholders were out of scope, data saturation was not achieved for this stakeholder group (see chapter 5.3).

Key findings from the desk research (chapter 3) and stakeholder analysis (chapter 4.2) were used to continuously revise the preliminary PFP model and contribute to its development (chapter 4.1). Last, the extent of ecosystem readiness was assessed to advise Roche Nederland B.V. whether the Dutch healthcare system is ready for the transition to new innovative payment models that are based on the level of clinical evidence (chapter 5).

3. Literature review

This chapter contains the findings of a scoping literature review in which current trends around EMA regulatory approval, reimbursement and access pathways in the Netherlands, as well as innovative pricing and reimbursement models are discussed.

3.1 EMA approval of novel drugs

3.1.1 Summary of market authorization procedure

When a novel medicinal product has been developed, it must obtain market authorization (MA) before it can be marketed and made available to patients. In the European Union, novel medicines are predominantly authorized via the centralized procedure, in which the European Commission (EC) grants an MA after a scientific evaluation within the Committee for Medicinal Products for Human Use (CHMP) of the EMA (28). A few months before this assessment, the EMA provides both general and disease-specific guidance to the manufacturer to ensure that the application and submitted data comply with legal and regulatory requirements, thereby also preventing delays in the process. The dossier that is submitted must include information on e.g. the way the product is manufactured, effects in laboratory studies, risks and benefits in patients, and a risk management plan. The CHMP adopts an opinion within 210 days after the start of an MA application (29).

Most of the data submitted for an application is derived from clinical studies that are funded by the manufacturer, preferably randomized and versus placebo or an established medicine of proven therapeutic value (30). Additionally, data from existing studies in literature might also be used for the assessment. The clinical studies that are used for the application must be conducted in highly regulated settings and have to be in line with Good clinical practice (GCP) – international standards that all clinical research must adhere to with respect to quality, ethics and scientific conduct (30). In order to receive an MA, a positive risk-balance must be established after assessment of the submitted data, meaning that the benefits of the medicine must outweigh its risk in the patient group whom it is intended for. Once the medicine has obtained an MA through the centralized procedure, it may be marketed in all member states of the EU (30).

Besides the standard MA, special pathways and programs have been set up by the EMA to facilitate early access to medicines that are expected to fulfill a high unmet clinical need (see Table 2) (31). Note that MA pathways used to follow a more fixed and rigid structure, where only in exceptional cases a drug could be granted MA prior to the completion of phase III clinical trials. Regulatory authorities have developed a growing acknowledgement to facilitate access to new types of treatments that fulfill a high

unmet need despite being associated with less comprehensive evidence, giving rise to the growing number of fast-track approval routes and programs (15).

Table 2: Overview of the expedited pathways and supportive programs of the EMA (31,32).

Conditional market authorization (CMA)	CMA allows authorization of a drug before comprehensive data is available, under the premise that additional data is submitted within an agreed timeframe. Medicines intended for life-threatening and seriously debilitating diseases (including orphan drugs) are eligible for CMAs, for which the benefit of immediate access outweighs the risks of incomplete evidence. Once the pending studies are completed and the remaining evidence has been provided, a CMA is converted to a standard MA.
Approval under exceptional circumstances (AEC)	AECs are a type of MA where the manufacturer is not able to submit comprehensive evidence that fully complies with the regulatory requirements, e.g. because of ethical issues or when the condition is rare. An AEC will normally not lead to a complete dossier, and will therefore not become a standard MA.
Accelerated assessment (AA)	Medicines approved via AA have a reduced assessment timeframe of ≤150 days in which the CHMP reviews the application. A medicinal product is eligible for AA if the CHMP decides that it is of major interest to public health. An AA is not an approval pathway on its own but complements a standard MA, CMA, or AEC.
PRIME	The PRIME scheme was launched in 2016 to support the development of medicines that fulfill a high unmet clinical need. PRIME promotes early dialogue between various stakeholders and was designed to facilitate identification of AA candidates.

3.1.2 Clinical evidence required to receive market authorization

The dossiers that are submitted during an MA application need to include results of pharmaceutical tests, pre-clinical tests, and clinical trials. More elaborately, the following topics must be addressed (30):

- The group of patients the medicine is intended for;
- Whether there is an unmet clinical need that is fulfilled by the product;
- Quality of the product and its chemical and physical properties;
- Compliance with international requirements on laboratory testing, manufacturing of product, and conduct of clinical trials;
- The mechanism of action of the medicine;
- Absorption, distribution, metabolism, and excretion (ADME) properties of the medicine;
- The benefits and risks associated with the medicine;
- How risks will be monitored and managed after MA;
- What information needs to be gathered from follow-up studies after MA.

The EMA has established specific requirements for MA applications regarding different therapeutic areas. The guidelines on the evaluation of anticancer drugs in humans were first adopted in 1996 and have been revised multiple times since then (33). RCTs using mortality-related endpoints, such as overall survival (OS) and progression-free survival (PFS), are in principle preferred, as favorable effects on survival are the most persuasive outcome of a clinical trial. However, deviation from these guidelines is often justifiable within oncology due to the large unmet clinical need and the rarity of many cancers (15,34). However, non-randomized trial designs are associated with significant methodological weaknesses – ORR supported by Duration of Response (DoR) is often used as primary endpoint in these study designs, despite it lacking a strong correlation with OS in specific solid tumors (15). Innovations associated with non-randomized trials are generally only approved under exceptional circumstances or on a conditional basis, although approval via standard MA may be possible if significant effects in tumor response are observed in a homogenous population without alternative treatments available (15).

By means of special approval pathways and disease-specific guidelines, the EMA supports the development of innovative (oncology) drugs and allows MA on the basis of less comprehensive evidence, aiming to foster timely patient access. However, these initiatives also limit the availability of data for subsequent reimbursement procedures and corresponding assessments on relative effectiveness and cost-effectiveness carried out by HTA agencies (34). Ultimately, this leads to many delayed decisions and negative recommendations rather than earlier patient access (15). With the average delay between EMA approval and actual patient access in the Netherlands being 345 days, a significant potential loss of health years may be the result – a problem that will only get more impactful as an increasing number of innovations is receiving market approval based on less comprehensive evidence (4,35,36).

3.2 Reimbursement and access pathways in the Netherlands

Once a novel drug has been granted MA in the EU, decisions on pricing and reimbursement take place at a national level in the context of healthcare systems in individual countries. In the Netherlands, the preferred and most common access route is through inclusion in the basic care package (chapter 3.2.1), although alternative pathways exist (chapter 3.2.2).

3.2.1 Reimbursement system

The national HTA agency in the Netherlands is ZIN, whose core responsibility is to advise the Ministry of Health, Welfare and Sport *(Volksgezondheid, Welzijn en Sport,* VWS) on which medicines should be included in the basic care package. During the assessment procedure, the Scientific Advisory Board

(*Wetenschappelijke Adviesraad*, WAR) supports ZIN during the scientific and practical assessment of the submitted data and the determination of cost-effectiveness, whereas the Package Advisory Committee (*Adviescommissie Pakket,* ACP) is consulted for the societal part of the assessment (37). ZIN adheres to four key principles that are known as the 'package criteria' (37):

i. **Necessity**: Is the burden of disease serious enough? Are patients unable to pay for the treatment themselves?
ii. **Effectiveness**: Is there sufficient evidence that the treatment works? What is the therapeutic value of the new intervention in comparison to alternative treatments?
iii. **Cost-effectiveness**: Is the balance between costs and benefits acceptable?
iv. **Feasibility**: Is inclusion of the treatment in the basic care package possible in practice?

In the Netherlands, only prescription drugs are eligible for reimbursement, in which different pathways exist for outpatient care (extramural) and inpatient care (intramural), see Figure 2. The extramural system includes all prescription treatments where patients do not need hospitalization. It is a closed system, meaning that all novel medicines are subject to an HTA assessment before they can be reimbursed. Upon a positive reimbursement decision, the medicine is (after possible price negotiations with VWS) included in the *Geneesmiddelenvergoedingssysteem* (GVS) on either list 1A, list 1B and/or list 2, depending on the extent of interchangeability and additional conditions that may apply (38). As this study primarily focuses on drugs in the intramural system, further details on the extramural system are out of scope.

The majority of Roche's portfolio resides in the intramural system, which includes all prescription treatments where patients need hospitalization. The intramural system is in principle an open system where novel products are generally not assessed by ZIN, but automatically enter the basic care package if they comply with the SvWP (39). Even though patients are directly entitled to reimbursement due to the open system, hospitals generally only use drugs after an add-on has been obtained, which arguably negates the open character of the intramural system (40). Further, open intake is not possible if the criteria for lock placement (*sluis voor dure geneesmiddelen*) are met, which is the case if either overall costs exceed €40M/year for all indications (prospective indications will also be placed in the lock), or €10M/year and €50k/patient/year for a single indication (39,41). If a medicine enters the lock, ZIN carries out an HTA assessment based on a pharmacotherapeutic dossier and a budget impact analysis submitted by the manufacturer. Additionally, a pharmacoeconomic dossier must be submitted if the product is claimed to have more therapeutic value than the SoC (41). ZIN assesses to what extent the product complies with the

four package criteria and establishes under which premises it can become eligible for reimbursement. Depending on these outcomes, negotiations take place between the MA holder and VWS, which (if successful) lead to inclusion in the basic care package. Note that a product may never enter the basic care package if ZIN establishes a negative therapeutic value (but alternative access routes still exist, see 3.2.2). During lock placement, a product is not reimbursed.

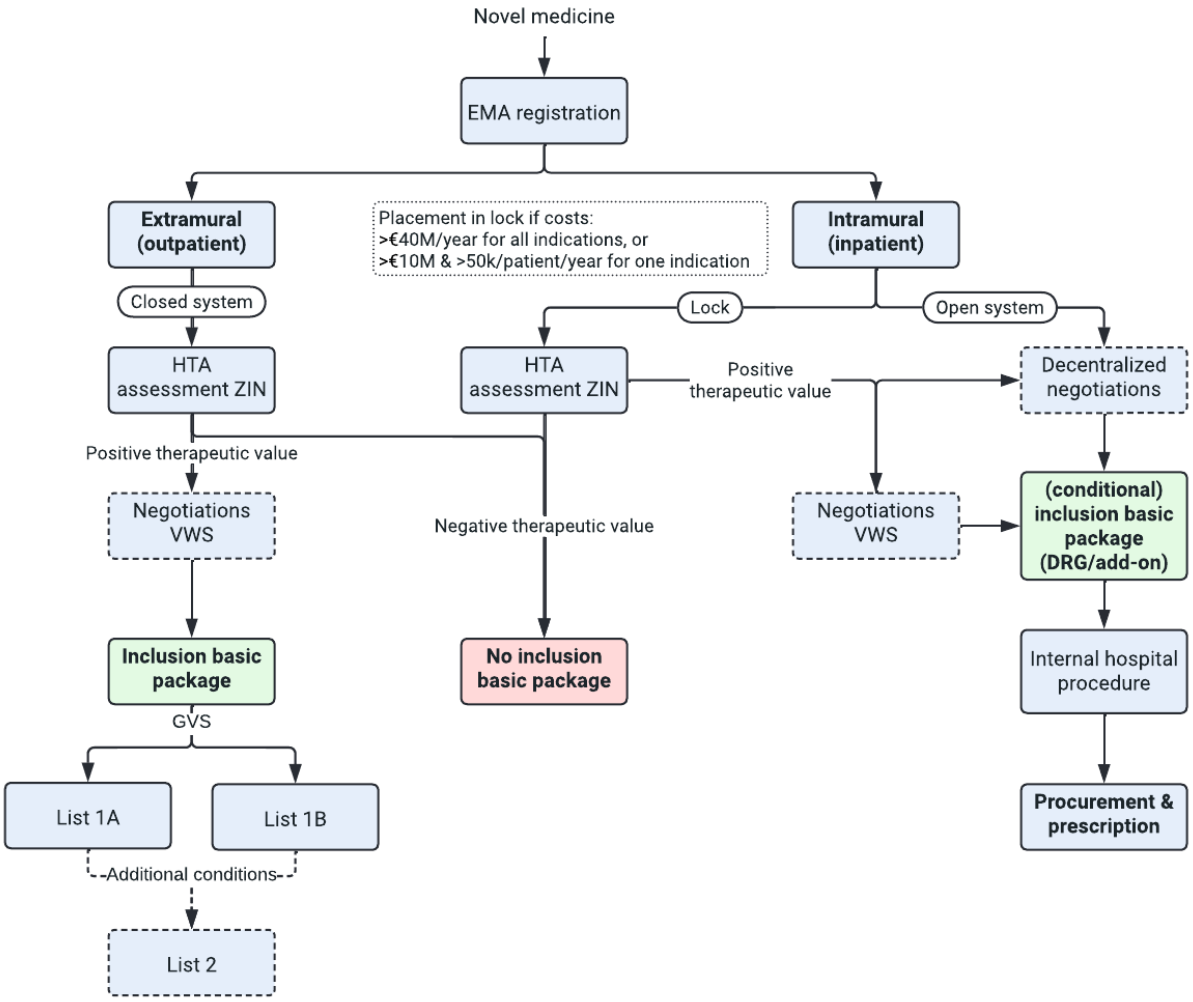

Figure 2: Simplified overview of the Dutch reimbursement system (42). DRG = diagnosis-related group.

The lock system has been subject to a growing amount of criticism; one of the main issues is that there are no fixed timelines in the procedure, resulting in many uncertainties for patients and pharma regarding the availability of a product that might fulfil a great unmet clinical need (40,43). In a recent letter from VWS, it is stated that the average time from EMA registration to patient access is 424 days based on the 33 completed lock procedures from 2015 until 2021, with timelines increasing across the years (Figure 3) (43,44). Another point of criticism regarding the lock revolves around the identification of lock candidates – the procedure itself is not transparent and the final decision is said to lack a risk analysis and

an objective balance of interests (40). Further, excessive assumptions regarding e.g. market penetration or eligible patients may lead to unjustified lock placements. With prospective plans to expand the criteria for lock placement, these issues will only become more prominent and impactful for patient access.

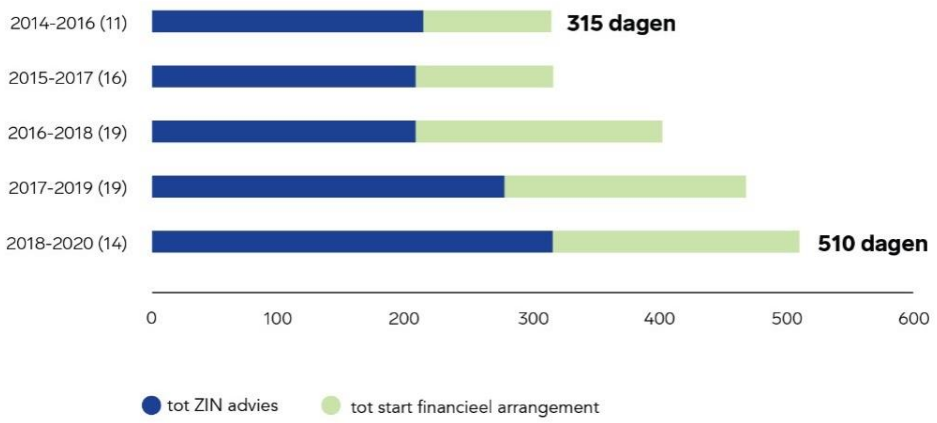

Figure 3: Average timelines of lock procedures since 2014 (image text in Dutch). The number of products is shown between brackets (43).

3.2.2 Alternative access pathways

Besides inclusion in the basic care package, several alternative access routes exist in the Netherlands:

Conditional inclusion *(voorwaardelijke toelating,* VT*)*: In 2019, VWS introduced the VT as a novel framework to facilitate controlled access to drugs that are expected to fulfill a great unmet need. The policy focuses on promising orphan drugs or medicines approved via CMA or AEC that are associated with insufficient evidence to comply with SvWP (45). During the VT trajectory, the manufacturer carries out additional research at their own expense to resolve the remaining uncertainties regarding the product's effectiveness. Throughout this period, the product is funded by VWS outside the basic care package and is available for all patients whom it is intended for, however, all patients involved are obliged to participate in the research study, and treatment may only take place in designated healthcare facilities that are suited for the research purposes (45,46). Hence, the research study must be set up in close collaboration with patient associations, medical professionals, and research institutes. Once ZIN has selected a drug candidate for the VT trajectory, VWS negotiates with the MA holder on a price for the product during the VT trajectory. The entire research period, including the final assessment by ZIN, should be completed within seven years, although a period of 14 years is allowed in specific circumstances (45). At the end of the research period, ZIN uses all available evidence to issue a new statement on the inclusion of the product in the basic care package (45). The MA holder can apply for conditional inclusion either before assessment

by ZIN, or after a negative advice on SvWP due to insufficient evidence. In 2021, €26.8 million was made available for VT products, which is expected to fund two to three products annually (even though this fully depends on the products and indications in question) (45). If this budget is exhausted, new VT applications are placed on a waiting list.

Recently, the VT procedure was evaluated by ZIN, which lead to the identification of several limitations. First, the application procedures are stated to be unclear and timelines are often exceeded (47). Further, an independent commission is required to advise on patient eligibility for treatment with a VT product, however, obtaining sufficient financing and guaranteeing independence of the commission was found to be unfeasible (47,48). ZIN recommended VWS to refine and clarify application procedures and to improve the coordination of consecutive phases. Moreover, it is explored if the requirements for the commission can be alleviated, while simultaneously increasing the allocated budget (47).

Drug rediscovery protocol (DRUP): The objective of the DRUP is to identify the clinical benefit of authorized oncology drugs outside their label, mainly in rare, molecularly defined subsets of patients who have exhausted or declined SoC therapy options (49,50). Eligible patients must have malignancies with potentially actionable aberrations, for which no authorized therapies are available. Further, the genomic variations must be identifiable using genomic profiling. With only a small number of patients exhibiting these aberrations, the execution of adequately powered RCTs is hampered, leading to a high unmet need in these patient groups (49). Medical oncologists, ZIN, health insurers, and the industry acknowledged this unmet need, eventually giving rise to the DRUP trial (49). During the DRUP trial, multiple parallel cohorts based on tumor type and profile are set up from which clinical outcomes are publicly recorded. As current practice does not mandate the reporting of clinical outcomes for off-label use, the DRUP provides an alternative framework in which both positive and negative outcomes are collected and used to translate novel insights into the use of anticancer drugs beyond their label.

Figure 4 shows the performance-based, personalized reimbursement scheme of the DRUP. The scheme starts with a Simon-like two-stage design in which eight patients are enrolled in stage II and up to 24 patients in stage II (51,52). If sufficient patients have exhibited clinical benefit after stage II, the cohort is considered successful and is extended to a third stage in which more patients are allowed to enter (50). During the first two stages, the manufacturer provides the medication for free as the drug is considered an investigational product. In stage III, on the other hand, the drug is provided for free only during the first 16 weeks, where after health insurers continue reimbursement for patients with adequate individual treatment

response. Here, response or clinical benefit is defined as complete/partial response (CR/DR), or stable disease (SD) (50).

The DRUP is a promising approach as it provides a framework in which the value of existing drugs is explored beyond their label, potentially expanding the range of patients who may benefit from the product. Simultaneously, treatment outcomes are continuously monitored and publicly recorded, thereby stimulating continuous learning of drug use in real-world settings (49). Among the first 500 patients treated in the DRUP, an overall clinical benefit rate of 33% was found (53). An example of a successful DRUP cohort involved patients with microsatellite-instable (MSI) tumors treated with nivolumab, in which 63% clinical benefit was observed (49). Besides these promising results, limitations of the DRUP should also be considered. First, the lack of comparator groups due to the nonrandomized trial design hampers treatment evaluation (49,53). However, van der Velden et al. (2019) emphasize that this issue may be addressed by the emergence of large-scale molecularly annotated databases (49). Further, the DRUP is complex in terms of administrative burden due to the personalized character of the scheme (50).

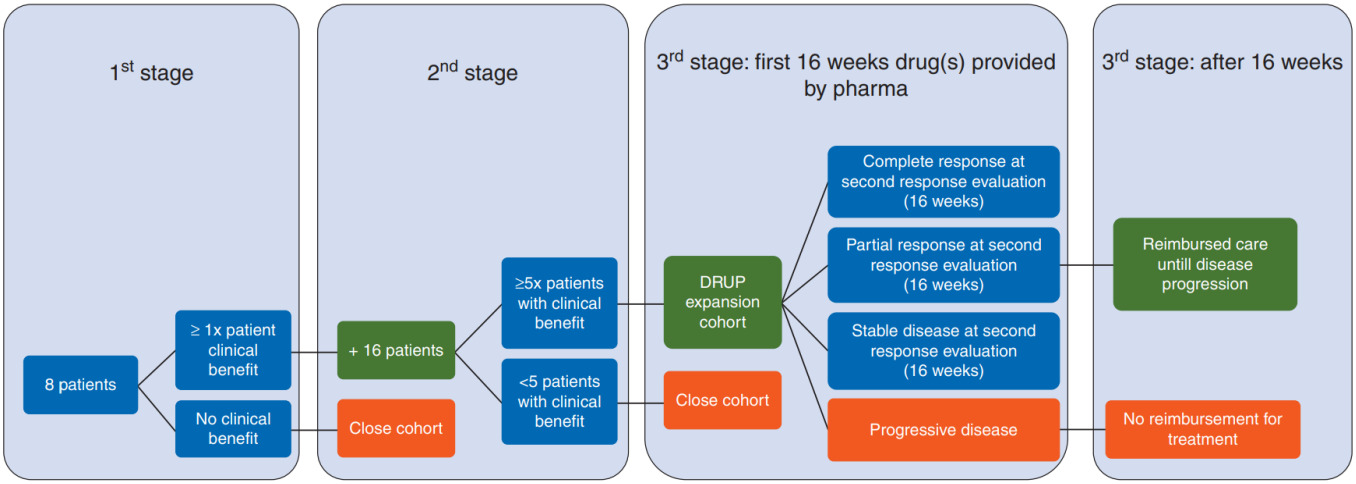

Figure 4: The performance-based, personalized reimbursement scheme applied in the DRUP (50).

Drug access protocol (DAP): The DAP is an initiative that uses a similar personalized reimbursement scheme as the DRUP (54,55). The objective of the DAP is to facilitate controlled access to on-label drugs that are under review by the EMA, authorized drugs that await a positive reimbursement decision in the Netherlands (e.g. during the lock procedure), and drugs of which SvWP cannot be established due to less comprehensive evidence. During the DAP scheme, RWD on the safety and efficacy is collected systematically to facilitate reimbursement evaluations, even though inclusion in the basic care package is not guaranteed nor integrated into the scheme (55,56). Note that the DRUP and DAP share many

similarities – both frameworks have been invented in co-creation through a multi-stakeholder need, focus on personalized reimbursement of oncology drugs for rare indications, collect RWD, and facilitate controlled access. A limitation of the DAP is that it results in a major workload and administrative burden for oncologists as data registries are not electronic (56). Furthermore, participation in the DAP does not guarantee reimbursement in any way (56). Last, critics state that the DAP acts as a shadow system and provides a parallel route that bypasses the regular reimbursement route instead of tackling the core problems of our healthcare system (55).

3.2.3 Clinical evidence required for reimbursement

Whereas regulatory agencies accept clinical evidence that solely demonstrates a product to be sufficiently safe and effective (i.e. a positive benefit-risk balance), reimbursement agencies generally require additional comparative evidence to allow quantification of the extent of added therapeutic value that the product has in comparison to alternative treatments. Especially in an era where healthcare costs are continuously rising, having sufficient amounts of high-quality comparative data on cost-effectiveness facilitates decision-making and minimizes unjustified healthcare expenditures (14,57,58). This comparative assessment is addressed by ZIN through a framework that is based on the principles of EBM and aims to evaluate if the intervention complies with the SvWP (see Annex 3 for more information).

The core of the EBM approach is that it distinguishes between different levels of clinical evidence based on the strength and precision of the applied research methods. Following this hierarchy, RCT studies are placed relatively at the top of the pyramid and are thereby considered one of the most reliable types of clinical evidence (2–4). RCTs make use of a study design in which participants are randomly assigned to either a control group or an experimental group. The process of randomization minimizes bias and ensures that any observed difference between the two study arms can be attributed to the intervention. However, the EBM pyramid, in particular the position of RCTs on top of the pyramid, has been receiving growing criticism over the years. First, the strength of the RCT study design is simultaneously its weakness – RCTs follow a strict protocol and are conducted under highly controlled conditions in which the selection of participants, outcome-measures, and interventions are standardized (7). This standardization prevents bias and results in a 'one-size-fits-all' approach based on the average patient. However, these results may be unrepresentative of patients and conditions that are found in everyday clinical care, causing critics to question if these averaged results can be used to inform decision-making in real-world settings (8). Especially with the concept of personalized healthcare growing in popularity, questions begin to arise if the EBM approach is still feasible – EBM is based on averaged effects measured as population means,

whereas personalized healthcare revolves around care that is tailored to fit the need of individual patients. Hence, in order to individualize patient care, clinical evidence must be individualized as well (8).

Furthermore, an RCT is a costly study design in terms of money and time (1,7). The demand for an RCT will therefore delay access to the intervention and drive up its price. This might incentivize pharmaceutical companies to stagnate the development of an innovation if the expected return on investment is limited, which may be the case for drugs intended for rare indications, or for small pharmaceutical companies that cannot afford such a risk (7). Last, it is in some cases simply not feasible or possible to conduct an RCT. This is, for example, the case for rare indications that are associated with patient populations that are too small to perform an RCT, but also due to ethical or legal objections (e.g. the inclusion of children or terminally ill patients) (7). The criticism regarding EBM results in a growing interest to combine evidence from clinical studies with RWD that is obtained after drug approval, as the two types of evidence act mutually supplementary and provide a very powerful source of evidence, possibly covering the evidence gap between regulatory agencies and reimbursement frameworks (2).

Even though RCTs are considered the gold standard, ZIN also accepts other types of evidence (e.g. observational evidence) and acknowledges that conducting an RCT is not always feasible or possible (59). This is the case when, for example, the disease is rare or there is no suitable comparator, but also when the effect of the intervention has already been proven sufficiently (e.g. there is a clear mechanism of action, clear dose-response curve, or consistent effect among multiple previous studies). Therefore, ZIN determines a *passend bewijs* profile to define the appropriate type of evidence needed for the intervention in question while taking into account the corresponding indication and patient population (59) (Annex 3). However, despite efforts as the *passend bewijs* profile, quantification of therapeutic value regarding non-randomized studies remains hampered as the current assessment framework is simply not competent for these types of innovations. Indeed, ZIN states in its advice letters on inclusion of Rozlytrek (entrectinib) in the basic care package that the assessment of single-arm studies using the current framework is difficult, and for tumor-agnostic drugs even impossible (60). However, ZIN is taking measures to expand and refine its framework in collaboration with the *commissie ter Beoordeling van Oncologische Middelen* (cieBOM), which has established novel PASKWIL criteria that allow the evaluation of non-randomized trials (61). ZIN will consider these criteria in its revision of the current assessment framework (60). The novel criteria allow assessment of ORR supported by DoR as primary endpoints, as a high response rate in combination with sufficient response duration increases the chance of the treatment having an actual clinical benefit (61). However, it should be noted that the evaluation of absolute as opposed to relative endpoints is not

applicable or feasible in all therapeutic areas. Further, the use of a relative parameter (the incremental cost-effectiveness ratio, ICER) is rooted in cost-effectiveness analyses, so relative assessments will remain important in HTA procedures.

ZIN has not yet finalized the revision of its framework, but with a growing proportion of submissions being based on non-randomized trials, it is becoming increasingly important to find a structural solution to prevent delays in patient access to promising drugs (5). For example, significant advances in personalized healthcare have resulted in the development of tumor-agnostic drugs that target specific genetic aberrations rather than more conventional tumor sites (62). Approval of these agnostic therapies is often based on evidence from single-armed basket trials, in which the performance of the treatment can be assessed for patients with various tumor types in one study, as long as they exhibit a specific genetic mutation (62). Assessment of these therapies poses challenges for HTA agencies at multiple stages, e.g. due to small sample sizes, lack of comparator arms, and response-based endpoints. However, the selection of patients based on a specific oncogenic driver has also shown to result in high response rates and consistent performance among different tumor locations (5). This emphasizes the importance of implementing strategies for HTA agencies that allows them to handle the changing landscape of clinical evidence.

3.2.4 Learning healthcare system

The changing landscape of clinical evidence requires the involvement of practice-based evidence in addition to EBM, thereby creating a context in which data from clinical trials integrates with RWD. The value that (real-world) data may deliver to healthcare, especially in an era with significant advances in data science and diagnostics, is currently not used to its full potential (63,64). To improve this, we must step away from the current one-off system and shift to a learning healthcare system in which continuous data monitoring enriches a real-world data-base which is subsequently used to inform decision-making. The concept of empowering healthcare systems by integrating clinical research and real-world experience was first introduced in 2007 by the National Academy of Medicine, which proposed certain systems to be the key pathway toward value-based healthcare (65–67). This was based upon the understanding that patients and healthcare professionals are often in a more appropriate position than external researchers to identify areas of uncertainty that form knowledge gaps on comparative effectiveness. Currently, ZIN is making efforts in diverting away from the one-off procedure by integrating a lifecycle approach (*cyclisch pakketbeheer*) in its assessments (68).

Learning healthcare systems can come in many forms, but each is characterized by a cycle of collecting, analyzing, and interpreting data, followed by bringing it back into practice (19). A certain healthcare system thereby enables early access and allows more efficient evaluation of the real-world value of innovations. Furthermore, significant advances in medical technology have created opportunities to embed prognostic and predictive models in clinical care that allow the identification of patient groups that are likely to experience a certain outcome or benefit from certain interventions (66). A data-driven learning healthcare system may not only contribute to the sustainability and efficiency of healthcare but also lower healthcare expenditures and stimulate innovation (63). Hence, these principles are in line with Roche's Pharma Vision 2030 to achieve 3-5 times more patient benefits for 50% less costs to society, and simultaneously contribute to *passende zorg* – the key focus area of the Dutch government that stimulates efficient care for fair prices (69).

Even though a learning healthcare system may be a prerequisite for more sustainable and future-proof healthcare, transforming to a certain system is a major challenge. Figure 5 shows a framework developed by Easterling et al. (2021) that illustrates the interlinked components and enabling conditions of learning healthcare systems (70). The Figure shows that supportive culture in terms of resources, data systems, and expertise is crucial to the success of a learning healthcare system. Further, the authors emphasize that data systems should meet rigorous standards regarding quality, privacy, and reliability, whilst promoting transparency and integrity (70). In our current healthcare system, patient data is stored in isolated silos that solely serve their purpose within a specific department as they were built around functionalities that previously did not require data sharing (71). Nowadays, however, these fragmented and interoperable silos result in many inefficiencies that may hinder improvements in healthcare and potentially even lead to distrust amongst healthcare sectors (72). To transform our system, these silos must be consolidated into one uniform and central data-infrastructure. Thus, this requires significant changes to the fundamentals of our healthcare system, which is a challenging transformation.

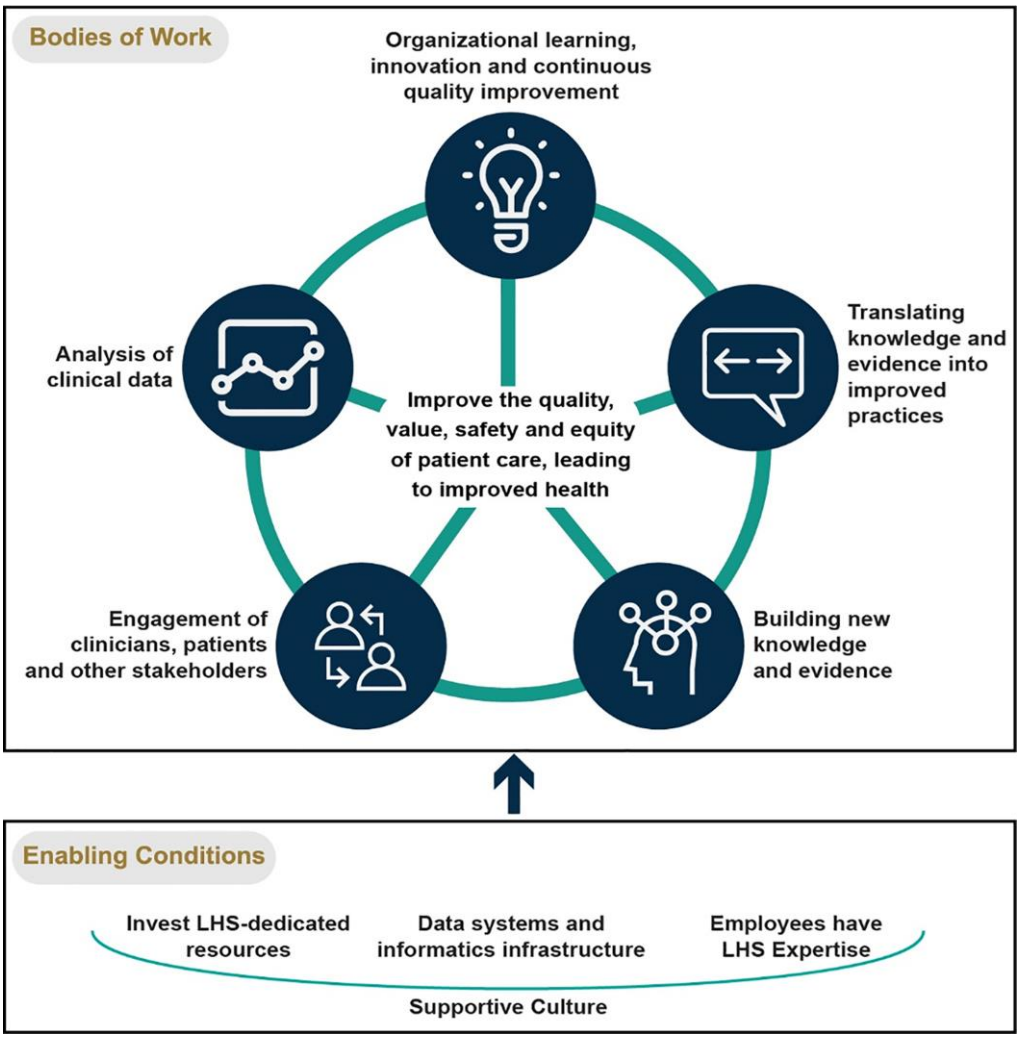

Figure 5: Schematic overview of learning healthcare systems and associated enabling conditions. LHS = learning healthcare system (70).

3.3 Innovative pricing and reimbursement models

3.3.1 Types of agreements

The growing number of high-cost innovative drugs is exerting growing financial pressure on healthcare systems over the world (21). Payers and pharmaceutical companies have been exploring many solutions to keep healthcare systems financially sustainable, while simultaneously ensuring quick patient access and preserving sufficient incentives for pharmaceutical companies to develop products with high value for fair prices. One of these approaches is the implementation of innovative pricing, payment, and reimbursement models through agreements between payers and pharmaceutical companies. These models are more commonly known as managed entry agreements (MEAs) and can be categorized based on the issues they address, including: i) managing budget impact, ii) managing uncertainties regarding clinical and/or cost-effectiveness, and iii) managing appropriate use to optimize performance (20). In practice, MEAs should be implemented using a systematic approach and with structured guidance to be successful. In addition, a

MEA should be tailored to the healthcare system in which it is used, as the way innovations are funded and decisions are made affects the feasibility of specific types of MEAs significantly (73). Hence, it is important to know which types of MEAs exist, how and at what level they can be implemented, what therapies are eligible, and what payment structure is suitable (21). Besides the fact that the scope and feasibility of MEAs are country-dependent, many MEAs are set up as confidential agreements, hampering the assessment of their impact and transferability to other countries. Neyt et al. (2020) identified several recommendations to ensure the success of a MEA (73,74):

- Establish a clear link between the remaining uncertainties and the required information and conditions included in the MEA;
- Tailor the MEA with respect to the type of uncertainties to address;
- Monitor if requirements in the MEA are fulfilled by stakeholders, and include consequences if this is not the case;
- Focus on implementing MEAs on well-considered cases, e.g. innovations that fulfill a great unmet need or that have a high potential of being cost-effective.

With countries defining MEAs in varying ways, different taxonomies have emerged for their classification. Figure 6 shows a three-level taxonomy that is based on the classification adopted by the Organization for Economic Co-operation and Development (OECD) and taxonomies described in previous studies (21,46,75,76). The taxonomy in Figure 6 distinguishes in the first place between financially-based agreements (e.g. simple discounts, price caps) and outcome-based agreements, in which payment is linked to clinical outcomes (e.g. pay-for-performance) (21,77,78). Experience with the latter type is scarce, whereas financially-based MEAs are utilized extensively (21). Next, MEAs are broken down based on the level at which they are applied (population or patient level). Last, a distinction is made between MEA designs according to the way the arrangement manages budget impact, clinical uncertainties, or performance. Several examples of MEA designs are shown in Figure 6.

A study by Koleva-Kolarova et al. (2022) assessed the current use of reimbursement models for personalized medicine and identified various barriers and disincentives that are associated with such models (79). For outcome-based models, this includes (among others) the following (79):

- Administrative and financial burden to implement data collection technologies that produce credible data;
- Lack of demonstrable benefit;
- Lack of accessible endpoints;

- Lack of clear governance regarding stakeholders' engagement, administrative/financial issues around data collection, linking outcomes to payments, and payment duration;
- Clash with current assessment paradigms and reimbursement systems;
- Data privacy.

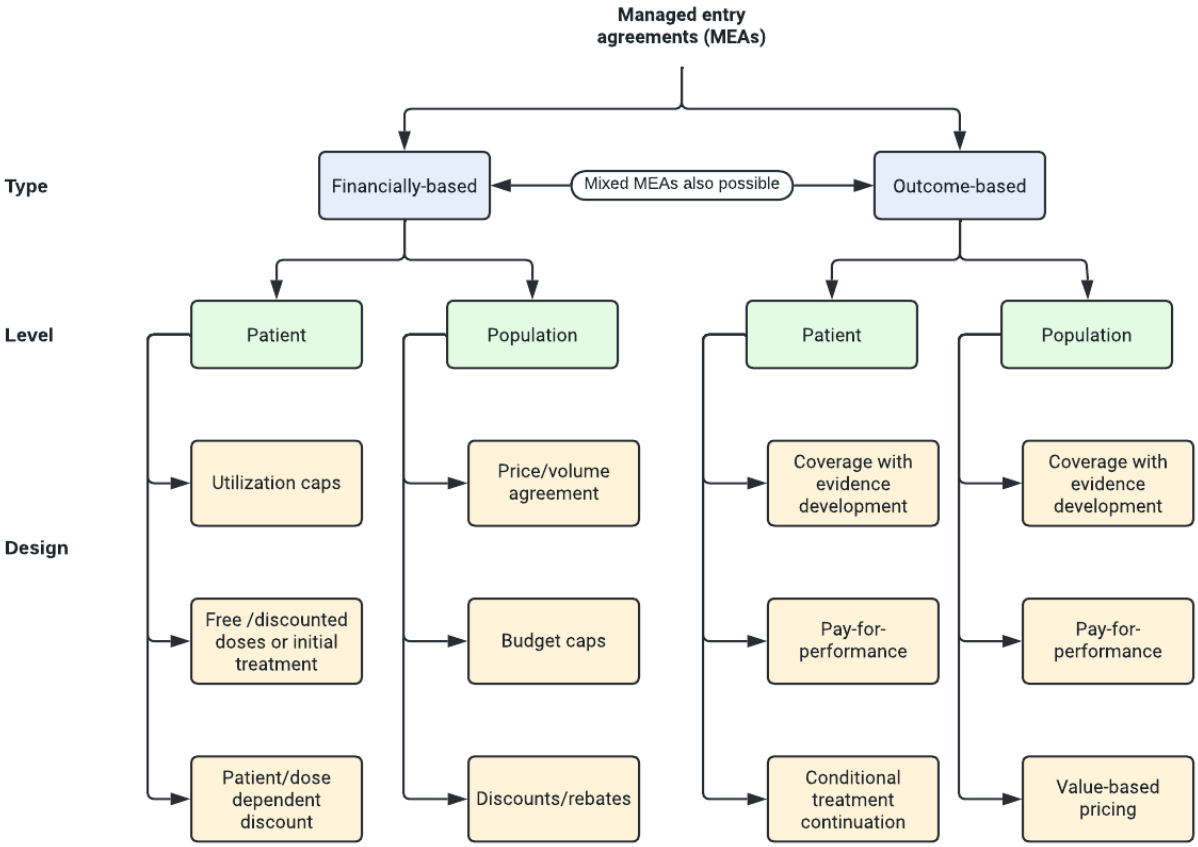

Figure 6: Taxonomy of MEAs based on the classification by the OECD and other studies (21,46,75,76).

The pay-for-proof model that we propose can be considered as a pay-for-performance-like scheme with an additional 'proof' plane that is tied to the regulatory process, resulting in robust endpoints for growing evidence, i.e. decreasing uncertainty. Specific characteristics, limitations and benefits of pay-for-performance schemes are shown in Table 3.

Table 3: Characteristics of pay-for-performance schemes (21,80).

Description	Risk-sharing agreement in which price and/or revenue depend on the performance of the product (usually in real-world).
Benefits	▪ Allows patient access to promising innovations despite uncertainty of cost-effectiveness and/or clinical benefit ▪ Risk-sharing lowers drug costs ▪ Incentive for manufacturers to develop products that have high benefits

	▪ Aligns rewards to manufacturer with the value that products deliver to patients ▪ Reduces unjustified use and costs of ineffective treatments
Limitations	▪ High administrative burden and financial investments leading to additional costs that may offset gains ▪ Difficult to measure effectiveness and determine cut-off points ▪ May incentivize higher drug prices to compensate risk for manufacturer ▪ Implementing and interpreting RWD poses methodological difficulties

3.3.2 Use of pricing and reimbursement models in the Netherlands

The use of MEAs in the Netherlands has increased significantly over time, in particular within the oncology field (see Figure 7) (81). A description of the use of MEAs in other European countries is included in Annex 4. In the Netherlands, conditional financing (CF) came into effect between 2006 and 2012 as a coverage with evidence development (CED) scheme, making the Netherlands one of the early adopters in the European MEA field (46). Under CF, expensive hospital and orphan drugs were reimbursed during a 4-year period with evidence development (20). A medicine was eligible for CF if it had a budget impact exceeding €2.5 million/year, a proven clinical benefit in relation to an alternative treatment, and a clear proposal for collecting additional research that would address the remaining uncertainties regarding cost-effectiveness and appropriate use (20). MA holders collaborated with hospitals to implement the proposed research to collect RWD. Four years into a CF trajectory, ZIN re-assessed the medicine and published a final decision on its reimbursement (20).

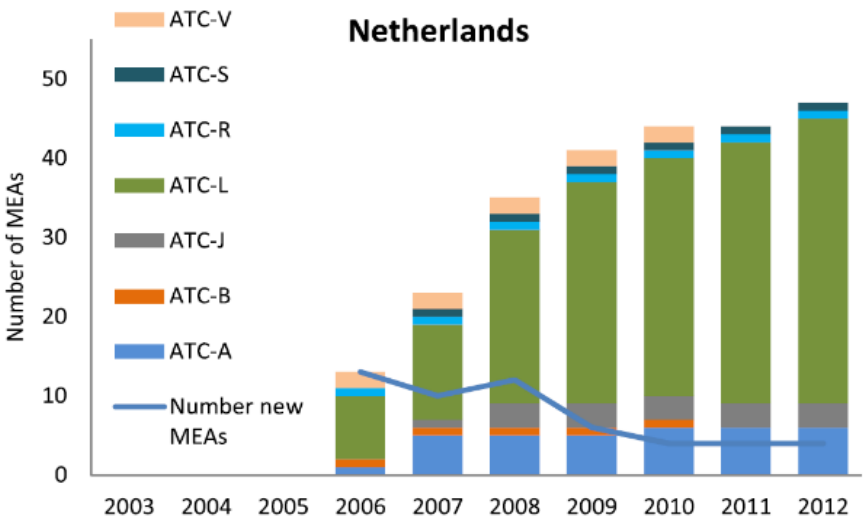

Figure 7: Use of MEAs in the Netherlands over time per therapeutic area. MEAs are most commonly used for antineoplastic (anticancer) drugs (ATC-L) (81).

Even though CF resulted in increased awareness of high-cost drugs, improved sustainability of the healthcare system, and increased flexibility to resolve uncertainties over time rather than a one-off assessment, the scheme has mainly been subject to criticism (46). First, it can be questioned if a fixed 4-year period is appropriate for all drugs that are eligible for CF (80). Instead, a tailored scheme could have been used in which a flexible timeframe is established depending on the intervention, corresponding indication, and remaining uncertainties. In addition, despite the establishment of a fixed period, only one drug was successfully processed within the stipulated timeframe (80). Another point of criticism was the lack of a clear-cut approach to implement outcomes of CF in the healthcare system, as there were no guidelines on how ZIN's final advice would be handled. For example, even though ZIN decided in its re-evaluation of ranibizumab that its reimbursement should be discontinued, the medicine was never removed from the basic care package (20). Critics therefore emphasize the importance of establishing *a priori* strategies on how outputs of such arrangement will be implemented (20). Further, the evidence generation under CF was shown to poorly address uncertainties due to weaknesses in the design of the MEA (73). A stakeholder analysis by Makady et al. (2019) showed that other shortcomings of CF include the lack of consensus on the relevance and objectives of the scheme, the absence of a clear framework to ensure that stakeholders take up their responsibilities, and the lack of an obligatory inclusion in outcome research to resolve remaining uncertainties in return for access (80). As the latter was done voluntarily rather than obligatory, this led to high selection bias and many underpowered studies. Ultimately, the CF scheme was not considered successful in its objectives and was therefore discontinued. Key differences between CF and the current VT are shown in Table 4.

Several other outcome-based schemes have been set up in the Netherlands since 2008 (82). However, research has shown that the data that was collected under these schemes generally addressed the remaining uncertainties poorly (82). The quality of the data collected was shown to depend significantly on the engagement of clinicians, who usually have little incentive to spend time and resources on data collection and analysis. Further, the validity of the collected data was often impacted by coinciding scientific evolutions, such as new product launches or changing clinical practices. This is in particular impactful for dynamic therapeutic areas such as oncology. Therefore, Pauwels et al. (2017) advise focusing on appropriate use rather than follow-up research (82).

Table 4: Important differences between the previous CF scheme and the current VT trajectory.

CF (2006 – 2012)	VT (2019 – present)
Intended for hospital and orphan drugs with a budget impact exceeding €2.5 million/year	Intended for drugs targeting a great unmet need that have limited clinical evidence
Objective of CF is to negotiate on high-cost drugs while still providing access	Objective of VT is to provide controlled access to drugs with high unmet need associated with less comprehensive evidence (orphans, conditionals, and exceptionals)
CF drugs should have proven added value compared to a relevant comparator	Comparative evidence is not required (usually challenging to obtain for target group, e.g. orphan drugs)
CF drugs comply with SvWP	SvWP of VT drugs is not yet established
Fixed 4-year period in which procedure should be completed	MA holder needs to stipulate a research period beforehand, but the procedure should be completed within 7-years (or 14-years in special cases)
Participation in research study is on voluntary basis	Patients accessing the drug are obligated to participate in the research study
All drugs meeting the criteria are eligible	If reimbursement limit is reached, new applications placed on waiting list
Drugs available via basic care package	Access to drugs on a research basis
Price of CF drugs is determined through negotiations leading to (small) discounts	Price of VT drugs is generally subject to high discount

3.3.3 Proposed pay-for-proof pricing model

The model that we propose to improve access to innovations based on non-randomized phase I/II trials is an outcome-based payment model that rewards innovations on growing evidence, i.e. decreasing uncertainty over time. The DRUP scheme was taken as the basis for the PFP model. In early stages of the PFP model, the drug is provided by the manufacturer (similarly to the DRUP), as it can still be considered an investigational product. In a later phase, the aim is to achieve personalized reimbursement for patients who have sufficient clinical benefit. Unlike the DRUP, the PFP model adds an extra dimension to the scheme by integrating decreasing discounts in the reimbursement phase that depend on predefined regulatory milestones. Furthermore, response is also monitored by the novel PASKWIL criteria during the PFP scheme to get more insights into response and facilitate the decision on SvWP.

Importantly, the PFP model is data-driven through a continuous cycle of data monitoring and analysis that takes place on an individual level first, but ultimately allows decision-making on a population level. The model may therefore be considered a step in the direction of a learning healthcare system. Luuk den Boer (Patient Access Manager at Roche Nederland B.V.) and Wendy Maas (Policy Lead at Roche Nederland B.V.) have developed a preliminary version of the model. Table 5 shows the core characteristics

of the preliminary PFP model. Note that the scope of this study is restricted to applying the model to line extensions within solid oncology.

Table 5: Characteristics of the proposed PFP model.

Type	Outcome-based pay-for-proof model
Aim	Provide a flexible framework for promising medicines associated with less comprehensive evidence to create earlier access and payments based on value.
Scope	The initial scope will focus on solid oncology products (line extensions) of Roche Nederland B.V. that are launched based on non-randomized phase I/II trials. However, the concepts may be applied to new molecular entities (NMEs) and other therapeutic areas as well.
Description	The proposed model provides flexible reimbursement for innovations that are associated with limited clinical evidence at launch. The design of the model is based on the principles and scheme of the DRUP in terms of patient cohorts, determination of clinical benefit, and provision of free medication during the initial phases. Pricing is linked to an incrementally decreasing discount scheme based on predefined regulatory milestones, thereby reflecting the real-world value of innovations.

4. Results

In this chapter, the revised PFP model and results of the stakeholder analysis are discussed. Note that revisions to the preliminary PFP model were based on both the results of the literature review (chapter 3), as well as the stakeholder analysis (chapter 4.2). For the sake of clarity, the final PFP model will be presented prior to results of the stakeholder analysis.

4.1 Final pay-for-proof model

A schematic overview of the final design of the PFP model is depicted in Figure 8, whereas key characteristics and inclusion criteria are shown in Table 6. The final scheme resembles the structure of the DRUP and consists of three stages (description per stage follows in chapters 4.1.1 and 4.1.2). Importantly for each trajectory, it should be defined at an early stage what uncertainties are remaining, what data is needed to address these uncertainties, and whether it is feasible to resolve these uncertainties through the PFP scheme. If the latter is the case, it should be defined how often disease monitoring should take place and what steps will be undertaken upon acquiring specific data. There should always be a link between remaining uncertainties, required information to address these, and conditions applied in the scheme.

Table 6: Key characteristics and inclusion criteria of the proposed PFP model.

Characteristics	Inclusion criteria
▪ Regulatory milestones are robust and define the discount that is applied during reimbursement phase ▪ Reference price is the negotiated price that is currently used for the product in existing indication(s) ▪ Rebate for patients whose treatment is terminated due to adverse effects is applied throughout the entire scheme ▪ Rebate for non-responders is applied even if drug is reimbursed from basic care package ▪ Potential decrease in list price post-registration will not be applied retrospectively in PFP scheme	▪ Applicability (currently) limited to line extensions within solid oncology that target identifiable tumor-specific molecular alterations ▪ Patients should have undergone molecular profiling to identify tumor-specific molecular alterations ▪ Only drugs with clearly defined uncertainties that are likely to be resolved through PFP scheme are eligible ▪ Patients should give consent before participating in the model, as it concerns treatments that are not yet SvWP ▪ Data of all patients should be available for analysis, including non-responders

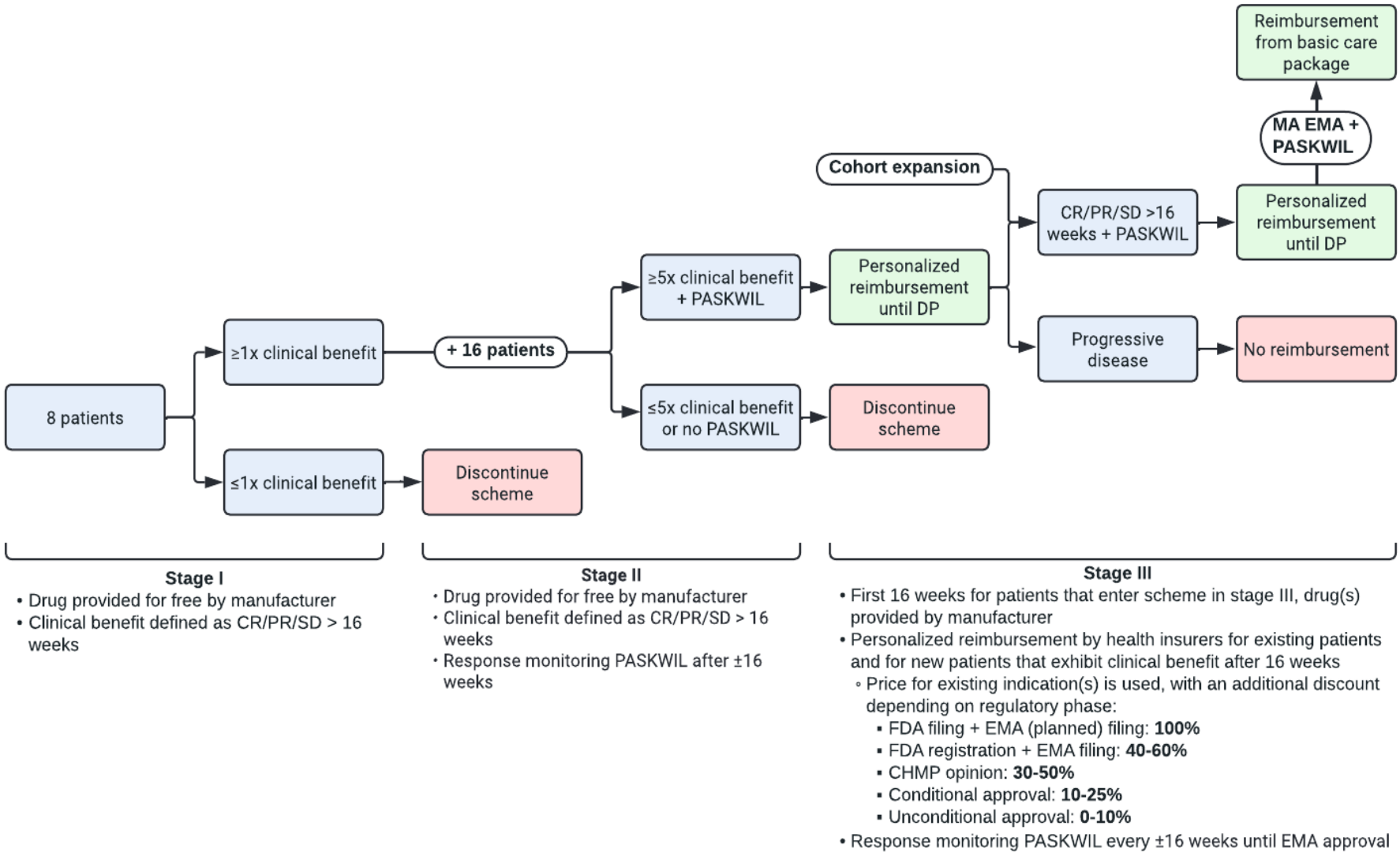

Figure 8: Design of the PFP model, consisting of three stages (DRUP-like) in which stage I and II are intended as a proof-of-concept, whereas stage III aims to confirm initial results. Stage III involves personalized reimbursement in which payment depends on the achievement of regulatory milestones. Upon receiving EMA approval and complying with PASKWIL criteria, the drug is reimbursed from the basic care package. DP = disease progression; FDA = Food and Drug Administration.

4.1.1 Stage I and II

In the first stage of the PFP scheme, eight patients are included which can be increased up to 24 patients if clinical benefit is observed for at least one patient in stage I. Clinical benefit is defined as CR, PR, or SD, which is measured after 16 weeks. In stage II, the PASKWIL criteria for non-randomized studies should be met and at least five patients should have clinical benefit for the cohort to continue to stage III. Note that the first two stages are intended as a proof-of-concept in which the drug is considered an investigational product. Therefore, the drug is provided by the manufacturer for free during these stages.

4.1.2 Stage III

The objective of stage III is to confirm initial results and allow personalized reimbursement of the drug for patients with clinical benefit. Health insurers from now on reimburse the drug for patients who entered via stage II, as PASKWIL criteria have been met and sufficient clinical benefit is observed on an individual level. Additionally, more patients are allowed to enter the cohort in stage III, for whom the drug is provided by the manufacturer for free during the first 16 weeks in order to establish individual response. Next, 16 weeks into stage III another evaluation moment takes place, after which personalized reimbursement comes into effect for patients with clinical benefit (provided that PASKWIL criteria have been met). The price that is adhered for the drug during reimbursement depends on the regulatory milestones that have been met (see chapter 4.1.3.). Once the drug is reimbursed from the basic care package, response monitoring should only continue if it has added value, which may be assessed by performing value of information analyses. Indefinitely collecting data should be prevented, as this may add to the administrative burden without having added value for patients (80).

Importantly, manufacturers should be incentivized to participate in PFP model, but cannot suffer disadvantages if the choice is made not to participate. Therefore, it is also a possibility to start mid-scheme at stage III instead of following the scheme from the beginning. Starting early is however encouraged, as this maximizes the amount of data that is collected. Therefore, a requirement for entering mid-scheme is that the product has a positive CHMP opinion in the designated indication, as this may compensate for the first two exploratory stages that were not followed.

4.1.3 Payment structure

As this study focuses on applying the PFP model in line extensions, the reference price that is used in the scheme is similar to the negotiated price of the product in existing indication(s). In that way, the discounts shown in the scheme are applied on top of the price discount that is already negotiated by HTA organizations for use in the initial indication(s), therefore taking existing HTA decisions into account. The

level of discount that is applied throughout the scheme depends on the regulatory milestones that are achieved as shown in Figure 9, in which innovations are rewarded for decreasing uncertainty. Furthermore, discounts in the PFP model are preferably applied as a retrospective claw back as this will align incentives of pharma and payer to resolve uncertainties, as well as prevent time-consuming negotiations about price adjustments. Claw backs can be applied based on historical data of regulatory milestones achievements.

Figure 9 shows that the drug is funded from the basic care package as soon as the milestone of EMA (conditional) approval has been achieved, as this marks the establishment of a positive benefit-risk ratio. Additionally, clinical meaningfulness of the product has also been proven by complying with the PASKWIL criteria established by the cieBOM. Therefore, reimbursement from the basic care package should be justified at this point. During this phase, a rebate for non-responding patients is still effective. Furthermore, a rebate for patients whose treatment is terminated due to adverse effects is applied throughout the entire scheme.

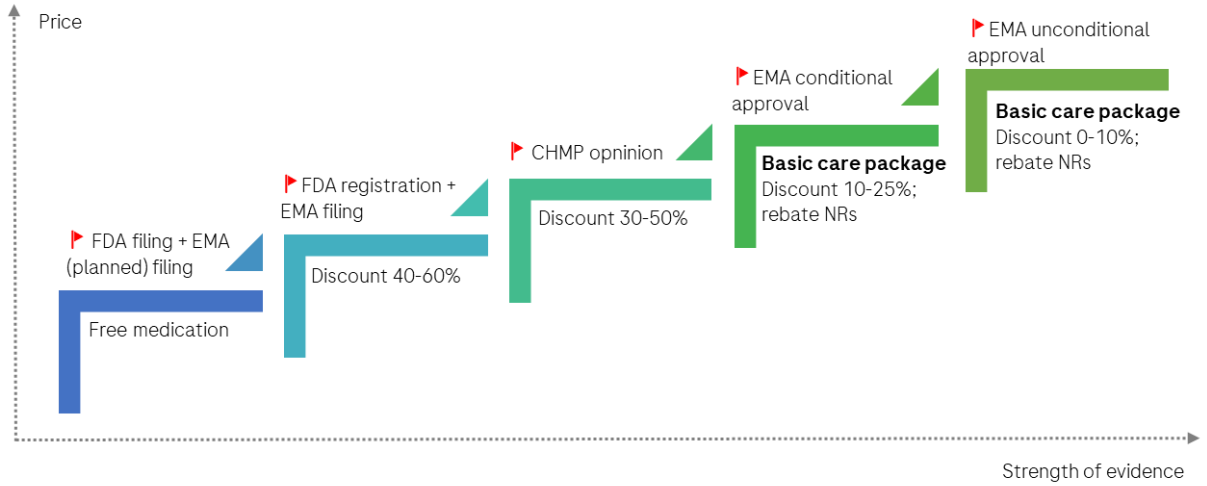

Figure 9: The discount applied in the scheme decreases incrementally depending on the achieved regulatory milestones, thereby aligning pricing with the level of evidence. NR = non-responder.

4.2 Stakeholder analysis

Tables 7 and 8 show a list of interview candidates and an overview of key results obtained from the internal and external interviews, respectively. The protocol used for internal interviews and core questions for external interviews can be found in Annex 1 and 2, respectively. More detailed overviews of interview results are enclosed in Annex 5 and 6.

Table 7: List of internal interview candidates of Roche (*i1-i8*) and external interview candidates (*i9-i15*).

Candidate no.	Role	Company
i1	Patient Access Chapter Lead	Roche Nederland B.V.
i2	Patient Access Manager	Roche Nederland B.V.
i3	Customer Value Solutions Chapter Lead	Roche Nederland B.V.
i4	Outcome Data Manager	Roche Nederland B.V.
i5	Rare Conditions Partner	Roche Nederland B.V.
i6	Head of Healthcare System Solutions	Roche Nederland B.V.
i7	Global Pricing & Reimbursement Lead	Roche Global
i8	Precision Medicine Partner	Roche Nederland B.V.
i9	Project Manager	HollandBio
i10	PhD candidate	Amsterdam UMC
i11	PhD candidate	Utrecht University
i12	Medical Access Manager	Novartis
i13	Market Access Lead	Bayer B.V.
i14	Medical Director	Amgen
i15	Pharmaco-economic adviser	National Healthcare Institute

Table 8: Key results of the interviews conducted with internal *(i1-i8)* and external *(i9-i15)* stakeholders of Roche to acquire insight in the views of the PFP model.

DRUP and DAP
Benefits – Creates a context for personalized reimbursement and payment based on value *(i1-i3,i5)* – Improves patient access by enabling earlier access for patients with an unmet need *(i1,i2,i4)* – Concepts form a solid basis on which can be iterated *(i1-i5,i8)* – The DRUP allows identification of clinical benefit of products beyond their label on the basis of molecular information *(i1,i2,i8)* Limitations – Fragmented initiatives that do not have any guarantee for EMA approval or inclusion in the basic care package *(i1,i8)* – There is a lack of clarity regarding DAP procedures (inclusion process, associated healthcare facilities, eligible products) *(i1-i3)* – The DAP is very labor intensive and not sustainable as it makes use of handwritten registers *(i1,i5,i8,i14)*

- The DAP requires a payment of €5000 for every patient participating in the scheme. Not all pharmaceutical companies can carry this financial burden, creating unequal opportunities *(i1,i8,i14)*
- Manufacturers do not own nor are allowed full access to the data that is collected during the DAP *(i1,i8)*
- Solely collecting real-world data from patients in the Netherlands may not be feasible/sufficient to address remaining uncertainties *(i4,i8,i9,i12)*
- Due to certain protocols existing, the need to tackle the core of the problem is attenuated *(i1,i4,i8)*
- Shadow systems with minimal efforts and resources *(i1,i3)*
- Participation in these protocols is equivalent to participating in a trial as patients must give consent to undergo an investigational treatment *(i1,i5)*

Benefits PFP

Concepts

- Provides a structured way of addressing uncertainties while facilitating patient access *(i9, i11,i13,i14)*
- Linking milestones to the regulatory process creates robust and clear cut-off endpoints, thereby alleviating financial and administrative burden *(i11,i13,i14)*
- Creates a context for defining SvWP on individual level, personalized reimbursement, and payment based on value *(i1-i3,i5,i11,i12,i15)*
- Drugs for solid oncology provide a well-defined and appropriate initial scope *(i7,i13,i14)*

Impact

- The collection and assessment of real-world data allows accurate predictions of therapy success in subgroups of patients, contributing to more efficient and sustainable healthcare *(i1,i2,i3,i5,i8,i9,i11,i15)*
- Creates incentives for pharmaceutical companies to continue developing potentially breakthrough but financially risky products *(i7,i11)*
- Patient access is more enhanced in comparison to other MEAs due to the pre-registration character of the PFP model *(i11,i12,i15)*

Limitations and challenges PFP

Concepts

- Difficult to determine whether the level of evidence is sufficient to resolve specific uncertainties and who should be responsible for making these decisions *(i1,i6,i10,i11,i12)*
- Not all products can follow the standard trajectory in terms of patient numbers and frequency of data monitoring *(i2,i4,i5,i7,i10)*
- Challenging to determine initial price on which discounts will be based *(i11,i12)**
- Privacy and legal aspects of the agreements must be considered *(i3,i5,i11,i15).* In particular important as the scheme is effective prior to EMA registration *(i6,i12,i13)*

Feasibility

- One central and uniform data infrastructure needed *(i2-i5,i7,i8)*
- Collecting data on a national level may not sufficient to resolve uncertainties *(i4,i6,i7,i8,9,i11,i12)*
- Lacking experience of RWD and corresponding statistics/methodologies *(i1,i6,i7)*
- Implementation of certain models is challenging. Results in high administrative and financial burden, requiring major capacity and collaboration of many stakeholders *(i1,i9,i11,i12,i15)*
- All involved stakeholders should be willing to share data, be aware of their responsibilities, and be well coordinated with each other *(i3,i7)*

Impact

- The model implies differential pricing (i.e. charging different prices for the same product in different settings). This requires a major change of perspective as it deviates significantly from the way we currently determine the value of innovations *(i1,i12,i14)*
- Perverse incentive for increased list prices *(i5,i6,i11)**

Conditions and suggestions PFP

Concepts

- Clearly define at an early stage: 1) which uncertainties remain, 2) what data is required to resolve this, and 3) how often this data should be collected. Tie possible outcomes to specific discounts/actions *(i3,i5-i9,i11-i13)*
- The data that is collected in the PFP scheme must be of added value in relation to the clinical data that is already available and should serve the purpose of improving healthcare. Reduce the likelihood of indefinitely collecting data without it having added benefit for patients *(i9,i12)*
- Prevent overcomplicating the model structure. Overall, the protocol should be easy to execute *(i8,i9,i10)*
- Uniform and solid data infrastructure needed *(i1,i2,i5)*
- Personalized reimbursement should be the ultimate goal *(i1,i8,i15)*
- Apply discounts preferably as retrospective claw back as this aligns incentives of payer and pharma *(i7,i11)*

Stakeholders

- Objective governance is needed for e.g. regulating data access and decision-making on discount percentages. Should be performed by a party that is accepted by all stakeholders involved *(i4,i5,i11,i15)*
- The stakeholder that is responsible for data registration should meet the following requirements: *(i1,i2,i4)*
    - Data is shared among involved parties, stimulating continuous learning
    - Data is collected and shared via the FAIR principles
    - Data is gathered directly from the source through an automated system
    - Even if patient is a non-responder, data should be available for analysis

**less relevant in present study, as initial scope of the PFP scheme focuses on line extensions*

4.2.1 Key findings of internal stakeholders

Access barriers as experienced by internal stakeholders are depicted in Figure 10. The primary access barrier that was perceived by almost all internal stakeholders (N=7) revolved around the applicability of the current assessment framework. Interviewees pointed out that the principles of EBM are vastly anchored in the current framework, whereas new types of evidence and corresponding outcome measures associated with personalized healthcare do not fit in the framework. Further, half of the internal stakeholders (N=4) stated the one-off nature of HTA evaluations in the Netherlands to be a limitation, as it does not allow reflection of the real-world value of innovations. In addition, interviewees declared that assessments on clinical benefit and cost-effectiveness are currently performed at the point in time that is associated with a high level of uncertainty regarding real-world effectiveness, inherently hampering the assessment itself. Moreover, lock procedures were experienced (N=4) as too long and assumptions as excessive, possible leading to unjustified lock placements. Main changes to the current healthcare system as proposed by internal stakeholders included a shift to a data-driven system (N=5) and wider acceptability of other types of evidence besides those associated with EBM (N=5). More information on access barriers experienced by internal stakeholders can be found in Annex 5.

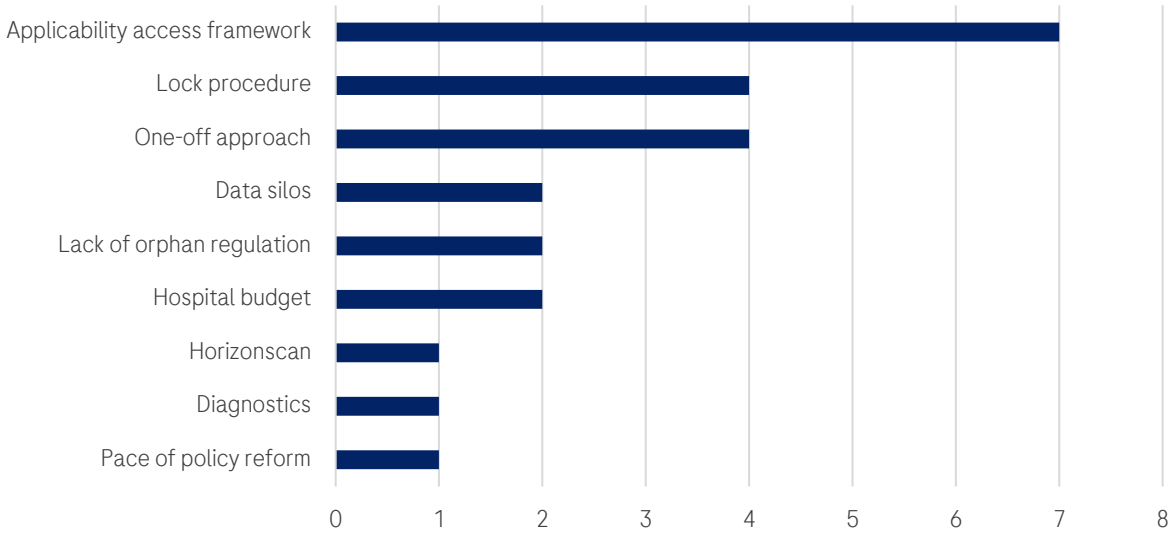

Figure 10: Access barriers experienced by internal stakeholders (N=8). See Annex 5 for more details on access barriers.

When addressing the DRUP and DAP (Table 8), it became clear that internal stakeholders experience many difficulties and limitations around these protocols. First, it was stressed (N=3) that the DAP is a very labor-intensive process that results in major administrative burden, while simultaneously a lack of clarity regarding DAP procedures is experienced by physicians and patients around eligible drugs, inclusion processes, and healthcare facilities involved. In addition, the required fee of €5000 per patient in the DAP was considered (N=3) as an unfair market value. Both the DRUP and the DAP were perceived as shadow systems (N=2) that bypass regular reimbursement routes instead of tackling the core of the problem (N=3). Last, internal stakeholders (N=2) experience the DRUP and DAP as fragmented initiatives that do not guarantee EMA approval or reimbursement in any way. Some benefits of the DRUP and DAP as identified by internal stakeholders included earlier access for a wider range of patients (N=3) and personalized reimbursement that is data-driven (N=4). These protocols were therefore considered (N=6) as solid blueprints on which can be iterated.

Upon addressing the concepts of a learning healthcare system and the proposed PFP model (see Annex 5), the majority of internal stakeholders (N=5) believed a certain data-driven system to be a prerequisite for the increased involvement of personalized healthcare and corresponding types of evidence, while additionally allowing identification of patients who will benefit the most from a treatment. Further, it was stressed (N=4) that it enables reflection of the real-world value of innovations, thereby contributing to value-driven healthcare.

Numerous challenges associated with a learning healthcare system and the proposed PFP model were identified (see Table 8). First, interviewees emphasized the need for a solid and uniform data-infrastructure for a certain data-driven system (N=6), preferably consisting of European or even global data to ensure sufficient data is collected (N=4). Further, objective governance was considered (N=2) as an important condition for secure regulation of data access. Involvement of RWD was also identified (N=3) as a hurdle, as RWD is more prone to bias and confounding, and requires more complex statistical methods compared to standardized clinical data. Further, required resources and investments were stated to result in a high administrative and financial burden (N=2), and the need to tailor the PFP trajectory for each eligible product was also mentioned as a challenge (N=4). Last, a few interviewees (N=2) stated a possible perverse incentive of the PFP model to be increased list prices due to higher financial risks for manufacturers.

4.2.2 Key findings of external stakeholders

Overall, external stakeholders were supportive of the PFP model and perceived it as a structured way of addressing uncertainties while facilitating patient access (N=4) (Table 8). Interviewees (N=3) expressed in particular a positive attitude to the robustness of the milestones applied in the model, as tying these to existing regulatory achievements provides clear cut-off points. Further, the pre-registration character of the model was also considered (N=3) as beneficial for facilitating patient access in comparison to other reimbursement schemes. Last, it was positively acknowledged that the PFP scheme creates a context for personalized reimbursement (N=3) and contributes to more sustainable and efficient healthcare due to the continuous involvement of data (N=3).

Interviewees (N=4) emphasized the importance of predefining several conditions beforehand, such as 1) which uncertainties are remaining, 2) which data is needed to resolve these uncertainties, and 3) how often this data should be collected. Involving early dialogue between pharma, EMA, payers, and ZIN, was suggested by a stakeholder as a way to facilitate this process. Further, it was declared (N=3) that a major challenge of performance-based schemes generally involves determining whether sufficient levels of evidence have been achieved to resolve uncertainties.

Moreover, several external interviewees (N=2) expected that the success of the PFP model heavily depends on the willingness to acknowledge and attribute different prices for the same drug used in different settings – i.e. to 'pay for proof'. This requires a major change of perspective as it deviates significantly from the way we currently determine the value of innovations. Last, external stakeholders (N=4) agreed that practical implementation of certain models remains a major hurdle due to e.g. the infrastructure and capacity that is required for a data-driven system.

5. Discussion

5.1 Summary of key findings

The PFP model that was ultimately obtained upon the results of the literature review and stakeholder analysis consists of a DRUP-like personalized reimbursement scheme based on performance. Payment is linked to a discount scheme based on regulatory milestones that are indicative of decreasing uncertainty, thereby enabling value-based pricing. The model aims to determine SvWP first on an individual level by defining clinical benefit for individual patients and to extend this to a population level if sufficient data is available. If the latter is the case, reimbursement from the basic care package should be justified (provided the product has EMA approval). The initial scope of the model focuses on line extensions within solid oncology; however, the concepts may be applied to other therapeutic areas as well.

The results of this study indicated that stakeholders perceive a clear need for improved access to the growing number of drugs that are authorized based on non-randomized trials. As the current assessment framework is not (yet) adequate for the evaluation of these types of innovations, the proposed PFP model may facilitate controlled access based on both clinical studies as well as real-world experience, while simultaneously creating a context in which data collection and analysis serve the purpose of improving efficiency and sustainability of healthcare. Stakeholders perceived existing alternative access routes as unsustainable and/or unfeasible, therefore expressing the need for a suitable alternative. Internal and external stakeholders expressed their support for the proposed PFP model. Several benefits of the scheme that were acknowledged include its data-driven nature, the robustness of the included milestones, enhanced flexibility of reimbursement, and its ability to reflect real-world value of innovations. Main challenges include the need for a uniform data-infrastructure, involvement of complex RWD methodologies, and potential resistance due to perceived unfairness regarding value-based pricing.

5.2 Relevance and implications

Even though regulatory authorities are undertaking efforts to authorize promising drugs associated with new types of evidence, patient access will not improve as long as HTA agencies do not adopt the same level of evidence. Previous studies have also focused on the potential of a data-driven learning healthcare system to fill these evidence gaps and improve healthcare in terms of efficiency and sustainability (19,67,83). Even though the concepts of learning healthcare systems have generated considerable amounts of support, large-scale implementation remains limited (19,64,67,83). In order for a learning healthcare system to be successful, multiple previous studies, as well as patients, researchers, caregivers and ZIN, have emphasized the need for a solid and uniform data-infrastructure that is interoperable and

secure in terms of privacy (19,66,67,84). Both internal and external stakeholders confirmed these findings and stated that a lack of capacity and infrastructure hampers benefiting from technological advances. To tackle this, various incentives have appeared that aim at creating a data platform that is fit for this purpose (84). Even though these efforts show a willingness to transform to a data-driven system, the emergence of manifold parallel initiatives with lacking governance leads to an incoherent data landscape rather than a uniform platform (84). This is in concordance with findings from our stakeholder analysis, in which we found interviewees to be unsupportive of the fragmented data silos in the Dutch healthcare system, as they result in major inefficiencies.

Similar to a learning healthcare system, the PFP model also requires a solid data-infrastructure that allows the involvement of RWD as well as efficient data sharing, which was identified as one of the major challenges of the model during the stakeholder analysis. To prevent the emergence of a novel data platform that adds to the fragmented data landscape, the use of existing infrastructures (such as the H_2O Health Outcomes Observatory or the European Health Data Space) should be explored (85,86). For example, the H_2O Health Outcomes Observatory is an initiative that aims at creating pan-European and national data infrastructures that enable robust data collection, analysis, and data sharing to inform healthcare decision-making in three disease areas – diabetes, inflammatory bowel disease, and cancer (64,86). The observatory includes a secure governance model that guarantees data protection under both national and EU jurisdictions. Further, the initiative is a strategic partnership between public and private sectors that is currently active in four participating countries (Austria, Germany, Netherlands and Spain), therefore amplifying the value of data sharing (86). In July 2022, the Dutch H_2O observatory was officially launched. Thus, by making use of an existing initiative that is already equipped for the continuous cycle of data collection and analysis, the PFP model can reflect the potential of a data-driven learning healthcare system with limited administrative burden before fully committing to one in the Netherlands.

Apart from the need for a secure data platform to capture and share RWD, the complex methodologies and difficulties to translate RWD into robust and meaningful real-world evidence (RWE) were also identified as major challenges during the stakeholder analysis. Indeed, previous research emphasized the methodological difficulties that are associated with successfully incorporating RWD in informing healthcare decision-making (80,87,88). However, many advances have been made in the analysis of RWD and an increasing number of guidelines have been developed that facilitate the conduct and reporting of real-world studies (80). Blommestein et al. (2015) emphasize that RWE has the potential to provide extremely valuable information for healthcare decision-making, but simultaneously warn that

assessment methods differ from evaluating evidence derived from more standardized clinical trials (88). Likewise, Mohseninejad et al. (2015) and Kristensen et al. (2020) state that patient registries using RWD pose efficient ways of gathering valuable information, however, registries must be carefully designed and governed to limit confounding (87,89). Again, this emphasizes the importance of using a (preferably existing) data-platform that is well governed and equipped for collecting RWD and translating this to robust and meaningful RWE. Note, however, that major investments are required for proper training of decision-makers owing to their (presumably) little experience in incorporating RWD in current practices (80).

Furthermore, another challenge of the PFP model, as identified during the stakeholder analysis, is that not every product can follow the standard trajectory in terms of patient numbers and frequency of response monitoring, as these highly depend on the indication and type of intervention (80). The patient numbers included in the proposed PFP model follow the design of the DRUP protocol that is based on a Simon-like two-stage design, which makes use of an optimal design specifically developed to represent a reasonable compromise between low false-positive rates, high power, and a desire for small sample sizes (51,52). Especially the latter is important, as certain protocols often involve rare diseases with small patient numbers. The use of a national data-infrastructure (such as the H_2O observatory) amplifies the available data and may guarantee the involvement of sufficient patients in the scheme. Furthermore, a 16-week period for assessing clinical benefit may not be feasible for some products. For example, potentially curative one-off cell and gene therapies are promising innovations as their clinical benefit may last a lifetime, however, measuring outcomes is difficult due to the time lag between administration and apparent benefit (21). Therefore, it should be defined at an early stage – before engaging in the PFP model – what uncertainties are to be addressed, which data is needed to do so, and how often this data should be monitored, which was also emphasized by several stakeholders. Based on these findings, it can be assessed whether it is feasible to engage in the PFP scheme, and to what extent the standard trajectory is applicable. This is in concordance with the recommendations of Makady et al. (2019) and Neyt et al. (2020) on the successful implementation of CED schemes and MEAs in general, respectively (73,74,80).

Another – arguably more complex – challenge of the PFP model as mentioned by multiple stakeholders, revolves around the concepts of the PFP model deviating significantly from the way we currently appraise value to innovations. The PFP model, as well as value-based pricing in a broader context, implies differential pricing (i.e. setting different prices for the same drug used in different settings), which may lead to resistance due to perceived unfairness (90). This poses a major hurdle in a successful transition to a value-based pricing system. Importantly, the differentiation in prices should be propagated in a way

that the highest price is considered the reference price, whereas any lower price is clearly linked to conditions that justify this difference – in the case of the PFP model, more clinical uncertainty (91). Furthermore, examples of how a certain pricing system could improve healthcare (e.g. expedite access, reduce costs) could illustrate its benefits and facilitate acceptance of value-based pricing and associated differential pricing.

Moreover, it is often assumed that list prices are the same irrespective of the presence of a MEA, which can subsequently lead to an over or underestimation of the financial savings that can be achieved by the agreement. In reality, manufacturers may anticipate the impact that a MEA can have and respond by adjusting their list price. Indeed, a study by Gamba et al. (2020) showed that the introduction of a MEA generally leads to higher list prices – a finding that was also identified as a perverse incentive during the stakeholder analysis (92). However, as the current scope of the PFP model is limited to line extensions that already have an established list price in the Netherlands, incentivizing higher list prices is not relevant here. When applying the PFP model to new molecular entities (NMEs), this perverse incentive would become more prominent. It can however be argued that a higher list price is justified for treatments that are subject to performance-based and personalized reimbursement, as payment is not based on the average patient but solely concerns responding patients, for whom the treatment is much more cost-effective than for non-responding or averaged patients. Thus, this is in concordance with the principles of value-based healthcare.

Last, as various alternative access routes and protocols exist, it is important to illustrate the added value of the PFP model. Table 9 shows a comparison between characteristics of the DRUP, DAP, VT and the proposed PFP model. The aim of the PFP model is mostly comparable to that of the DAP, as both provide access to drugs for (expected) on-label indications for which the evidence does not fit in the current assessment framework while simultaneously collecting RWD (54). Compared to the DAP, the PFP scheme has several advantages. First, the PFP aims to make use of a solid data-infrastructure that automatically collects data directly from the source, whereas data collection in the DAP is very inefficient and labor intensive (56). The administrative and financial burden of data collection is therefore expected to be much lower in the PFP model in comparison to the DAP. Furthermore, as the DAP requires a €5000 fee per patient and obliges the manufacturer to provide the drug for free in early phases, major financial risks are carried by pharmaceutical companies that result in unequal opportunities as not all companies can commit to this (see Table 8). In addition to these financial risks, the DAP does not guarantee inclusion in the basic care package in any way, and the data that is collected is not fully owned or accessible by the manufacturer.

Thus, these limitations of the DAP show that its design is neither sustainable nor efficient. The PFP scheme solves these issues by integrating inclusion in the basic care package in the scheme, ensuring transparent data sharing, employing value-based prices, and allowing mid-scheme entrance to alleviate financial risks. Further, the proposed PFP should be easy to use for physicians, pharmacists and/or other medical specialists in order to be fully superior to the DAP – it should be clear which products are accessible through the PFP model and how the procedures work. Last, collaboration with relevant stakeholders and the allocation of clearly defined responsibilities is crucial during the implementation of the PFP model, as this aligns incentives and enhances the success of the scheme (80). Stakeholders should jointly decide on consequences in the case responsibilities are not met, contrary to the CF framework that lacked certain sanctions (which was perceived as a major weakness) (80).

The DRUP, on the other hand, specifically focuses on identifying potential clinical benefit off-label in patients that have exhausted SoC, and therefore serves a different purpose than the PFP model (49). Further, the aim of the VT is somewhat comparable to the PFP model, as it also facilitates access to drugs that are associated with less comprehensive types of evidence of which SvWP cannot be determined. However, the VT involves a 7-year trajectory in which the drug is funded outside the basic care package through a fixed budget, and in which the price is generally subject to a high discount (45). Further, provision of the drug before EMA registration is not possible in the VT. Therefore, the PFP model also poses multiple advantages over the VT trajectory.

Table 9: Comparison between characteristics of the DRUP, DAP, VT, and PFP model (45,47–50,53–56, Table 8, Annex 5-6).

	DRUP	DAP	VT	PFP
Aim	Collect RWD and provide access to off-label drugs	Collect RWD and provide access to drugs associated with less comprehensive evidence	Provide access to promising drugs associated with less comprehensive evidence, while additional research is performed	Collect RWD and provide access to drugs associated with less comprehensive evidence
Scope	– Off-label targeted oncology treatments – Patients that have exhausted SoC – Patients must have rare malignancies with potentially actionable and identifiable aberrations	– Rare, on-label indications pre- and post-registration – Focus on drugs for solid oncology of which evidence does not fit in framework – Authorized drugs awaiting reimbursement decision and unauthorized drugs with EMA filing	– On-label indications post-registration – Orphans, conditionals, and exceptionals – Drugs targeting a great unmet need that have limited clinical evidence – Products should have EMA registration	– Line extensions within solid oncology that target identifiable molecular alterations – On-label indications pre- and post-registration – Focus on products of which evidence does not fit in framework – Products should have planned EMA filing

Payment	– Personalized, performance-based reimbursement – Manufacturer pays for drug in initial phase – Insurers continue reimbursement for patients with clinical benefit	– Personalized, performance-based reimbursement – Manufacturer pays for drug in initial phase – Insurers continue reimbursement for patients with clinical benefit – €5000 fee per patient applied	– Price of VT drugs is generally subject to high discount – Drug funded by VWS outside the basic care package through designated yearly budget – Once the budget cap is reached, new VT applications are placed on waiting list – MA holder responsible for funding research	– Personalized, performance-based reimbursement – Manufacturer pays for drug in initial phase – Insurers continue reimbursement for patients with clinical benefit – Reimbursement linked to discount scheme based on regulatory milestones – Uptake basic care package integrated in PFP
Benefits	– Identify clinical benefit of drugs beyond their label – Value-based healthcare – Earlier access for a wider range of patients – Risk sharing lowers costs – Continuous learning in real-world setting	– Value-based healthcare – Earlier access for a wider range of patients – Risk sharing lowers costs – Continuous learning in real-world setting	– Provides controlled access to drugs targeting great unmet need – Poses a way to address uncertainties for drugs with limited clinical evidence	– Value-based healthcare – Facilitates access while addressing uncertainties- – Leads to reimbursement from basic care package – Risk sharing lowers costs – Continuous learning in real-world setting – Incentivizes manufacturers to develop high benefit products – Robust regulatory milestones
Limitations	– Administrative burden due to personalized scheme – Does not lead to EMA registration – Implementing RWD poses methodological challenges – Shadow system rather than regular access route – Patients must give consent as treatments are not yet SvWP – National data may not be sufficient	– High workload due to handwritten registries – Data not fully owned or accessible by MAH – €5000 fee creates unequal opportunities – No guarantee for inclusion in basic care package – Shadow system rather than regular access route – Unclear procedure for healthcare practitioners – National data may not be sufficient – Implementing RWD poses methodological challenges – Patients must give consent as treatments are not yet SvWP	– If reimbursement limit is reached, new VT applications placed on waiting list – Procedure takes up at least 7 years – Timelines often exceeded – Application procedures unclear – Treatment limited to designated facilities – Patients must give consent as treatments are not yet SvWP – National data may not be sufficient	– Solid data infrastructure needed – High administrative burden and financial investments needed – Implementing RWD poses methodological challenges – Requires recognition of value-based pricing – Patients must give consent as treatments are not yet SvWP – Potential resistance due to differential pricing – Standard trajectory not always applicable

5.3 Strengths and limitations

This study distinguishes itself from previous research, as it focuses on a well-defined approach to improve access to innovative drugs while simultaneously placing this in a broader context. Furthermore, combining literature research with qualitative findings from interviews yielded a strong fundament for exploring the feasibility of the proposed pricing model. Last, a wide variety of interview candidates was selected – both from within Roche as well as outside the company – to ensure that diverging perspectives were taken into account.

This study has limitations. First, we restricted ourselves to assessing the applicability of the PFP model in line extensions of drugs within solid oncology, whereas NMEs and drugs for other therapeutic areas were out of scope. As a line extension considers a product of which a positive benefit-risk balance has already been established – albeit in a different indication – it is inherently associated with less clinical uncertainty in comparison to an NME. It can therefore be argued that in those cases provision of the drug pre-registration is associated with minimal risks and may have considerable chances of being beneficial for patients. As financial risks are mostly carried by the manufacturer, it is justified from both a financial and a patient perspective. NMEs, on the other hand, are associated with a higher level of clinical uncertainty before market authorization, as the benefit-risk balance of the original formulation has not yet been established in any indication. Application of NMEs in a certain discount scheme is therefore more prone to ethical or legal concerns and requires a different roadmap. There are, however, alternative options for patients with a high unmet need for whom treatment with an unauthorized NME would be beneficial, such as the DAP, compassionate use programs, or named patient programs (93).

Further, we solely focused on the application of the model within solid oncology, as clinical endpoints within this therapeutic area exist that allow assessment of products based on non-randomized trials (61). Traditionally, OS is considered the most robust endpoint within oncology, but the use of other endpoints is becoming more prevalent in clinical trials (although the reliability of these endpoints is under debate) (94). The recently proposed PASKWIL criteria for non-randomized studies provide well-defined guidance for evaluating the efficacy of drugs for solid oncology that are associated with novel types of evidence, whereas this is lacking in other therapeutic areas (61). The success of performance-based models is often limited by the inability to measure outcomes and the lack of demonstrable value (79). Therefore, using robust and clear-cut endpoints enhances the success rate of the scheme and simultaneously reduces the administrative burden that comes with response monitoring and analysis.

Moreover, even though a diverse variety of stakeholders was included, a few important stakeholders were out of scope, including VWS, healthcare professionals, and healthcare insurers. Future research could focus on involving these stakeholders to further assess the feasibility of the model. Last, a case study in which the potential PFP trajectory is compared to existing pathways was out of scope. However, a certain analysis may clarify timeline differences and potential savings, thereby showing the possible impact and relevance of the model.

5.4 Recommendations

Based on all previously stated results, the following recommendations are made for the successful implementation of the PFP model:

i. The PFP model should be easy to use for physicians, pharmacists and/or other medical specialists. It should be clear which products are accessible through the PFP model and how the procedures work. Complicated entry requirements must be avoided.

ii. We advise making use of an existing data platform for the PFP model as this will prevent the emergence of more fragmented data initiatives. Preferably, this data platform should be well governed in terms of privacy and legal requirements and should be equipped for the translation of RWD to robust RWE. An example of a possible data platform is the H_2O Health Outcomes Observatory or the European Health Data Space. As both are pan-European initiatives, the amount of available data is amplified.

iii. Differential pricing within the same product should be recognized and acknowledged by all parties involved. It should therefore be propagated that doing so is justified as it contributes to value-based healthcare and leads to more sustainable care. The highest price should be considered as the reference price, whereas discounts must be clearly linked to specific conditions.

iv. There should always be a link between remaining uncertainties, required information to address these, and conditions applied in the scheme. Avoid indefinitely collecting data without it having added benefit. This can be acquired by defining at an early stage: 1) what uncertainties are remaining, 2) what data is needed to address these uncertainties, and 3) how often this data should be monitored. Upon these results, it can be determined whether it is feasible to resolve these uncertainties through the PFP scheme and to what extent the standard trajectory is applicable.

v. Last, ensure the active involvement of relevant stakeholders in the implementation of the PFP model, clearly allocate responsibilities to different stakeholders, and agree on consequences if responsibilities are not met.

5.5 Conclusion

This study assessed the feasibility of a pay-for-proof reimbursement model that aims at facilitating access to innovations associated with less comprehensive evidence obtained from non-randomized phase I/II studies. A multi-stakeholder analysis was performed to explore views around the current healthcare system, existing alternatives, and the PFP scheme as a potential pricing model. Overall, stakeholders were supportive of the PFP model and expressed their need for a data-driven healthcare system that allows and stimulates data sharing and continuous learning. A challenge of the PFP scheme is the need for a solid infrastructure, however, existing initiatives may be applicable in the PFP scheme (such as the H_2O observatory). Furthermore, recognition is needed to acknowledge the value-based pricing that is used in the PFP scheme and to prevent resistance due to perceived unfairness.

Once effective, the PFP scheme facilitates access to promising innovations, while simultaneously collecting RWD that reflects the real-world value of drugs and stimulates continuous learning. This will not only benefit patients but possibly also lower healthcare expenditures due to the risk-sharing agreement and performance-based character of the scheme. Our study showed that the PFP scheme is a step in the direction of a learning healthcare system that undeniably tackles a great unmet need and poses advantages over currently existing alternatives. Therefore, we advise Roche Nederland to engage in the PFP model as a pilot while taking into account the recommendations listed in chapter 5.4. Interim evaluations of the scheme may then show its potential and contribute to the advance towards a full learning healthcare system in the Netherlands. Ultimately, the PFP scheme will then contribute to Roche's Pharma Vision 2030 to achieve 3-5 times more patient benefits for 50% less costs to society.

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Appendix

Annex 1: Interview protocol for internal use.

Vragen per onderwerp

Introductie kandidaat

1. Wat is uw functie binnen Roche Nederland B.V.?
2. Hoe lang werkt u bij Roche?
3. Heeft u nog andere relevante (werk)ervaring (bijvoorbeeld een eerdere functie buiten Roche)?

Beoordeling nieuwe interventie

Bij het beoordelen van toegevoegde therapeutische waarde maken veel HTA instanties, waaronder het Zorginstituut, gebruik van een beoordelingskader dat berust op evidence-based medicine (EBM), waarin de meeste waarde wordt gehecht aan de fase III RCT studie.

4. Is het terecht dat de RCT als gouden standaard wordt gezien in veel beoordelingskaders?
5. Wat zijn access barrières binnen het huidige systeem die u momenteel ervaart of verwacht te ervaren in Nederland?
6. Wat zou er veranderd moeten worden aan het huidige systeem?
7. Tijdens een HTA assessment wordt ook de prijs van het geneesmiddel beoordeeld op basis van de bewijslast die op dat moment beschikbaar is. Wat vindt u ervan dat de prijs enkel op dit moment beoordeeld wordt?
8. Zijn er bepaalde componenten uit systemen van andere landen waar we in Nederland een voorbeeld aan zouden kunnen nemen?

Nu een groeiend aantal geneesmiddelen op de markt komt op basis van niet-gerandomiseerde fase I/II studies, blijkt dit in steeds meer gevallen een knelpunt te zijn. Denk hierbij aan tumor-agnostische middelen, geneesmiddelen voor zeldzame indicaties, of veelbelovende bispecifics en CAR-T therapieën. Het gevolg is dat de toegevoegde waarde van dergelijke innovaties niet beoordeeld kan worden, wat uiteindelijk leidt tot grote vertragingen in de beschikbaarheid voor patiënten. Er is dus een groeiende vraag naar een **continu lerend systeem** die gecontroleerd toegang kan bieden tot geneesmiddelen, terwijl tegelijkertijd een cyclus plaatsvindt van monitoring, analyse en bijsturing. Het verzamelen van data is cruciaal in dit systeem.

9. Wat is uw visie op een continu lerend systeem in Nederland?
10. Wat zijn enkele barrières waar u aan denkt bij een continu lerend systeem (bijv. bij de ontwikkeling/implementatie)?
11. Wat is uw mening over het gebruik van real-world data (RWD) in het beoordelen van de therapeutische waarde van geneesmiddelen?

Er zijn in Nederland al enkele alternatieve toegangsroutes die ernaar streven om toegang te bieden tot veelbelovende medicijnen die (nog) niet in het basispakket zitten. Hieronder vallen bijvoorbeeld voorwaardelijke toelating (VT), de DRUP, en de DAP.

12. Vindt u dat deze alternatieve routes toereikend zijn?
13. Welke elementen uit deze initiatieven vindt u goed?

Pay-for-proof model

Vergoedingsmodellen kunnen uitkomst bieden in het gecontroleerd toegang verschaffen van geneesmiddelen terwijl tegelijkertijd aanvullend bewijs wordt verzameld. Specifiek voor innovaties die zijn gebaseerd op niet-gerandomiseerde studies, zou een kortingsschema op basis van afnemende onzekerheid relevant kunnen zijn, een zogenoemd **pay-for-proof (PFP) model**. Het PFP model bevat meerdere stadia waarbij doorstroom naar het volgende stadium plaatsvindt wanneer een bepaalde *milestone* is behaald die indicatief is voor afnemende onzekerheid/toenemende bewijslast. Doorstroom naar een volgend stadium kan samengaan met bijv. een kortingsverlaging of overdracht van funding, waarbij er uiteindelijk uitzicht is op opname in het basispakket. Tevens wordt de respons op de behandeling gemonitord d.m.v. PASKWIL criteria voor niet-gerandomiseerde studies. Op deze manier kan er op een gecontroleerde wijze toegang verleend worden tot belangrijke innovaties, waarbij de prijs gefaseerd op mag lopen in lijn met de mate van onzekerheid. Een dergelijk model draagt dus bij

aan een **datagedreven, continu lerend systeem** en versnelt zo de beschikbaarheid van geneesmiddelen die gepaard gaan met te veel onzekerheid om vergoed te kunnen worden. In eerste instantie focust het PFP model alleen op geneesmiddelen binnen de solide oncologie van Roche, maar zou later ook toepasbaar kunnen zijn in andere therapeutische gebieden en/of buiten Roche.

14. Wat zijn belangrijke randvoorwaarden van een dergelijk PFP model?
15. Zoals benoemd hanteert het PFP model *milestones* die indicatief zijn voor toenemende bewijslast. Een voorbeeld van een milestone kan bijvoorbeeld FDA registratie of een positieve CHMP beoordeling zijn. Zijn er nog andere, non-regulatory milestones die belangrijk kunnen zijn om mee te nemen?
16. Wat zijn belangrijke uitdagingen in de ontwikkeling en implementatie van een PFP model?
17. Welke stakeholders zouden betrokken moeten worden bij het ontwikkelen en implementeren van een PFP model

Annex 2: Core questions that were predefined prior to external interviews.

- What is your overall impression of the PFP model?
- Do you have any suggestions or remarks regarding the model structure and/or design?
- Can you think of any challenges or limitations of the model (e.g. implementation)?
- What are some conditions that should be considered (e.g. inclusion criteria)?
- What are conditions for successful implementation?

Annex 3: The three steps of ZIN's assessment procedure on SvWP following the EBM approach (59).

Step 1: Literature search and selection
The PICOT questions are used to argue which aspects are relevant in the determination of relative effectiveness of the intervention, and subsequently search databases for relevant (peer-reviewed) literature: ▪ Patient = what is the relevant patient population of the intervention? ▪ Intervention = what intervention is assessed? ▪ Comparison = what is the control-intervention? (SoC, placebo, (in)direct comparison) ▪ Outcome = what are relevant outcome-measures? ▪ Time = the follow-up time that is required at minimum Furthermore, ZIN determines the difference in outcome-measures that is minimally required in order to establish an added therapeutic value. Last, the appropriate type of evidence (*passend bewijs* profile) is established based on the type of intervention and its corresponding indication.
Step 2: Evaluating and quantifying quality of evidence
The information that is found in step 1 is subsequently assessed on its quality with regard to methodological aspects, relevance of results, to what extent the results can be generalized, and study design. The GRADE method is used to estimate the quality of the obtained results and treatment effect. GRADE distinguishes between four levels of evidence quality (high, medium, low, and no quality).
Step 3: Determination of final assessment
Last, a conclusion is drawn regarding the relative effectiveness of the novel intervention, in which the following aspects play a role: ▪ Risk-benefit balance; ▪ Quality of evidence; ▪ Appropriateness of evidence (*passend bewijs*); ▪ Views of patient groups and associations of professionals.

Annex 4: Use of MEAs in comparable countries.

A recent survey by the OECD showed that 28 countries out of the 41 members of the OECD/European Union were using or had been using MEAs, of which most are financially-based agreements (46). Studies have shown that payers are in general more cautious with the utilization of outcome-based MEAs because of challenges in measuring relevant outcomes and a high administrative burden associated with the implementation (46). Below, we will discuss several examples of the usage of MEAs in the context of some European healthcare systems. Note that the confidential nature of most MEAs forms a significant barrier in assessing the impact of such arrangements (46). Thus, we heavily rely on the (incomplete) data that is publicly available.

Germany: In 2011, Germany introduced the Arzneimittelmarkt-Neuordnungsgesetz (AMNOG) to align drug prices more properly with their benefits, ultimately ensuring patient access while incentivizing pharmaceutical innovation. Under AMNOG, a novel drug is automatically eligible for reimbursement after it has been authorized, resulting in immediate patient access (95). In the first year after market launch, the manufacturer may set the price of the product freely, during which the national HTA bodies G-BA and IQWiG assess its additional relative risks and benefits. After this assessment, price negotiations take place between the manufacturer and the umbrella organization of German health insurers. If an added benefit has been determined, the price of the innovation may be set above the price of the existing SoC in a commensurate degree with the level of added benefit (96). If no (or non-quantifiable) added benefit has been found, the price of the SoC may not be surpassed. As the level of added benefit can vary across patient subgroups (e.g. age differences), different prices may be employed for subpopulations. A study from Lauenroth et al. (2020) showed that implementation of the AMNOG resulted in an average price decrease of 24,5% in relation to launch prices, ultimately leading to drug prices being more closely aligned with their clinical benefit (96). Hence, components of the AMNOG system could be taken as examples when considering pricing strategies.

Furthermore, if a product is associated with too much uncertainty at the time of market launch, the G-BA may apply a time limit to its resolution, during which the manufacturer is required to re-submit a dossier using newer/more mature evidence (97). These time-limited resolutions (TLRs) take on average 2.7 years but can range between five months and seven years (97). TLRs are a way of dealing with the growing number of drugs that are authorized based on less comprehensive data, however, research shows that the G-BA often does not specify what information is lacking from the dossier, making the process inefficient (98).

Last, contracts between sickness funds and pharmaceutical companies allow pricing agreements; however, as these agreements do not address coverage, they are mostly not considered MEAs (46). Furthermore, unlike in other countries, price agreements in Germany are generally applied to products that have been on the market for several years rather than novel products, which has resulted in stakeholders commenting on the greater potential of arrangements for new innovative drugs (99). Hence, Germany is considered to be far behind in horizon scanning approaches as implemented by e.g. the Netherlands and Italy (100).

United Kingdom (UK): The UK makes use of a highly centralized reimbursement process in which the national HTA agency NICE is responsible for decision-making. The UK employs a free-pricing policy, although products that are not cost-effective are not eligible for reimbursement (101). Reimbursement decisions predominantly depend on the cost-effectiveness of a product, which is quantified trough the Incremental Cost-Effectiveness Ratio (ICER). NICE has adopted several thresholds for ICER values that indicate the likelihood of reimbursement, although more flexible limits are used for life-extending treatments (102). Moreover, the Cancer Drugs Fund (CDF) came into effect in 2011 as a MEA to reimburse promising oncology drugs that are associated with limited clinical evidence. In the CDF, drugs are funded for a fixed period while they await a reimbursement decision by NICE, during which the manufacturer can submit supplementary evidence to proof their effectiveness. The CDF makes use of an expenditure control mechanism with a fixed budget of £340 million; in the case of an overspent, a proportional rebate is applied to all pharmaceutical companies that have arrangements in the CDF (103,104). Since 2016, more than 73.000 patients have benefited from the 91 CDF-funded therapies treating 205 types of cancer. Of these, 30 have eventually received full approval for routine use after assessment by NICE.

The CDF went through a reform in 2016, as the former system was not managed properly and was considered unsustainable. Before 2016, the fund acted independently from NICE, which caused critics to state that it was undermining and bypassing HTA-informed decision-making. Indeed, research shows that there was a significant decline in NICE's recommendation rate during the former CDF, implying that it provided an alternative access route for expensive drugs (105). However, the CDF became more properly integrated with NICE's evaluation process after the reform, making the two agencies more aligned with each other. Another shortcoming of the former CDF was that it did not mandate healthcare services to collect outcome data of patients who were treated through the fund, making it impossible to assess the impact of the CDF (106). Most of these issues are addressed in the reformed CDF, with successful characteristics of the current policy including clear entry and exit criteria (including mechanisms to terminate coverage), a clear temporary reimbursement period with requirements for evidence generation, integration of the fund in the HTA process, and solely inclusion of products that have a high chance of being cost-effective (46).

Italy: Italy is similar to the Netherlands one of the early adopters of MEAs and is currently even considered the most active practitioner (99). The national HTA agency (AIFA) can decide on three reimbursement decisions, including no reimbursement, unconditional reimbursement, or reimbursement through a MEA. For the latter, several types may be utilized that either manage uncertainties about budget impact, uncertainty in clinical and cost-effectiveness, or appropriate use. Whereas most countries mainly apply financially-based MEAs, Italy primarily makes use of outcome-based MEAs; 46 of the 71 MEAs (65%) that were active in 2019 were outcome-based, of which most had a payment-by-result design (46). An important instrument in the light of these types of MEAs is a national drug-monitoring registry, which has been set up by AIFA to provide an infrastructure to assess patient eligibility, collect utilization data in clinical practice, and collect epidemiological data, aiming to track appropriate use and collect outcome data (103). Although this system has been praised for informing AIFA and other parties on the impact of novel products, it has also resulted in a great administrative burden for healthcare providers (46,107).

Annex 5: Elaborated overview of internal interview results, sorted by theme. PHC = personalized healthcare. List of interview candidates depicted in Table 7.

Huidig zorgsysteem

EBM

- Historisch gezien terecht dat RCT als gouden standaard wordt gezien, heeft wel duidelijk meerwaarde. (i1,i2,i3,i4)
- EBM gericht op populaties, terwijl er steeds meer een shift is naar personalized healthcare. Dat vereist andere manier van beoordelen. (i1,i2,i3,i8)
- Door strenge inclusie en exclusie criteria zijn patiënten uit klinische studies niet per se representatief voor patiënten die je in de praktijk ziet. (i2,i5)

ACCESS BARRIÈRES

Toereikendheid beoordelingskader

- Het gezondheidsniveau in Nederland is op dusdanig niveau dat de winst die we kunnen halen vooral in personalisatie zit, echter loop je daar met de populatiegemiddelde methode waar de RCT en EBM op zijn gebaseerd mee vast. (i1,i8) We zien steeds vaker andere typen studies die voortkomen uit andere types medicijnen, namelijk meer gericht op biomarkers, en zulke studies passen niet in het huidige framework. (i1,i2,i3,i7,i8)
- We zien dat er een versnippering van de populatie gaande is en er steeds meer gefocust wordt op de moleculaire veranderingen die ten grondslag liggen aan een ziekte, maar het vaststellen van SvWP gebeurd op populatieniveau. (i1,i2)
- De uitkomstmaten die horen bij PHC passen niet in het huidige kader. Er wordt bij oncologie nog erg veel vastgehouden aan OS, terwijl patient reported outcomes misschien waardevoller zijn. (i5)
- Bij PHC wordt ook de diagnostiek steeds belangrijker, dat is ook nog een horde in het huidige systeem. (i1)
- De EMA denkt wel mee over nieuwere soorten innovaties en bewijslast, maar lokale payers niet. Dat creëert ongelijkheid tussen landen. (i3,i4)
- Er wordt nu (te) snel gegrepen naar veelbelovende zorg/conditionele vergoeding op het moment dat het meer gepersonaliseerde zorg is. (i1)

One-off systeem

- Wanneer de waarde groter is dan in eerste instantie werd gedacht, is er amper de mogelijkheid om de prijs omhoog aan te passen, terwijl andersom de markt zijn werk doet wanneer een middel minder waarde blijkt te hebben. (i1,i2)
- Door onzekerheid in effectiviteit, krijg je ook onzekerheid of men ervoor wilt betalen. Er wordt vaak gezegd dat er te veel onzekerheid is om voor een geneesmiddel te betalen, maar ons systeem is er wel zo op ingericht dat er direct een prijs wordt vastgesteld (op het moment van de grootste onzekerheid) – geen duurzame samenwerking. (i1,i4,i5)

Horizonscan

- Er wordt input gevraagd aan fabrikanten, welke vervolgens niet (compleet) wordt overgenomen. Horizonscan is dus niet volledig, informatie ontbreekt. (i2)

Sluisprocedure

- Sluisprocedure duurt te lang, tijdslijnen worden onduidelijk berekend; de manier hoe dit gecommuniceerd wordt naar buiten doet geen recht aan de werkelijke tijdslijnen. (i2,i3,i4,i7)
- Er worden soms onrealistische aannames gedaan waarbij van de maximale impact uit wordt gegaan, waardoor er soms producten in de sluis komen die daar niet horen. (i2)

Budget ziekenhuizen

- Zelfs als je access hebt, wil het niet zeggen dat ziekenhuizen voldoende budget hebben om het middel ook daadwerkelijk toe te passen voor patiënten. (i3,i6)

Specifiek beleid rare diseases

- Er is in Nederland geen specifiek beleid voor rare diseases, in tegenstelling tot andere landen. (i1,i4)

Doorvoeren van verbeteringen

- Er is data beschikbaar over hoe de zorg in Nederland efficiënter zou kunnen worden, maar de implementatie gebeurt te traag en te weinig gecentraliseerd, waardoor we terugvallen in oude gewoontes. (i6)

Silo's in de zorg

- De zorg in Nederland is ingericht in silo's van belangen die niet goed op elkaar zijn afgestemd. Leidt tot wantrouwen. (i5,i6)

Diagnostiek

- Nu er meer focus is op personalized healthcare, wordt ook de diagnostiek belangrijker. Dat is op dit moment ook nog een horde/onvoldoende. (i1)

VERANDERINGEN HUIDIG ZORGSYSTEEM

Criterium SvWP

- Het criterium SvWP zou ruimer/anders geïnterpreteerd moeten worden. (i1,i2)

Shift naar PHC

- Voor gepaste zorg moeten we overgaan op personalisatie, waarbij we EBM moeten loslaten en meer moeten kijken op persoonsniveau. Het access framework moet worden aangepast op de nieuwe soorten bewijslast die hierbij horen. (i1,i3,i8)
- Daaraan ligt ten grondslag dat we opnieuw moeten kijken naar de toekomst van EBM. (i1,i5,i8) Shift van evidence based practice naar practice based evidence. (i5)
- Pragmatische blik aanhouden, wanneer een RCT niet nodig/haalbaar is zou er flexibeler omgegaan moeten worden met andere soorten studies. (i3,i4)

Efficientere beoordeling

- Duidelijkere en kortere tijdslijnen (i.e. sluisprocedure) en meer samenwerking tussen pharma/payer. Meer duidelijkheid vooraf over wat er verwacht wordt qua bewijslast. (i4)

Lerend systeem in plaats van one-off

- We moeten toe naar een data-gedreven lerend systeem. (i1,i2,i3,i5,i8)
- Ook nadat de SvWP beslissing is genomen, zouden we door moeten gaan met (real-world) data verzamelen van een medicijn in een bepaalde patiëntengroep. Data monitoring, analyse en bijsturing. (i2,i5)
- Op het moment dat een innovatie een andere plek krijgt in de praktijk dan in eerste instantie werd gedacht, zou daar iets mee gedaan moeten worden. (i1,i2,i3,i5)
- In het huidige systeem kan de prijs maar een kant op aangepast worden, maar prijzen zouden stapsgewijs op moeten kunnen lopen aan de hand van dataverzameling die continu is en die vanuit klinische data overloopt in RWD. (i1,i2,i3,i5)
- Het zou mooi zijn als ons systeem erop ingericht is om te kijken naar historische controles. (i3,i7)
- Shift van volume naar waarde om perverse prikkels weg te nemen. (i6)
- De technische infrastructuur die ten grondslag ligt aan dataverzameling moet robuust zijn en de interoperabiliteit moet goed zijn. (i5)

Rare disease aanpak

- Speciale regulations voor orphan drugs. Begin al vroeg te kijken naar niet alleen de development, maar ook de access kant van rare diseases. (i1,i4)

Uitkomstdefinities helder

- Meer duidelijkheid scheppen over de definities van de uitkomsten waarop te sturen, en meer richting patient reported outcomes. (i2,i5)

Silo's doorbreken

- Silo's doorbreken, zorg beter op elkaar af te stemmen en afkomen van wantrouwen. (i6)
- Meer samenwerking op Europees niveau, maar ook tussen EMA en payers. (i4)

VISIE DRUP/DAP/VT

Goede initiatieven

- Geeft ruimte aan gepersonaliseerde behandeling waarin wordt bekostigd naar waarde en dataverzameling (en het leren hiervan) centraal staat (DRUP en DAP). (i1-i3,i5)
- Het geeft bredere en soms eerdere toegang (DRUP/DAP/VT). (i1,i2,i4)
- Uitgangspunt van de DRUP is behandelen op basis van moleculaire informatie en kijken of producten clinical benefit hebben off-label en tumor-agnostisch behandelen; je gaat veel meer de richting op van systems biology en gepersonaliseerde behandeling. (i1,i2,i8)
- Kan een mooie blauwdruk zijn waarop we verder itereren (DRUP/DAP). (i1-i5,i8)

Slechte opzet

- Patiënten moeten consent geven dat ze een experimenteel middel ondergaan, en in die zin staat het eigenlijk gelijk aan deelnemen aan een studie, op basis van een protocol (DRUP/DAP/VT). (i1,i5)
- De opzet van de DAP is niet duurzaam/efficiënt, er wordt gebruik gemaakt van handgeschreven registers. Zou geprofessionaliseerd moeten worden d.m.v. geautomatiseerde dataverzameling. (i1,i5,i8)
- Data verzameling beperkt, niet het juiste criterium om alleen peer-reviewed data te gebruiken (VT). (i1)

Integratie zorglandschap

- Er is veel onduidelijkheid bij betrokken partijen over hoe de DAP precies werkt; artsen zijn lang niet altijd op de hoogte hoe een patiënt in de DAP komt, welke geneesmiddelen meedoen, en welke centra zijn aangewezen voor de DAP. (i1,i2,i3)
- Het zijn losse initiatieven die niet per se uitzicht hebben op inclusie in het basispakket/registratie (DRUP/DAP/VT). (i1,i8)
- In de DAP is het in principe ook mogelijk om voor EC goedkeuring iets al beschikbaar te stellen, maar in de praktijk werkt dat gewoon niet. (i2)

Kosten

- Het is niet redelijk om bij een middel dat al EMA registratie heeft ook nog lange periodes gratis medicatie te moeten verstrekken. Daar zit een perverse prikkel in om ook met hogere prijzen te starten. (i3)
- De bijdrage van 5000 euro in de DAP is voor kleine farmaceuten niet te betalen, waardoor je ongelijkheid in de markt krijgt. Geen fair market value, en de data is dan niet eens van jezelf. (i1,i8).

Pleister op het huidige systeem

- Je onttrekt eigenlijk alles aan het echte systeem en zet een soort schaduwsysteem op met minimale middelen en minimale efforts. Er kan geen marktwerking optreden, dat kan de betaalbaarheid ook niet ten goede doen. (i1,i3)
- Omdat er zulke mechanismen zijn, wordt er ook sneller naar gegrepen i.p.v. dat het voor de hele patiëntengroep beschikbaar wordt gesteld. De urgentie om de kern van het probleem aan te pakken wordt hierdoor ook minder. (i1,i4,i8)
- Als het internationaal al lastig is om voldoende data te verzamelen, is het binnen Nederland al helemaal moeilijk om genoeg betekenisvolle data te genereren in de DAP waar je een statistische analyse op kan doen. (i4,i8)

Lerend zorgsysteem en PFP model

VISIE LEREND ZORGSYSTEEM en PFP

Positieve punten

Reflecteert waarde

- Lerend systeem reflecteert de waarde die een innovatie daadwerkelijk heeft in de praktijk d.m.v. RWD. Dit is vooral van belang om sterker bewijs naar voren te brengen (andersom reguleert de markt wel). (i1-i3,i5)
- Slechts een klein deel van de ervaring zit in studies. RWD representeert daadwerkelijke patientgroep beter, kan helpen met verdere optimalisatie van behandeling en plaats van de behandeling. (i1,i2)
- Specifiek PFP: solide tumoren goede start omdat relevante uitkomstmaten daar al vrij duidelijk gedefinieerd zijn. (i7)

Prerequisite PHC

- Op individueel niveau toetsen of iets werkt, leren van data en voorspellen welke patiënten wel/geen baat hebben. RWD hierin cruciaal, artsen hoeven niet alleen meer te putten uit eigen ervaring uit de eigen praktijk met eigen patienten, maar uit nationale en liever nog internationale databases waardoor je veel meer kan voorspellen wat de prognose is van een patiënt met vergelijkbare karakteristieken. (i1-i3,i5,i8)

Verduurzaming zorg

- Voorspellen wie wel/geen baat heeft om zo efficiënter te kunnen behandelen, minder overbehandelen, voorkomen waste of resources. (i2,i3)
- In- en uitstroom basispakket is beter te managen, brengt zorgkosten omlaag. (i2)

Bezwaren

Concept

- Het is wankeler voor de industrie, een product kan makkelijker van de markt afgehaald worden en daar moet je je prijs ook weer op aanpassen. Daar zit dus een perverse prikkel in. (i5)
- Vertrouwen in specialistische centra is nodig, daar vinden de metingen plaats waar veel afhangt voor patiënten. (i4)
- Op individueel niveau worden behandelingen gestopt als er onvoldoende effect is, dat legt een bepaalde druk op patiënten. (i4)
- Als ontwikkelingen door elkaar heen gaan lopen (bijvoorbeeld tussentijds nieuwe SoC), dan geeft dat moeilijke situaties omdat je baseline verandert. (i4)

Omgaan met (real-world) data

- Je hebt een centrale/uniforme plek nodig om alle data te verzamelen en samen te brengen tot een nationale infrastructuur. Geen versnipperde registries, de data moet met elkaar kunnen communiceren (FAIR), gecentraliseerd, interoperabiliteit. (i2,i3,i5,i7,i8)
- Capaciteit, je hebt een efficiënte methode/algoritme nodig om de data te kunnen verwerken. (i1) Tevens objectief om fraude te voorkomen. (i4)
- Enkel op nationaal niveau is het niet realistisch om in zo'n korte tijd genoeg (heterogene) data te kunnen verzamelen in een niet-gestandaardiseerde setting en daar vervolgens betekenisvolle conclusies uit te trekken. Idealiter Europees of zelfs wereldwijd. (i4,i6,i7,i8)
- Men moet bereid zijn data te delen. (i3,i7)
- Governance van bovenaf, wie heeft wanneer toegang tot welke data. (i4,i5)
- Het betrekken van RWD past nog niet in ons huidige systeem. Gevoeliger voor bias en confounding, minder goed te interpreteren. Je moet vantevoren helder hebben welke criteria je toepast, bij welke level van certainty je bereid bent stappen te nemen, welke statistiek en methodes je gebruikt; dat is bij RWD veel complexer. (i1,i6)
- We overschatten misschien hoe voorspelbaar de verkregen data gaat zijn om daar grote winsten mee te maken, we moeten onze verwachting over de zeggingskracht van big data en AI wat temperen. (i6) De stap van data naar bruikbare informatie is groot. (i8)
- Privacy moet beschermd worden, hier zijn oplossingen voor maar daar is ook weer heel veel keuze in. (i3,i5)
- Er moet veel geïnvesteerd worden in registries en andere voorzieningen, de vraag is wie daar verantwoordelijk voor moet zijn. (i4)
- EPD is ontstaan voor declaratie doeleinden, we willen nu graag EPD's gebruiken om informatie te verzamelen en te laten communceren met elkaar, maar daar zijn ze niet per se voor ingericht. (i3)

Implementatie

- Past niet goed in ons huidige zorgsysteem/kader. (i1)
- Je moet een afweging maken tussen hyper personalisatie gebaseerd op RWD en decision-making gebaseerd op gegeneraliseerde standaarden en richtlijnen. Je kan niet een advisory board hebben voor elke beslissing van een patiënt. (i7)

<u>VOORWAARDEN PFP</u>

Uitvoerbaarheid

- Weinig administratieve last. (i1,i5)
- Geen handgeschreven registers. (i1)
- Geen ingewikkelde toegangseisen, het moet makkelijk in gebruik zijn voor de arts/apotheker. (i1,i5)
- Niet te ingewikkeld qua structuur (e.g. tussenstadia), misschien wat versimpelen (approval, conditional approval, geen approval). (i8)

Data

- Er moet een centrale en uniforme data infrastructuur zijn. (i2,i5)
- Dataverzameling moet vanuit EPD's solide gebeuren volgens de FAIR principes (Findable – Accessible – Interoperable – Reusable); data moet ontsloten worden. (i1,i2,i4)
- Heldere uitkomstdefinities. (i5)

Concept

- Governance is belangrijk, wie mag toegang tot welke data/wanneer. (i5)
- Gepersonaliseerde vergoeding zou het einddoel moeten zijn. Loskomen van SvWP op populatieniveau, dan is stoppen met vergoeding ook geen issue. (i1,i8)
- Patiënt moet consent geven, want het gaat om zorg die nog niet SvWP is. (i1)
- Uitzicht op reëel businessmodel, het liefst zo snel mogelijk bekostigen vanuit basispakket. Basispakket moet het einddoel zijn. (i1,i2) Vereist garantie van payers, pharma moet ook weten waar die aan toe is. (i4)

Vooraf vastleggen

- Wat gebeurt er met de patiënten op behandeling als er uiteindelijk geen toegang komt. (i4) Maar is geen issue als je gepersonaliseerde vergoeding hebt. (i1,i8)
- Voor zover mogelijk al bepalen waar de onzekerheid zit, hoeveel patiënten je includeert, hoeveel korting je toepast, welke uitkomsten relevant zijn, en hoeveel datapoints je nodig hebt om conclusies te trekken. (i3,i5,i6,i7) Hoe zet je de stap van data naar bruikbare informatie. (i5,i8)
- Garantie van payers zodat pharma weet waar die aan toe is. (i4)

<u>SPECIFIEKE UITDAGINGEN PFP (meer algemene uitdagingen bij "VISIE LEREND ZORGSYSTEEM en PFP")</u>

Bekostiging

- PFP zegt nog niks over wat een middel in een bepaalde indicatie mag kosten, er is een heel ander traject nodig als je een middel hebt waar heel veel patienten voor zijn vs heel weinig. Je kan wel bekostigen naar waarde, maar een middel dat ontwikkeld wordt voor 100 patiënten moet de kosten op een andere manier terugverdienen dan voor 1 miljoen patiënten. (i3)
- Momenteel wordt de prijs van een geneesmiddel vastgesteld op basis van groepsgemiddelden, de trials en de total value, dus inclusief de failures. Door een PFP model zouden alle prijzen drastisch omhoog gaan op het moment dat je alleen een return krijgt op de producten die werken. Je moet dan ook de prijs van een product zetten voor iemand die respondeert. Dus daar zit een perverse prikkel. (i6)
  - Echter, de korting die je geeft moet gezien worden als een prijs die je betaald om minder klinische onzekerheid te krijgen. Dus dat is wel gerechtvaardigd, (i7)
- Het is makkelijk om je prijs naar beneden te brengen, maar lastiger om hem naar boven aan te passen. Als je start met een X% discount, neemt de payer aan dat het voor die prijs kan blijven. Dus wellicht beter om te beginnen zonder korting, en dan achteraf clawbacks op basis van hoeveel onzekerheid er nog is. Ook kan je achteraf beter bepalen welke onzekerheden bijv. zijn opgelost, en welke discount daar dan tegenover mag staan.
  - Daarnaast zal anders elk moment waarop je de korting aanpast een onderhandeling worden, wat ook weer tijd kost. (i7)
  - Een hoge startprijs is ook belangrijk om incentives van payer en pharma op elkaar af te stemmen om zo snel mogelijk de data te verzamelen om de onzekerheid aan te pakken. (i7)
- Double discounting; bestaande onderhandelingsprocessen (die zijn gebaseerd op assessments/QALYs) brengen de prijs al naar beneden, en als je dan daarop je korting toepast die gebaseerd is op klinische uitkomsten of RWD, dan tel je dat twee keer mee omdat die eerste onderhandeling op dezelfde uitkomsten is gebaseerd. (i7)
- Hoeveel korting wordt er dan precies gegeven, en wie beslist dat. (i4)

Vereist maatwerk

- Idealiter maak je een loop, maar je moet gaan tailoren op elk medicijn; patiëntenaantallen verschillen per middel, je moet verschillende data-cut offs hanteren. (i2,i4,i5) De 16 weken periode vanuit de DRUP ook misschien niet geschikt voor elk traject. (i7)

Data

- Solide en uniforme data-infrastructuur nodig, idealiter Europees/globaal *(zie "uitdagingen lerend zorgsysteem/PFP")*
- We hebben weinig ervaring met betrekken van RWD ("*zie uitdagingen lerend zorgsysteem/PFP"*); het koppelen van evidence aan reimbursement decisions is lastig en misschien een stap te ver. (i6,i7)

Betrekken stakeholders

- Alle betrokken partijen moeten ervoor open staan en alle neuzen dezelfde kant op wijzen. Dat gaat tijd kosten. (i2,i4)
- Het kan zijn dat de payer/pharma spijt heeft van deelname, e.g. pharma company heeft geld misgelopen, payer niet genoeg benefit gekregen. (i7)

Design

- Lastig om al beginnen met geld te krijgen voordat je EMA registratie hebt, dus voordat de afweging is gemaakt of een middel veilig is en de veiligheid/werkzaamheid tegen elkaar opwegen. (i6)
- Sommige geneesmiddelen slaan een deukje in een pak boter, en sommige enorme deuken. Daar differentieert dit nu nog niet tussen. (i6)
- Bij het koppelen van evidence aan reimbursement decisions en het rationaliseren van keuzes schiet vaak de dataset, statistiek en opzet tekort om daar iets mee te doen, dus dan is het meer schijnzekerheid. (i6)

Praktische implementatie en uitvoering

- Het past lastig in de praktijk en onze (huidige) manier van werken. (i1)
- Iedereen vind het allemaal complex en kijkt vooral naar zijn eigen domein, dat we soms vergeten dat iedereen hier baat bij heeft. Misschien een soort taskforce oprichten en dan samen vanuit een clean sheet beginnen. (i3)
- Als men eenmaal toegang geeft, kan je vaak moeilijk stoppen. Juist daarom is die personalisatie van vergoeding zo belangrijk. (i1)

Annex 6: Elaborated overview of external interview results, sorted by theme. PHC = personalized healthcare. List of interview candidates depicted in Table 7.

Voordelen PFP model

Goed concept

- Gestructureerd kijken wat de onzekerheden zijn en die aanpakken d.m.v. een model. (i9,i13,i14)
- De huidige manier van geneesmiddelenvergoeding loopt tegen zijn grenzen aan; het is goed dat dit soort initiatieven verschijnen. (i9,i11,i15)
- Gepersonaliseerde vergoeding en bepalen van SvWP op individueel niveau (i10,i15)
- Interessant dat het al voor EMA approval van toepassing is. (i11,i12,i15)
- Door het plaatsen van het model in het gereguleerde proces, is de administratieve last waarschijnlijk minder dan bij andere modellen. Robuuste milestones. (i11,i13,i14)
- Fair dat een prijs ook omhoog mag gaan op basis van praktijkervaring. (i11)
- Logisch concept dat de prijs het bewijs volgt. (i12)
- Goed geniched voor solide tumoren en line extensions. (i13,i14)

Impact

- Stimulans voor farma om risky producten te ontwikkelen met high unmet need. (i11)
- De performance-based vergoeding laat zien dat je als fabrikant gelooft in je eigen middel. (i13)
- Meerwaarde voor patiënten, eerder toegang en inzicht krijgen in de werking van geneesmiddelen in subpopulaties (i11,i15)
- Data-gedreven systeem is key om de zorg beter te maken en duurzaam te houden. (i9)

Uitdagingen en limitaties PFP model

Design

- Elk geneesmiddel moet waarschijnlijk een eigen traject doorgaan, dus lastig om alles vooraf al vast te leggen. Maatwerk nodig. (i10)
- Het definiëren van uitkomsten en bepalen wanneer je iets voldoende vindt om verder te gaan is lastig. (i11,i12)

Data

- Je begint vergoedingsonderhandeling al voordat je EMA registratie hebt, waardoor je dus nog minder data/zekerheid hebt. (i9)
- Data uit NL niet voldoende om onzekerheid aan te pakken (i9,i11,i12)
- Grote administratieve last om data te verzamelen en monitoren, grote belasting voor het systeem om bijv. elke 8 weken een beoordeling te doen. Capaciteit is al een probleem in het huidige systeem. (i9,i11)
- De benodigde overhead zou de besparingen die je doet weer teniet kunnen doen. (i9)

Bekostiging

- Welke referentieprijs hanteer je, lastig te bepalen. (i11,i12).
- Een dergelijk model differentieert tussen prijzen voor eenzelfde geneesmiddel; ons systeem is daar niet op ingericht, dat vereist een verandering in onze perceptie van geneesmiddelenprijzen. (i12)
- Hoge kortingen in het begin van het model zouden de indruk kunnen wekken dat de winstmarge heel hoog is. (i13)
- Het verhogen van prijzen (i.e. verlagen kortingen) blijft lastig accepteerbaar, dan moet de rationale daarachter duidelijk zijn. (i14)
- Kortingen non-responders worden op geaggregeerd niveau onderhandeld en via het zorgsysteem teruggegeven aan ziekenhuizen, dus ziekenhuizen zien niet direct iets terug van die kortingen. (i14)
- Hogere lijstprijzen kan perverse prikkel zijn (maar in het geval van line extensions minder relevant). (i11)

Praktische implementatie en uitvoering

- Legal aspecten moeten ook meegenomen worden (hoe contracten gemaakt worden, hoe geldstromen werken, privacy). (i11,i15) Zeker als je voor EMA registratie gaat beginnen. (i12,i13)
- Praktisch implementeren is vaak de grootste barrière van dit soort (goede) initiatieven. Zeker als het nog niet duidelijk is hoeveel het op kan leveren. (i11,i12,i15)

Voorwaarden en suggesties PFP model

Praktische implementatie en uitvoering

- In een vroeg stadium al nadenken over welke data er nodig is om de onzekerheden aan te pakken, wanneer je voldoende data hebt, en wanneer je vervolgstappen neemt. Hoe ga je met bepaalde uitkomsten om. Hierbij met verschillende partijen om tafel gaan (ZIN, zorgverzekeraars, farma, patienten) (i9,i11,i12)
  - Selecteer alleen producten met een hoge kans van slagen, dus waarbij er onzekerheden zijn, maar een grote kans dat die opgelost kunnen worden in een dergelijk model. (i11)
- Het verzamelen van data moet in dienst staan voor verbeterde zorg, niet onnodig data blijven verzamelen om bijv. een andere vergoeding te krijgen. Value of information analyses kunnen nuttig zijn in het beoordelen of additionele dataverzameling van toegevoegde waarde is. (i9)
- Solide en objectieve governance, er moet regie zijn. Die partij moet door iedereen geaccepteerd worden (i11,i15)
- Eventueel gebruik maken van bestaande registers/systemen waar dit in zou kunnen passen. (i11)
- Wanneer je een database aanlegt zou je op een keer zelf een soort vergelijkende arm kunnen modelleren. (i12)

Design

- Kortingsranges zijn nog erg breed, zou je kunnen koppelen aan bepaalde grenswaardes van je uitkomsten. (i13)
- Ook als patiënten stoppen met behandeling door bijwerkingen, zou je een full rebate kunnen hanteren. (i13)
- Voorkom overcompliceren van structuur, dat leidt ook tot meer beslissingen over prijzen/doorstromen. (i9,i10)

Overig

DRUP/DAP

- De DAP levert vaak ook niet de noodzakelijke data die we nodig hebben op aanvulling van klinische studies, de RWD die daar wordt verzameld heeft niet per se toegevoegde waarde. (i12)

- Bij dit soort nationale alternatieven geldt in het algemeen dat het onrealistisch is om te denken dat er in Nederland voldoende data wordt verzameld om de onzekerheid op te lossen, als dat in wereldwijde klinische studies al lastig is. (i9,i12)
- DRUP protocol mooi initiatief. (i14)
- DAP geen goed initiatief, arbeidsintensief, 5000 euro per patient, je krijgt amper een vergoeding. Niet duurzaam. (i14)

Vooruitzichten

- Toepassing op NME's zou een mooi toekomstperspectief zijn, wel een lastigere procedure. Van EMA goedkeuring tot vergoeding heb je niet zulke robuuste milestones. (i14)
- Benieuwd hoe ziekenhuizen en de overheid hierover denken, die houden vaak erg vast aan wat autoriteiten zeggen. (i14)
- Uiteindelijk toe naar een model waarin betaald wordt voor uitkomsten; betere uitkomsten, hogere prijs. Niet meer betalen voor middelen, maar echt uitkomsten. Maar dan spelen ook andere aspecten een rol (persistentie, adherentie, etc). (i14)