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SCIENCE IS THE PRESCRIPTION

WHY SCIENCE MATTERS FOR APPROPRIATE PHARMACEUTICAL CARE

ADVISORY REPORT

Royal Netherlands Academy of Arts and Sciences

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SCIENCE IS THE PRESCRIPTION

WHY SCIENCE MATTERS FOR APPROPRIATE PHARMACEUTICAL CARE

Royal Netherlands Academy of Arts and Sciences
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FOREWORD

We all want to live a long and healthy life, and good healthcare is crucial in that regard. And yet the healthcare system in the Netherlands is under threat. People are living longer, and while this is a positive trend, it also means a rising demand for care and staff shortages. In addition, more and more medical treatments are becoming available, some of which are extremely expensive.

The advisory report *Science is the prescription* shows how science can contribute to sustainable, meaningful, affordable healthcare, grounded in evidence-based pharmaceutical research. The systematic use of scientific research is the key to minimising uncertainty and facilitating better decision-making, both in policy circles and in the consulting room.

Drugs are often registered based on outcome measures that are not always clinically relevant, or on studies involving selected patient groups, leaving the drug's real-world effectiveness unclear.

This report demonstrates that research is essential throughout a drug's life cycle, for example in the form of post-registration trials that examine long-term use by specific patient groups, clinically relevant outcome measures, differences between patient groups, and optimised treatment strategies such as drug dosing regimens.

Such continuous knowledge building makes it possible to use medicines responsibly, lower costs, and make timely adjustments when outcomes fall short of expectations. *Science as a prescription* offers practical guidance to this end and shows how science and healthcare practice can complement each other.

I hope and expect that its recommendations will be broadly adopted by policymakers, healthcare providers, researchers, patient organisations, health insurers, and research funding bodies, both in the Netherlands and abroad, thereby ensuring that the healthcare system meets the needs of today's patients and tomorrow's society.

I would like to thank the members of the advisory committee and all the experts and staff involved for their hard work and dedication.

Marileen Dogterom
Academy President

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SUMMARY

The long-term viability of the healthcare system in the Netherlands, and beyond, is at risk. An ageing population, the growing incidence of chronic diseases, and medical innovations offering ever more treatment options are all driving a rise in the demand for care; at the same time, staff shortages are increasing, supplies of some drugs are limited, costs are rising, and there is growing awareness of the healthcare system's negative impact on the environment. These trends and developments require us to make clear-cut choices, where possible based on evidence, so that we can safeguard the quality of care, and to deploy human and other resources as effectively as possible without compromising other public interests.

It is against this backdrop that an advisory committee appointed by the Royal Netherlands Academy of Arts and Sciences (KNAW) has explored how scientific research[1] can systematically contribute to improving appropriate pharmaceutical care: care that works, is affordable, where possible arranged close to the patient, and based on joint decision-making by the patient and the care provider. The committee's report reveals the indispensable role of scientific research throughout the entire life cycle of a medicine – from bench to bed – in mitigating uncertainty and improving decision-making.

This advisory report builds on previous Academy recommendations and employs case studies drawn from pharmaceutical care to illustrate its points. The committee organised expert meetings to ensure that its analysis had broad support and incorporated practical expertise. The committee notes that the Netherlands is very

1 See the text box on page 12 for a definition of 'scientific research' as it is used in this report.

active in promoting the prudent and thus appropriate use of drugs and can therefore achieve an even greater impact with the support of scientific research.

The committee's main conclusions are as follows:

1. **Better use can be made of scientific research in certain components of the pre-registration phase of drug development, subject to a relevant trial design.** Drug innovations can and should be guided more by public needs. Above and beyond commercial interests, which largely determine which drugs are developed, research findings can help set priorities based on disease burden, unmet medical needs and sustainability. Independent research agendas and research at academic institutions are essential to develop drugs for indications that represent a significant public health burden. Scientific research can also contribute in other ways: by developing innovative methods for conducting relevant and efficient research; by developing and validating relevant biomarkers; by using objective, clinically relevant outcome measures that better reflect what truly matters to patients; and by helping to establish transparent agreements and criteria for evidence quality.

2. **Targeted follow-up research in the post-registration phase of a medicine should boost the 'learning capacity' of the healthcare system, thereby improving patient care and the use of medicines and reducing unnecessary costs and environmental impact.** Even after marketing authorisation, scientific evidence remains crucial. In many cases, drug registration is based on surrogate outcome measures – which are not always clinically relevant – or on studies involving selected patient groups, leaving the drug's real-world effectiveness unclear. Marketing authorisation is regularly granted to drugs that offer limited value to patients compared with other options. Whenever gaps in relevant knowledge are identified immediately after a medicine has been registered, scientific research can help reduce such uncertainties. Targeted, pragmatic post-registration trials – which the pharmaceutical industry often finds less interesting – can then help bridge the gap between efficacy under ideal conditions and real-world effectiveness, known as the 'efficacy-effectiveness gap'. Follow-up research into effectiveness, appropriate use and efficiency offers further opportunities to boost the effectiveness, cost-effectiveness and targeted use of drugs, for example by lowering the dose, extending the dose interval or establishing explicit criteria for commencing treatment and treatment duration. Such adjustments are not only important for improving patient care but can also reduce side effects in patients, lower costs, optimise healthcare staff utilisation, and reduce the burden on the environment. Equally important is understanding which drugs can substitute for others, particularly given the frequent shortages that we are currently experiencing.

3. **Scientific research can be utilised more effectively to ensure that investments are better aligned with public needs.** Science can offer policymakers even greater support in drafting rational policies and establishing productive partnerships for appropriate pharmaceutical care. Doing so will improve the likelihood that investments are more closely aligned with public needs. As public funding of drug research and development entails considerable expenditure for the Netherlands, it is vital that we continue examining whether such investment is aligned with public preferences and whether the country's medicine reimbursement policy stimulates the intended level of innovation, in particular in the private sector.

4. **Scientific evidence is essential for making fair, socially responsible, and sustainable choices.** Solidarity is one of the pillars of the Dutch healthcare system. This means that we must make choices in healthcare, for example whether or not to reimburse certain expensive medicines. Given the prospect of long-term scarcity, making informed decisions of this kind will require policy frameworks that go beyond medical criteria. The humanities and social sciences (including economics, sociology, ethics, and law) can offer valuable knowledge in support of fair, socially responsible, and sustainable choices in healthcare. This will require further research into the underlying rationale and effects of policy and other choices.|

5. **Collaboration is vital.** Many obstacles, including drug shortages, involvement in decision-making on drug registration, the changing pharmaceutical research landscape in Europe, and the need for post-registration research and clinical trials – specifically but not exclusively for rare diseases – require international action and collective efforts. To this end, close cooperation is needed between scientists and relevant parties, including patient and civic organisations, regulators, medical professionals, and, where appropriate, the pharmaceutical industry.

In the report, the Academy makes specific recommendations for each phase of drug development; it also summarises recommendations for specific target groups.

The main recommendations are as follows:

1. **Increase the level of scientific input in the pre-registration phase.** Doing so will help improve trial design and lead to better research outcomes. Science can also ensure that drug development is more closely aligned with public needs and priorities by identifying knowledge gaps and initiating or facilitating relevant research. Scientific research can also contribute by establishing core principles and by applying novel methodologies to improve endpoints and biomarkers in drug development. In addition, research findings can be used to develop strategies for optimising the Netherlands' support for private-sector innovation.

2. **Continue building a Learning Healthcare System for appropriate pharmaceutical care**, with science as a vital component and with the involvement of relevant care stakeholders. Encourage knowledge generation on appropriate pharmaceutical care with a view to improving quality of life, drug affordability, and access to care, and to reducing environmental impact. Targeted follow-up research into the most effective dose and duration of treatment will help optimise care and facilitate cyclical review, ensuring that relevant evidence is available for decision-making.

3. **Define explicit criteria for data exchange**, prioritising patient interests, establishing well-defined research questions and roles, preferably centralising data collection, specifying how stakeholders should collaborate, and minimising the burden on care providers, with the aim of supporting cyclical medication reviews and a Learning Healthcare System, among other objectives. When the authorities are faced with decisions that affect society as a whole – for example, during a pandemic – they must have quick access to sound data on how the disease will impact various vulnerable population groups. International cooperation has added value in this context, especially when dealing with rare diseases.

4. **Harness Dutch and international partnerships to conduct joint (pragmatic) clinical drug trials.** Provided they are well designed, internationally organised, and aligned with EMA, such trials may also lead to new registrations and can be used in Health Technology Assessments of drugs. In addition, by harmonising procedures where possible, delivering outstanding quality, and making even greater use of leading-edge technologies, European researchers and relevant partners will re-establish the European Union as an attractive environment for conducting innovative trials in cooperation with the pharmaceutical industry, thus reversing the downward trend.

5. **Organise meaningful patient and public involvement** during the pre-registration and post-registration phases, for example when prioritising and evaluating trials and drafting and assessing benefit-risk analyses of medicines. Utilise good practices when measuring patient perceptions.

The Academy calls on the Dutch government and relevant parties to join forces in bolstering scientific underpinnings for drug development and pharmaceutical care, and to do more to position the Netherlands as an international standard-bearer in this field. To do this will require making smart choices about when science should contribute and in what manner, how to protect and encourage independent research, and how best to collaborate internationally to avoid fragmentation. Only in this way can the promise of appropriate pharmaceutical care become reality – care that is effective, patient-centred, affordable, and sustainable.

SCIENTIFIC RESEARCH

Scientific research is understood to mean research conducted systematically and based on observable facts and logical reasoning. It is replicable and verifiable, pursues objectivity, and is independent and ethical. Pharmaceutical research is conducted at research institutes, university medical centres, tertiary care hospitals (known in the Netherlands as 'top clinical care hospitals'), universities, and pharmaceutical companies. It may be funded by the public sector, for example by government ministries, the Dutch Research Council (NWO) or the Netherlands Organisation for Health Research and Development (ZonMw), or by private parties such as industry or fundraising organisations. In this report, we use the term 'scientific research' to refer to research conducted at or in collaboration with academic institutions.

1. INTRODUCTION

1.1 Background

Health is a precious commodity, and in times of illness, proper care is essential. Although we assume that everyone in the Netherlands has access to quality healthcare, ensuring its availability is becoming increasingly challenging. The ageing population, growing number of chronic patients, and innovations offering ever more treatment options are driving a rise in the demand for care. These and other factors – growing staff shortages (European Commission, 2010), drug shortages,[2] rising costs and, in some cases, the prohibitive price of new medicines,[3] as well as the environmental footprint of healthcare (Lenzen, 2020; KNAW, 2023) – make it clear that the sector is facing tough choices. Making the right decisions is critical to safeguarding the quality of care and the efficient deployment of human and other resources, without compromising other key public sectors (NZa & Zorginstituut Nederland, 2020; WRR, 2021).

This report focuses on the role that scientific research [4] plays in making appropriate choices in the development and use of pharmaceutical drugs, in order to define the scope of the broad field of 'care'. Given the challenges listed above, there is ample opportunity to improve appropriate pharmaceutical care. It is also an area of

2 https://www.cbg-meb.nl/onderwerpen/medicijninformatie-medicijntekorten.
3 Total healthcare costs under the Health Insurance Act. https://www.zorgcijfersdatabank.nl/.
4 See the text box on page 12 for a definition of the term 'scientific research' as it is used in this report.

healthcare well suited to this type of analysis because it involves a clearly defined and largely monitored system, thanks in part to the European Medicines Agency (EMA) and the Netherlands' National Health Care Institute (Zorginstituut Nederland), both of which assess the effectiveness and added value of new medicines. In addition, Dutch researchers are heavily involved in and have acquired considerable expertise on the safe, effective and efficient use of pharmaceuticals.[5]

Appropriate care

In 2022, the National Health Care Institute and the Dutch Healthcare Authority (NZa) introduced the concept of 'appropriate care', defined as 'care that works, is affordable, where possible arranged close to the patient, and based on joint decision-making by the patient and the care provider' (NZa & Zorginstituut Nederland, 2020). 'Care that works' refers to care that has been shown to be effective. The concept was well received, for example by the Minister of Health, Welfare and Sport, who wrote in 2023: 'In recent years, I have noticed an increase in the number of drugs being registered that offer only limited added value. All the parties involved now need to make choices so that we can manage expenditure and ensure that innovative drugs remain available and affordable for patients. The basic premise here is that patients should receive appropriate care.'[6]

The importance of researching the effectiveness of care and treatment has long been recognised. In 1993, the precursor of the National Health Care Institute, the Health Insurance Council (Ziekenfondsraad), recommended that new, expensive procedures should only be reimbursed in the insured standard healthcare benefit package if research had proven their value (Ziekenfondsraad, 1993). In the 1990s, the Dunning Committee presented a report on reimbursements in times of scarcity that featured the 'Dunning funnel', in which 'proven effectiveness' was one of the four criteria (Commissie Keuzen in de zorg, 1991). With regard to pharmaceutical care, the question is whether a drug in fact represents added value for patients, how it compares with non-treatment or alternative treatments, and what human and other resources it requires. Several different terms are used to describe this concept, most of which have similar meanings, including 'appropriate care', 'value-driven care', 'appropriate use', and 'proper use'.

Pharmaceutical care

Medicines are critical to treating illness. Ideally, the potential benefits of a medicine should be known in advance. After all, both undertreatment and overtreatment are undesirable: medicines have side effects, administering them is time-consuming for

5 See, for example, the findings obtained in a ZonMw programme that has been underway since 2012, i.e., Goed Gebruik Geneesmiddelen (https://www.zonmw-geneesmiddelenmagazines.nl/magazine/tien-jaar-ggg/10-jaar-ggg/).

6 https://open.overheid.nl/documenten/d3581004-1a72-4ace-a995-96de8b8d897d/file.

patients and care providers, and they impact the environment. Drug use, therefore, involves direct and indirect costs, making it vital that we use the available medicines and time resources of medical professionals as effectively as possible. This does not eliminate 'expensive' medicines altogether, but means that they should be administered to individuals for whom they are truly effective (including from a cost perspective) based on patient-relevant outcome measures. The Netherlands is already on the right track in this regard; we spend less money on pharmaceuticals than other, comparable OECD countries,[7] while anticancer drug therapies, for example, are still readily available here.[8] Nevertheless, we face a number of challenges.

Throughout the lengthy process of drug development, the pharmaceutical company must comply with strict regulatory requirements and demonstrate the drug's efficacy and safety across a designated patient population. Despite these precautions, there is often uncertainty when deciding whether to include expensive pharmaceuticals in the insured standard healthcare benefit package. That is the case, for example, if the efficacy is based on a trial using surrogate outcome measures, in the absence of a control group, or in selected populations that are not representative of the Netherlands. The real-world effects may then be disappointing; patients may not see enough benefit from a drug, or side effects may only emerge later on. The effectiveness of a medicine is determined in part by relevant long-term outcomes.

Scientific research can assist in reducing uncertainty at every stage of drug development and use by delivering reliable data that facilitates better decision-making. This report argues that sound, evidence-based knowledge is essential for the appropriate use of pharmaceuticals. It ensures that patients have access to more effective treatments with fewer side effects, and that society as a whole benefits from more affordable care and a robust healthcare system.

1.2 Advisory committee members

The advisory committee appointed by the Academy Board consisted of the following members:

- Liesbeth de Vries (chairperson), professor of Medical Oncology, University Medical Center Groningen

7 OECD Health Statistics 2024. https://www.oecd.org/content/dam/oecd/en/publications/reports/2024/11/health-at-a-glance-europe-2024_bb301b77/b3704e14-en.pdf.

8 One example is in the field of oncology. In the OECD report *Access to oncology medicines in EU and OECD countries* (Hofmarcher, 2024), Figure 3.5 shows that, in a sample of indications of cancer medicines with the highest clinical benefit in treating breast and lung cancer, the Netherlands covers/reimburses 92% of the indications in the sample, and the time from EMA marketing authorisation to coverage of cancer medicines is relatively fast.

- Jako Burgers, general practitioner and endowed professor of 'Personalised Care in Clinical Practice Guidelines', Maastricht University and Dutch College of General Practitioners (NHG)
- Marleen Kemper, hospital pharmacist and clinical pharmacologist, Apotheek A15
- Xander Koolman, professor of Health Economics, Vrije Universiteit Amsterdam
- Rob van Marum, endowed professor of Geriatric Pharmacotherapy, Amsterdam University Medical Centre; clinical pharmacologist and clinical geriatrician, Jeroen Bosch Ziekenhuis
- Sjoerd Repping, professor of Sensible Care, Amsterdam University Medical Centre; chair of the Care Evaluation and Appropriate Use (ZE&GG) programme; chair of the Appropriate Use of Expensive Medicines working group, part of the National Consultation on Expensive Medicines (LODG)
- Ghislaine van Thiel, associate professor of Medical Ethics, Utrecht University Medical Centre
- Christiaan Vinkers, professor of Stress and Resilience at Amsterdam University Medical Centre, and psychiatrist at inGeest Mental Health care
- Adriaan Voors, professor of Cardiology, University Medical Center Groningen

The committee was assisted by: Eva Naninck and Maartje Aukes (Academy Bureau).

1.3 Approach and methods

The Academy Board asked the committee (see Annex 1, 'Resolution establishing the committee') to identify issues in the current Dutch healthcare system, using pharmaceutical drugs as an example, and to assess how science can contribute to a 'Learning Healthcare System' that uses clinical data to generate a steady stream of new findings on which to base medical decision-making.

The committee completed its assignment by identifying opportunities, obstacles, and critical decision points for appropriate pharmaceutical care. These are described in Chapter 2. The committee has taken the life cycle of a drug as its guideline, from initial development to registration and through to everyday use. Its aim in doing so has been to identify, in each phase, the opportunities, obstacles, and decision points where the scientific underpinnings for appropriate pharmaceutical care can and must be improved. Chapter 3 looks more closely at the challenges and contingencies involved in ensuring that scientific research can collect and deliver the necessary evidence in a manner that a 'Learning Healthcare System' can utilise and apply. The concluding chapter summarises the suggested improvements and makes recommendations to the relevant parties.

This report builds on existing analyses and recommendations regarding pharmaceutical care and offers new, complementary insights. The approach pursued here can be extended to other areas of healthcare.

The Academy previously issued an advisory report on how science can foster efficiency gains in drug discovery research, development, and access without compromising quality and safety (KNAW, 2021).That report led in part to the establishment of the Centre for Future Affordable Sustainable Therapy Development (FAST) as a national centre of expertise and collaboration. The present report makes recommendations that echo those in the previous report, for example, timely dialogue between scientists and regulators. Whereas the previous report focused on efficiency gains in drug development, the present report delves into the appropriate use of new and existing pharmaceuticals.

In preparing this report, the committee consulted the literature and a significant number of experts (see Annex 2, 'List of individuals consulted'). In addition to its regular meetings, the committee organised four expert meetings in order to gain a better understanding of the following four questions, answers to which can be found at various points in the report:

I. When can and should scientific evidence be used to provide meaningful guidance during the life cycle of a drug?
II. What methodological obstacles arise in the assessment of pharmaceuticals?
III. Where and how can scientific research support decision-making and policy, with a view to serving the public interest vested in appropriate pharmaceutical care?
IV. How can patients play a role in making scientific research more meaningful for appropriate care?

The committee also paid working visits to the European Medicines Agency (EMA) through its Regulatory Science and Academia workstream and Innovation Task Force, the Pharmaceuticals and Medical Technology Department of the Dutch Ministry of Health, Welfare and Sport, and the Committee on Societally Acceptable Expenditure on Medicines (MAUG). The committee is very grateful to all the experts for their valuable input during these meetings.

The draft report was finalised after review by external parties (see Annex 3) and the Academy's advisory councils. The reviewers' comments and suggestions were gratefully received and have been incorporated into the final draft.

2. RELEVANCE OF SCIENTIFIC RESEARCH THROUGHOUT A DRUG'S LIFE CYCLE

A prescription for a medicine is the result of a long process involving a whole series of steps: the medicine has been developed, its efficacy and safety have been tested, the application for registration has been reviewed by regulatory authorities, a decision has been taken on reimbursement, and medical guidelines have often been drawn up describing who should use the medicine, when and how. If we examine the drug life cycle systematically – from initial concept until the drug's withdrawal from the market or its long-term use – we see that there are important decision points at each stage that do or could benefit from the collection and use of scientific evidence.

This chapter includes a section on the pre-registration phase, i.e. prior to approval by EMA or the Netherlands' Medicines Evaluation Board, and on the post-registration phase, i.e. after approval, as shown in Figure 1. For each phase, we describe the most important opportunities, obstacles, and decision points, and explain how research findings can lead to improvements. We start with a brief description of the various life cycle phases.

2.1 The life cycle of a medicine

Research and development
Research institutes, university medical centres, universities, and pharmaceutical companies play an important role in drug development. The first phase involves determining whether a medicine will be developed at all and for which disorder. This is largely a decision taken by the pharmaceutical industry, with academic institutions playing a lesser role.

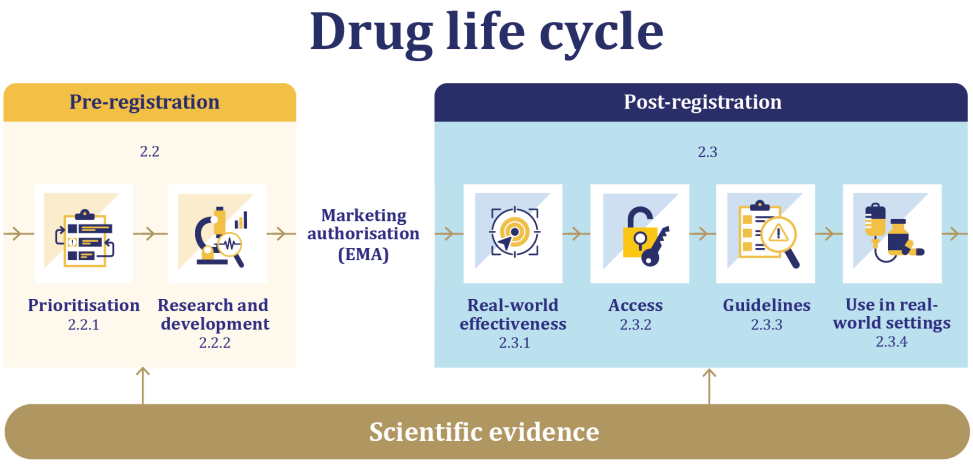

Figure 1. Decision points in the life cycle of a medicine at which scientific research can support appropriate pharmaceutical care (citing the relevant section of this report).

Drug registration

Once a drug has shown promise in pre-clinical and clinical trials, an authorised party applies for registration. In the European Union, it is EMA that manages the first step in the registration process. The party that wishes to market the drug, usually a pharmaceutical company, delivers the scientific data to EMA and therefore identifies the indication for which the drug will be prescribed, as well as the dose and duration of treatment.

Based on the available data, EMA assesses the quality of the drug and whether its effects/efficacy outweigh its side effects and risks. If its 'benefit-risk ratio' is judged to be positive, then registration of the drug proceeds. Such decisions are usually taken centrally in the EU by EMA's Committee for Medicinal Products for Human Use (CHMP) and therefore apply to all Member States. Only rarely does the Netherlands approve and register a drug decentrally through its own Medicines Evaluation Board.

National marketing authorisation

After authorisation has been granted to sell a drug in the European Union, the individual Member States in turn assess its clinical benefits and the associated economic, ethical, and organisational issues to determine which drugs do or do not qualify for reimbursement under the insured standard healthcare benefit package, partly by means of a health technology assessment (HTA). This assessment involves comparing the drug's effectiveness (and cost-effectiveness) with that of existing treatments. In the Netherlands, it is the Minister of Health, Welfare and Sport who decides whether a pharmaceutical is eligible for reimbursement. Under the Dutch Health Insurance Act, care may only be covered under the insured standard package if it meets the 'established medical science and medical practice' criterion.

In other words, there must be sufficient evidence that the healthcare interventions concerned are effective (Zorginstituut Nederland, 2023). The minister takes advice from the National Health Care Institute, which in turn is advised by two independent committees, the Scientific Advisory Board (WAR) and the Insured Package Advisory Committee (ACP). When considering their recommendations, these committees consult medical science associations and patients, both for their expert knowledge and for advice on practical implementation.

The Dutch reimbursement system offers various pathways for including drugs in the insured standard healthcare benefit package. Outpatient medicines available through public pharmacies are covered by the Medicine Reimbursement System (GVS). A different pathway applies for inpatient or hospital pharmaceuticals, used in specialist medical care. They may be made available immediately or they may first have to go through what is known as the 'lock procedure'. In that case, the costs associated with the drug must be shown to be reasonable, given its efficacy. The Minister of Health, Welfare and Sport can then negotiate the price and procurement volume with the pharmaceutical company. The ministry recently published a new leaflet explaining the various steps and decisions involved in admitting medicines to the market.[9]

The gradual rollout of the EU Health Technology Assessment (EU HTA, Regulation 2021/2282) has meant that, since 1 January 2025, EU Member States have been preparing Joint Clinical Assessments for new oncological treatments and Advanced Therapy Medicinal Products (ATMPs), i.e. somatic cell therapy, gene therapy, and tissue-engineered medicines. Previously, EU Member States largely performed these assessments separately. There will now be a single, harmonised clinical assessment comparing the efficacy and safety of a new drug or medical technology with the available standard care. The assessment does not consider economic, ethical, organisational, social, environmental, or legal issues. These are factors that the individual Member States will continue to assess themselves when deciding which drugs are or are not eligible for reimbursement.

From market admission to the end of the life cycle

Once a medicine becomes available to patients in the Netherlands, the relevant professional groups often develop user guidelines for it. Under recent Dutch legislation, i.e. the Healthcare Quality, Complaints and Disputes Act, care providers are bound by what is referred to as 'the professional standard', which includes guidelines. The national government supports the funding of guideline development and review, given the key role that guidelines play in the law and regulations.

9 https://www.tweedekamer.nl/kamerstukken/brieven_regering/detail?id=2024Z21509&did=2024D50793.

The average life cycle of a medicine varies greatly but is roughly ten to thirty years. A patent for a drug is valid for twenty years from the date the patent application is filed. Owing to the lengthy development period, this often gives the manufacturer some eight to twelve years to market the product exclusively. Once their patent expires, medicines may become available as generic drugs or, in the case of biologics, as biosimilars. Both are generally offered at a lower price and can help reduce costs significantly within the reimbursement system.

The life cycle of a medicine ends when the marketing authorisation holder (the formal owner) withdraws the marketing authorisation for its product and ceases supplying it. If the product still enjoys market protection (for example under a patent), the active pharmaceutical ingredient (API) will no longer be marketed. If the drug patent has already expired and there are generic versions available, the impact is limited and the molecule remains available. In addition, the National Health Care Institute may recommend that a medicine be off-listed. The medicine may still satisfy generic requirements, but there are reasons for advising the minister to exclude it from reimbursement. Social considerations usually play a role here, for example with regard to the clinical effectiveness, cost-effectiveness, necessity, or feasibility of the therapy, and, going forward, its potential environmental impact.

2.2 Drug discovery and development

Many questions arise in the pre-registration phase of a medicine that we can divide into two categories:

1. Prioritisation: which medicines are being developed for which indications?
2. Research and development.

2.2.1 Prioritisation: which medicines are being developed for which indications?

Questions that arise before drug development and research include: Which drugs need to be developed? Who or what will decide this, and for which indication? Should we focus on drugs that treat disorders with a large disease burden or disorders for which no other therapy is available? Should the focus be on drugs with the greatest potential to reduce the disease burden, or on drugs with commercial potential? And to what extent does scientific knowledge play a role in the decision which medicines are (or should be) developed? Which drugs do we truly need?

The opportunities, obstacles, and decision points that scientific research can and should address in this phase concern better prioritisation of drug development based on the principles of appropriate care: care that works, is affordable, and, where

possible, arranged close to the patient, and based on joint decision-making by the patient and the care provider. Both public health needs and private investment play a role here. We explain below.

Public health needs

Scientific evidence is indispensable in determining which public health needs should be prioritised or receive greater attention in drug development. The aim is to understand the burden of disease and unmet medical needs, but also the causes of existing health disparities, the environmental impact of medicines and their development (more details in section 2.3.4), and the necessary investment in drug research and development (R&D). A drug that treats a common illness helps many people, while one that treats a serious disease may well represent the difference between life and death. Medicines designed for small, specific populations, such as children, warrant attention. New technologies can also assist in the development of some drugs, for example the CRISPR-based gene-editing therapy (Clustered Regularly Interspaced Short Palindromic Repeats), approved by the FDA and EMA for sickle cell disease, which reactivates healthy haemoglobin production.

One significant public health need is the 'unmet medical need' (see an example in Box 1). This refers to a situation in which treatment options for patients with a particular disorder or symptom are limited or non-existent. The public health perspective would then attach greater importance to developing a new therapy. Scientific research can identify this need, but that does not automatically lead to the development of appropriate pharmaceutical care. On the other hand, there is a risk that the term will be used too freely, to justify reimbursement for treatments that offer minimal or unproven added value for patients. To provide more guidance in this complex landscape, the EU (European Commission, 2025) is working on a new definition of 'unmet medical need' in its reform of pharmaceutical legislation. Specifically in the case of orphan drugs – i.e. medicines designed to treat rare diseases affecting a small patient population and therefore unlikely to be developed by pharmaceutical companies – it has defined the term 'high unmet medical need' to encourage the development of innovative drugs in these underserved disease areas.

Both public-sector and private-sector investment is needed to encourage drug development. Pharmaceutical companies decide whether or not to develop or refine a new drug largely on the basis of its projected financial return and commercial potential (SiRM, L.E.K. Consulting, RAND Europe, 2022). Their commercial interests do not always align with the public health need for new medicines, however (see Box 2 for examples).

The Dutch Ministry of Health, Welfare and Sport commissioned a study to identify gaps in drug development and their underlying causes.[10] Alongside a lack of commercial potential, other factors also play a role, such as the latest scientific advances, the availability of trial populations, and the quality of the collaborative infrastructure between the parties involved. Which factor weighs heaviest varies from one disease to the next.

Scientific research is indispensable in setting priorities in drug development because it identifies knowledge gaps and in initiating or facilitating relevant research. Independent research into issues of public interest that investors fail to address merits particular attention. In addition, scientific research lends support by identifying underlying principles and developing better methods of prioritisation in drug development. Such research can be facilitated by drawing up research agendas or by establishing targeted research programmes.

Private-sector investment

Private-sector investors play an important role in scaling up and accelerating the development of new drugs. Unlike national governments, private parties can turn a global profit if their drug development programmes are successful. As a result, they are in a better position to attract venture capital to finance their R&D. Private-sector parties are more likely to invest in R&D if the risks associated with ongoing research into an API can be reduced.

Major pharmaceutical companies can earn high returns on average. This raises questions, as it suggests that investors may avoid developing certain drugs with potential benefits for society because they deem the financial return on these products insufficient. However, the most plausible explanation for underinvestment is the sector-wide uncertainty about the financial returns. Although there are several reasons for this uncertainty, unpredictable behaviour on the part of governments amplifies the risks. One important question is how much of a financial return an investor can expect (see Box 2).

Government can introduce market protection measures to stimulate private-sector investment in R&D; without such measures, the relevant drug prices would fall by more than 95%. If we consider how expenditure breaks down across groups of medicines that do and do not enjoy market protection, we see that market protection costs Dutch society an estimated five billion euros per year and more.[11] It is therefore

10 https://www.rijksoverheid.nl/documenten/rapporten/2023/08/17/kwalitatieve-verdieping-hiaten-geneesmiddelenontwikkeling.

11 https://www.farmacotherapeutischkompas.nl/algemeen/kosten and https://www.tweedekamer.nl/kamerstukken/brieven_regering/detail?id=2025D40668&did=2025D40668.

in the public interest for the Dutch government to develop a strategic vision and policy regarding such expenditure. On the other hand, the Dutch market for pharmaceuticals with market protection accounts for only around 1% of the global market. Any change in the Netherlands' policy will have little impact on worldwide investment. Another issue is that international conventions allow the Dutch government very little scope to deviate from other countries' market protection policies. A sound strategic vision based in part on scientific evidence will support the Dutch government in international collaboration, allowing it to adapt incentives so that private-sector investment aligns more closely with public health needs.

One area that requires government intervention is the development of orphan drugs for rare and serious diseases. Private-sector investors are often reluctant to develop these drugs, even if they come with a very high price tag. Their development therefore depends in part on whether governments and insurers are willing to pay for them. In addition, the authorities have the option of reducing investor risk, for example by bearing part of the financial risk, guaranteeing long-term market exclusivity, or relaxing the requirements imposed on development. One example is EU Regulation (EC) No. 141/2000 on orphan medicinal products. When a novel drug has been granted 'orphan designation' under the Regulation, the manufacturer is guaranteed a monopoly period of at least ten years after marketing authorisation. This incentive has led to the market launch of only a small number of registered medicines with orphan designation, however.[12] In fact, incentives of this kind can be counterproductive, for example if they unintentionally encourage commercially motivated parties to exploit or capitalise on them (Van den Berg, 2021).

All this explains why it is important to review the implications of the Netherlands' current policy. For the Netherlands to play a role in incentivising innovation worldwide, that policy must be viewed in an international context. Doing so will help navigate the conflict between the pursuit of profit with best-selling medicines – including 'blockbusters' that generate at least USD 1 billion in annual sales – and policies that are specifically designed to combat rare diseases. These two options represent different schools of thought in ethics: the first is consistent with a utilitarian perspective, focused on maximising wellbeing and happiness in absolute terms, while the second aligns with ethical approaches that offer other interpretations of compassion and fairness, and seek to care for small groups of patients even if doing so is not economically advantageous.

> *Scientific findings that can help encourage private-sector investment in publicly beneficial drug development have their origins in economics research into the effect of various incentives in the market for innovations. To ensure the development*

12 See: https://health.ec.europa.eu/medicinal-products/medicines-children/evaluation-medicines-rare-diseases-and-children-legislation.

of drugs that meet public health needs, we need to understand what rewards or incentives encourage capital providers to invest in certain novel therapies or drugs, for example vaccines, but not in others. It is important to know whether the Netherlands' medicine reimbursement system does an adequate job of encouraging the desired level of innovation, for example by means of market protection and other policies that affect costs, and whether measures designed to promote drugs without commercial potential are truly effective.

Value of information

Governments have strict rules regarding the evidence that pharmaceutical companies must provide prior to marketing authorisation or inclusion in the insured standard healthcare benefit package. These rules increase the cost of developing novel drugs and therefore act as a discouragement. The effect of such higher costs depends on the type of drug, for example, a potential 'blockbuster' drug versus one that has only a limited market.

The rules governing burden of proof are obviously very strict, given the possible serious consequences for public health, but also owing to the significant financial interests at stake – interests that can encourage unethical behaviour. The media have, in fact, reported several cases where pharmaceutical companies acted unethically and unlawfully, reinforcing this impression. The strict burden of proof rules come at a price, however: they create tough financial barriers for parties that do not have major financial interests. Examples include academic research into lower doses, tapering schedules, and the repurposing of drugs initially developed to treat other conditions.[13]

The authorities are therefore careful to investigate and consider the level of evidence required and what impact this will have on the incentive to innovate. Value of information (VOI) analysis is crucial in this context; it examines the rational prioritisation of research funding and policies and estimates the expected gain from reducing risks or uncertainties in decision-making.

Scientific research can assist in rationalising government burden of proof requirements, for example with regard to repurposing medicines, and in this way help to optimise incentives for research and innovation. One way to do this is to weigh the quality of a pharmaceutical dossier against the impact of its cost on innovation. This approach can also encourage research concepts emanating from academic institutions that can be investigated at minimal cost but are not considered worth pursuing owing to government requirements.

13 See, for example, the report by FAST on drug repurposing as a fast route to affordable new therapies (FAST, 2023).

BOX 1. UNMET MEDICAL NEEDS

An unmet medical need may affect large groups of patients. One example is Treatment-Resistant Depression (TRD). Some 800,000 people in the Netherlands experience depression every year (annual prevalence).[14] There are effective and well-researched treatments available for patients with TRD, including psychotherapy, antidepressants, and neuromodulation, for example repetitive Transcranial Magnetic Stimulation (rTMS) and Electroconvulsive Therapy (ECT). Yet there are still many patients who derive little benefit from these standard therapies and who often suffer recurrent episodes of depression. Psychedelics such as ketamine and esketamine have recently been added to the therapeutic arsenal for depression, but their precise classification and long-term effectiveness remain unclear (Kishon, 2024). There is also a major medical demand for innovative and effective treatments for depression, and we still have an inadequate understanding of which persons respond extremely well to antidepressants and which derive little benefit from them (Stone, 2022).

BOX 2. WHAT IS THE ANTICIPATED RETURN ON INVESTMENT?

In emergencies, it is important to have a new antibiotic on hand to treat dangerous bacterial infections. Such a drug is of greatest value when it is not used, because the bacteria will not develop resistance to it then. This means investing in the antibiotic's development and perhaps stockpiling it without having a predictable use for it, making its development commercially uninteresting. There is a similar situation with respect to antibodies for patients infected with the Ebola virus. These medicines need to be available in the event of a widespread outbreak.

If society wants such medicines to be available, and if we expect private parties to invest in them, then we must offer them an incentive to do so. The Dutch government has the option of developing policies that create market conditions conducive to R&D investment in publicly beneficial medicines. The results of realist evaluation research can support such policymaking. The Netherlands will need to partner with other countries in this context, given that private parties operate globally to access a large enough market.

14 https://www.trimbos.nl/kennis/cijfers/depressie/.

2.2.2 Research and development

The phase prior to marketing authorisation, the pre-registration phase, mainly involves research and development. Because EMA assesses the efficacy and safety of medicines during the registration process, the focus in this phase is on demonstrating a favourable benefit-risk ratio.

Opportunities, obstacles, and decision points where scientific research can and should play a role in this phase concern methodology, the quality of evidence, the use of objective clinically relevant outcome measures, measures of patient experience, optimised collaboration between regulators, academic institutions, medical professionals, and industry, and the understanding and use of biomarkers. Below, we explain how scientific research can be useful in all of these areas. The Academy has previously described the challenges posed in the preclinical phase and how scientific research can contribute throughout the development chain to streamline drug development (KNAW, 2021).

Quality of evidence

To ensure that the R&D phase goes smoothly, firm agreements and well-defined boundary conditions regarding the quality of evidence are essential. Quality of evidence refers to the research methodology used, preferably a randomised controlled trial (RCT), a double-blind trial design, the timing of follow-up measurements, and clinically relevant outcome measures.

To demonstrate that a substance is effective, its health benefits must be examined. In other words, what is the trial's outcome measure, and how are the side effects being examined? There are 'hard', patient-relevant outcome measures and surrogate outcome measures. The first involves determining whether patients will benefit from the medicine in real-world situations, or what health gains can be achieved among patients. Examples of hard outcome measures include survival rates, i.e. how many people being treated for a specific indication are still alive after a specified amount of time, their quality of life, their ability to function physically, mentally, and socially, and their subjective evaluation of these dimensions.

Surrogate outcome measures are used as a substitute for hard outcome measures. Examples include blood pressure, cholesterol and HbA1c levels (blood glucose levels), or tumour size. High readings are risk factors, but do not necessarily cause symptoms. Surrogate outcome measures are assumed to be associated with clinical outcomes, but a significant effect on a surrogate outcome measure may not be clinically relevant. Just because an anticancer drug has a significant effect on tumour size does not mean that it will extend patient survival time (Schuller, 2018). But measuring tumour size instead of survival rate allows the drug to be registered sooner because it reduces the trial time period. Registration-enabling

trials, therefore, tend to opt for indirect, surrogate outcome measures of health gains rather than hard, clinically relevant outcomes (Brinkhuis, 2024). Although surrogates provide valuable information, explicit and relevant outcome measures are preferable where possible. The timing of the measurements matters as well. Sometimes trials only study the outcomes for a short period of time, or they lack data on quality of life, making it difficult to assess the added value of an existing or novel medicine.

In short, surrogate outcome measures are 1) not necessarily relevant for patients and 2) lead us to accept greater uncertainty than we would when investigating a drug's actual effects. The identification and validation of outcome measures have broad relevance for appropriate use, well beyond the phase prior to the reimbursement decision. However, the uncertainty associated with surrogate outcome measures complicates HTA-based and other decisions regarding a medicine's eligibility for reimbursement (see also section 2.3.1). This uncertainty should be brought to the attention of regulators at the international level, for example by advocating conditional or cyclical review. Under the EU's reformed pharmaceutical legislation, it is also likely that *not-for-profit* organisations in the European Union will be able to submit dossiers to EMA and thus influence choices.

Scientific research is indispensable for the development of innovative methodologies and trial designs that underpin research of the highest relevance and efficiency, and for laying down firm agreements and well-defined boundary conditions for the quality of evidence. In part, this involves drawing up and validating clinically relevant outcome measures in the phase prior to marketing authorisation for inclusion in the dossier. To do this requires an understanding of relevant outcome measures and how they can be used to optimal effect.

Patient perception and involvement

Patient and public involvement is essential to meeting the social challenge of delivering appropriate care. Patient and public involvement throughout the process, from drug development to policymaking, enhances the relevance, quality, and impact of scientific research.

There is growing support for giving patients, as the end users of medicines, a say in research that will ultimately affect their life (Groot, 2022). Relevance and impact improve when patients and the public are actively involved, for example, because patients and their loved ones can offer a unique insider's perspective on how it is to live with and manage their illness, and because members of the public can contribute valuable practical knowledge and experience. Patient input is crucial to establishing which outcome measures are relevant for them and what is needed to make research feasible. Regardless of the phase, however, it appears that research is not always patient-centred and is unnecessarily burdensome at times, or that patients feel it

does not dig deep enough to answer the relevant question. That is why in research evaluations and in preparing and assessing drug benefit-risk analyses, for example, researchers must utilise good practices when measuring patient perceptions and involvement.

Patients can help identify research priorities and outcome measures that reflect their daily reality, such as being able to live independently for as long as possible. This will ensure that research findings are transferred to clinical practice more effectively, and that patient involvement goes to promote policy measures addressing their actual needs. It also reinforces the ethical foundations of science. It recognises patients as equal partners and promotes transparency in research and trust between researchers and the public. Meaningful patient involvement requires collaboration at an early stage of research, with each side's input being taken seriously by the other.

Meaningful patient and public involvement is also required when drafting research agendas that address public needs. There are a growing number of studies considering how best to do this (Cavers, 2020; Rathenau Instituut, 2024). The European Patients' Academy on Therapeutic Innovation (EUPATI) and – on national level – INVOLV are among the organisations engaged in promoting patient involvement in the Netherlands, for example by training patients to become patient representatives. It is important to note that these organisations are not affiliated with industry. Numerous other patient organisations are sponsored by the pharmaceutical industry, however, potentially compromising the impartiality of their views.

In addition to training programmes, there are opinions, reports, and manuals that consider how best to design meaningful patient involvement. For example, EUPATI publishes guidance documents intended to support patient involvement throughout the entire process of drug research and development.

Measures of patient symptoms and perceptions, such as quality of life, are the basis for developing patient-reported outcome measures (PROMs) and patient-reported experience measures (PREMs). It appears, however, that PROMs and PREMs are factored into marketing authorisation decisions in less than half of all cases, mainly because of missing information, and that clinical trials tend to include them only as secondary or exploratory outcome measures (Meregaglia, 2023). The use of PROMs is considered essential in EMA's regulatory science strategy to 2025.[15]

15 https://www.ema.europa.eu/en/documents/report/european-union-medicines-agencies-network-strategy-2025-protecting-public-health-time-rapid-change_en.pdf and https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/ema-regulatory-science-2025-strategic-reflection_en.pdf.

Scientific research findings ensure the development of reliable and relevant methods for measuring patient perceptions, including PROMs and PREMs. Scientific evidence is also important for identifying and prioritising relevant outcome measures, such as symptom reduction and quality of life, ensuring that drug development better meets patient needs. Researchers can facilitate meaningful patient and public involvement in the various phases of drug development.

Cooperation between regulators, academic institutions, medical professionals and industry

After a drug has been registered, many questions often remain in clinical practice, for example regarding the most appropriate dose. Better interaction between regulators, academic institutions, medical practitioners, the pharmaceutical industry during the pre-registration phase would facilitate discussion of such questions *before* registration. Recently, the US Food & Drug Administration (FDA) and EMA have highlighted the need to determine the most effective drug doses. The FDA, for example, supports initiatives focusing on dose optimisation for anticancer treatments (see Box 3).

Close cooperation between regulators such as EMA and academic institutions, medical professionals, and industry in the R&D phase will help to clarify regulatory expectations and prevent situations where the data regulators require is unavailable. EMA not only advises pharmaceutical companies but is also open to engaging with academic researchers and has therefore begun offering them free consultations (as of 2025). Researchers and medical professionals could engage more proactively with EMA prior to drug registration (as described in Box 4). They could join forces at EU level, for example, to raise awareness of relevant outcome measures and methodologies. Conversely, EMA could also be more proactive when it comes to consulting leading research groups. In turn, these groups could alert EMA to forthcoming applications for registration and solicit opinions. Close cooperation between the parties involved makes it possible to optimise drug doses and other factors with a view to maximising the effectiveness, safety, and tolerability of novel drugs.

Regulatory science research improves our knowledge of how drugs and other regulated technologies should be developed, evaluated, and monitored. This branch of research plays a key role in promoting transparent, sound decision-making and effective, evidence-based policy. An in-depth understanding of regulatory systems – attained by analysing the relevant frameworks and their effectiveness – is essential for effective cooperation between regulators, scientists at academic institutions, medical professionals, and industry, and is therefore a vital component of appropriate pharmaceutical care.

Optimal cooperation between regulators such as EMA, academic institutions, medical professionals, and industry in the pre-registration phase yields clarity on such matters as dose optimisation, relevant outcome measures and methodology, maximising the effectiveness, safety, and tolerability of novel medicines. Regulatory science promotes a more evidence-based approach to regulatory matters and, in doing so, encourages transparent and sound decision-making and effective policy. Researchers working in industry and at academic institutions may request scientific advice from EMA at an early stage of drug development in parallel with joint scientific consultations (JSC). Doing so can help them determine the correct dose or identify outcome measures, potentially resulting in better and faster alignment with patient care practices and, consequently, appropriate pharmaceutical care.

Biomarkers and pharmacogenetics

Whether a drug yields health benefits, and to what extent, varies from one patient to another. Biomarkers are quantifiable indicators of a biological process or a response to treatment or intervention. They can be used in disease diagnosis, prognosis, and progression monitoring or to predict the effectiveness of a treatment, and can therefore be helpful when selecting patients to participate in a clinical trial for a specific drug and for identifying the health gains. Examples of commonly used biomarkers include blood pressure, as a clinical measure of cardiovascular health, and CRP (C-reactive protein), as a biochemical marker of systemic inflammation.

Research into biomarker development contributes to drug development, more personalised drug therapy, and therefore to more appropriate pharmaceutical care.

One area of research that makes use of biomarkers is pharmacogenetics. Data on a patient's genetic profile (DNA) or phenotypic traits, which are measured using biomarkers, can help in determining their response to certain medicines, for example the rate at which they metabolise it. Based on this information, the dose may be adjusted or another drug chosen as treatment. Pharmacogenetics therefore helps in optimising trial design for drug development. Genetic analysis of tumour tissue, for instance to identify specific mutations, can inform the choice of drug treatment and promote appropriate use.

A better understanding of biomarkers, including genetic variants, blood biomarkers, or through molecular imaging, may promote the safer and more effective use of certain medicines. A case in point is the use of pharmacogenetic biomarkers in guiding the dosing of anticoagulants (Shaw, 2015). Less obvious is their usefulness for other categories of drugs, for example psychotropic medications (Vinkers, 2019).

Scientific research contributes to appropriate pharmaceutical care by investigating the role of biomarkers in drug development and use. Such research supports personalised drug therapy and the development of new precision medicines. It also promotes better trial design, for example by improving patient selection. In addition, research into the relationship between biomarkers and drug effectiveness and safety, for example in pharmacogenetics, makes an essential contribution to the research and development phase.

BOX 3. DOSE OPTIMISATION PRIOR TO REGISTRATION

In the USA, the FDA Oncology Center of Excellence's 'Project Optimus' is an initiative aimed at optimising the selection of doses to maximise not only a drug's effectiveness but also its safety and tolerability in new oncological treatments (Levit, 2025). By collaborating with pharmaceutical companies, academic institutions and international regulatory authorities, and by offering guidelines and workshops, Project Optimus is meant to improve dose characterisation using all available information and to move it forward in the drug development process.

BOX 4. INTERACTION BETWEEN REGULATORS AND ACADEMIC INSTITUTIONS

Oncologists often attend patients whose cancer has metastasised to the brain, with associated symptoms. These patients have always been excluded from clinical trials, but because brain metastases are relatively common, routinely excluding this group distorts research outcomes. Oncologists who flagged this problem contacted the FDA and recommended that registration-enabling trials also include this group of patients.[16] Initiatives such as this ensure that more evidence becomes available early on, and preferably before registration, about a drug's effect on relevant outcome measures like this.

2.3 Medicines during use

One critical moment in the life cycle of a drug is the marketing authorisation phase, in which a legal licence is issued allowing the drug to be sold. A drug that has been granted marketing authorisation has official approval, for example by the European Commission (EC), the authorising body for all centrally authorised products to be sold in the EU Member States, based on EMA's recommendation. The price to be charged for the product and its reimbursement status are determined by the individual countries.

16 https://www.fda.gov/media/121317/download.

In this section, we discuss areas in which additional scientific evidence is needed after a medicine has been granted marketing authorisation. These areas can be divided into four categories: the drug's real-world effectiveness (2.3.1); access to drugs in the healthcare system (2.3.2); guidelines (2.3.3); and medicine use in real-world settings (2.3.4). The following questions are pertinent in this phase:

- For which widely used or expensive medicines do we still lack evidence of their effectiveness or a correct indication?
- Which choices are preferable in the drug reimbursement system from a societal and ethical perspective?
- Is there enough scientific evidence to justify overhauling existing guidelines?
- Is it useful to study specific groups, such as the elderly, to better support decision-making with regard to starting or terminating a course of drug therapy?
- For which drugs would a new administering system allow care to be arranged closer to the patient?
- How do we make responsible choices from among the medications in a particular drug class?

We look at each of these questions in this section.

2.3.1 Real-world effectiveness of the drug

Generally speaking, the more uncertainty there is early on in the life cycle of a drug, the longer it will take to determine whether a patient will derive any real benefit from it. Such uncertainty at the point of marketing authorisation has an impact on establishing relative effectiveness.[17] Relative effectiveness is the efficacy of a drug compared with other treatments or other drugs. Understanding a drug's relative effectiveness supports sound decision-making regarding its use in every subsequent phase, for example in HTA analyses concerning its inclusion in the medicine reimbursement system, its adoption in treatment guidelines, and its use in clinical practice.

The opportunities, obstacles, and decision points for scientific research in this phase lie in narrowing the efficacy-effectiveness gap, undertaking pragmatic and independent studies, and utilising data from clinical practice, as we explain below.

Narrowing the efficacy-effectiveness gap

A drug's effectiveness refers to how well it does what it is meant to do in clinical practice, i.e. how well it treats or prevents a specific disorder in patients. Effectiveness is often compared with efficacy, a mark of how well a drug works under ideal circumstances, for example in clinical trials. The real-world effectiveness of

17 https://open.overheid.nl/documenten/d3581004-1a72-4ace-a995-96de8b8d897d/file.

a drug varies, giving rise to frequent discussions about whether the drug is fit for purpose. The question then is whether the effect of the drug is clinically relevant and relevant for the patient (see Box 5).

Experience shows that data on a drug's effectiveness as measured in clinical or registration-enabling trials (efficacy) does not always match its clinically relevant effectiveness as measured in the patient population (effectiveness). This phenomenon is referred to as the efficacy-effectiveness gap. It has several causes, including i) the composition of the trial population, ii) the health gain measure used, and iii) the relevant control group. For a medicine to be considered effective, there must be evidence that the group of people to which it was administered recorded significantly more 'health gains' than the control group. However, the population that participates in a registration-enabling trial is not always representative of the patient population encountered in the real world. The former are often younger, fitter, and have a better prognosis than their real-world counterparts. Exclusion criteria, for example co-morbidities (having multiple health conditions, illnesses, or disorders), mean that around 50% of patients are not eligible to participate in such trials, a figure that can climb to up to 80% in some cases (Taipale, 2022). The measured effect of a medicine in a trial depends on how a health gain is measured, for example by using indirect or surrogate outcome measures or hard clinically relevant outcomes. The timing of outcome measurements is also important. We discussed this above in section 2.2.2, which addresses quality of evidence. The control group in a randomised trial may receive treatment that deviates from standard care in the Netherlands, and the outcomes may therefore be irrelevant for the Dutch context. In addition, there is a growing trend towards waiving the traditional requirement to perform comparative efficacy trials before registration, for example for medicines intended for small patient populations and rare diseases. Another point is that a drug's effectiveness may change over time, for example due to habituation, interactions with the environment or diet, and can vary across population groups and across individuals of different genetic ancestries within the same population. Randomised clinical trials must continue wherever possible so that we can accurately determine the impact of a drug within the healthcare system. Researchers can contribute by producing sound trial designs and choosing patient populations that will generate the most informative data.

The pharmaceutical industry makes a notable contribution to research up until a drug is launched on the market. It is less apt to participate in studies investigating whether a drug is less effective in the real world than it appeared in its registration-enabling trials, or benefits fewer people. There is therefore a significant need for pragmatic, independent, researcher-driven post-registration trials that address relevant questions, for example how best to establish indications and criteria for

commencing treatment and treatment duration.[18] Such trials often employ broad inclusion criteria, only collect data relevant to decision-making, and focus on clinically relevant, patient-centred outcomes.

It is important for academic institutions and EMA to discuss the value and benefits of pragmatic clinical trials and to make policymakers aware of the need to include such trials and their outcomes in the changing pre-registration and post-registration regulatory and legal landscape.

Scientific research can help reduce the efficacy-effectiveness gap. Where possible, randomised clinical trials based on a sound trial design are the best means of assessing the impact of a drug within the healthcare system. It is also crucial to increase opportunities for and to conduct pragmatic post-registration trials that examine relevant issues, including how best to establish indications and criteria for commencing treatment and treatment duration. It is important for academic institutions and EMA to discuss the value and benefits of pragmatic clinical trials and to make policymakers aware of the need to include such trials and their outcomes in decisions concerning the use of medicines.

Using real-world data in a Learning Healthcare System

Collecting real-world data (i.e. data drawn from clinical practice), for example, from a registry, is one way of determining whether a medicine shown to be effective in a clinical trial is also effective in the real world. There are, however, three important challenges inherent in collecting data in this way: 1) the extent to which the data can tell us anything about the (relative) effectiveness of the drug in question; (2) reliability of the data recorded in clinical practice; and (3) restrictions on data access and use under the General Data Protection Regulation.

Although real-world data is useful for obtaining realistic estimates of the effect of a certain substance in clinical practice, it is less suitable for other purposes, for example for determining the relative effectiveness of a drug compared with no treatment or another intervention, or for identifying the most efficient use in terms of dosing issues. This is largely due to the absence of a reliable or comparable control group. That is why it is almost always necessary to randomise patients, but so far, that simply never happens in everyday practice. Randomised controlled trials, therefore, remain the gold standard for establishing relative effectiveness. The implication is that real-world data is of limited use for the purposes mentioned. Real-world data (measuring the actual effect) and clinical trial data (measuring relative effectiveness) can complement each other, however.

18 https://www.ema.europa.eu/en/documents/presentation/presentation-pragmatic-clinical-trials-preliminary-shared-experience-under-ctr-d-lacombe-eortc_en.pdf.

At present, we lack a good system for learning from the treatments administered to patients in everyday practice. This is in part because it is difficult to record and collect this data in the real world due to privacy legislation, to share this data for purposes of scientific research, and to develop a system for randomising patients as part of standard care.

Secondary use of healthcare data – in other words, reusing patient information collected primarily for care purposes, for example from secure clinical data registries, in scientific research – requires due diligence, with the patient's interests being paramount. The terms and conditions for data sharing must be unambiguous, and the burden on healthcare providers must be minimal. In addition, when society faces critical decisions, for example during a pandemic, it is important to quickly share clinical data on how such decisions impact various vulnerable groups.

A Learning Healthcare System, as envisaged in the European Commission proposal for a regulation on a European Health Data Space[19], will facilitate the reuse of electronic health data for research, innovation, decision-making, and policymaking. Certain provisos are attached, however: research questions and roles within the system must be clearly defined, data should preferably be collected through a central platform, and the mechanism for collaboration between all stakeholders must be specified. Health-RI is a Dutch initiative that is developing an integrated health data infrastructure to promote data-driven research, policymaking, and innovation. It is a good example of a non-profit that is working to reuse data from the health and life sciences.[20]

The Open Science movement seeks to promote more open and collaborative research practices, with publications, data, software, and other academic output being shared and made available for reuse at the earliest opportunity.[21] It would also be helpful to give researchers easier access to data – for example scans and tumour tissue – from trials sponsored by the pharmaceutical industry to use in other, additional analyses (Kok ,2024). This would serve to move research forward and ensure that fewer people are unnecessarily burdened with supplementary trials.

Other current initiatives involve prospective observational studies targeting specific diseases or medicines; here, researchers follow a group of people over a certain period of time without actively intervening in their treatment. Such studies collect specific data on the effects of a treatment in real life. This approach has shown itself to be useful, for example in the Drug Access Protocol (DAP) (see Box 6).

19 https://eur-lex.europa.eu/legal-content/Nl/TXT/?uri=OJ:L_202500327.
20 https://www.health-ri.nl/.
21 https://www.nwo.nl/en/open-science.

Promoting well-structured registries along with observational studies and randomised trials makes it possible for science to contribute to appropriate pharmaceutical care. That contribution is needed to fully understand the real-world impact of treatments. Reusing electronic health data in research and development and in decision-making and policymaking supports a Learning Healthcare System. Scientists can collaborate with other parties on finding methods to collect and record such real-world data without contravening privacy legislation. It is in the spirit of the Open Science movement to share such data within the context of scientific research.

BOX 5. WEIGHING CLINICAL RELEVANCE AGAINST COSTS

In 2024, EMA's Committee for Medicinal Products for Human Use (CHMP) recommended granting a marketing authorisation to lecanemab for treating mild cognitive impairment or mild dementia due to Alzheimer's disease. Lecanemab, a monoclonal antibody, reduces the harmful amyloid beta plaques that form in the brains of patients with Alzheimer's. It must be administered as an infusion once every two weeks, with MRI scans being performed at regular intervals to monitor the patient for potential side effects, specifically swelling or bleeding in the brain.

Alzheimer studies often use the Clinical Dementia Rating Sum of Boxes (CDR-SB) as an outcome measure. This composite measure is the sum of a patient's scores in various cognitive and functional domains and ranges from 0 to 18. The registration-enabling trial of lecanemab found a difference of 0.45 between the intervention and control groups after 18 months of treatment. The registration-enabling trial considered a difference of 0.373 between intervention and control groups to be relevant (Van Dyck, 2023). In the literature, however, a minimum difference of 1.0 is generally deemed clinically relevant. By the standards of the company that set up the trial, then, the drug is clinically relevant, but many Alzheimer researchers dispute this. Medical professionals active in this field also question whether such limited benefits justify the enormous costs and considerable burden on patients and the healthcare system. In the Netherlands, for example, 7,000 additional patients would have to visit the hospital's day treatment centre every two weeks for an infusion. The anticipated impact on the national budget would be nearly 170 million euros annually.[22]

22 Limited to the direct cost of the medication for an estimated 7,000 patients who may be eligible for treatment; care-related costs are not included (Horizonscan).

BOX 6. INITIATIVES FOR PROSPECTIVE OBSERVATIONAL STUDIES

To examine the real-world effectiveness of what are often expensive oncological drugs for rare indications, several Dutch organisations have joined forces to set up the DRUG Access Protocol (DAP) initiative. They are the Dutch Society of Medical Oncology (NVMO), the Dutch Association of Physicians in Chest Medicine and Tuberculosis (NVALT), Netherlands Cancer Institute (AVL), the National Health Care Institute and Zorgverzekeraars Nederland (the representative body for Dutch health insurers). The protocol is meant to facilitate faster, controlled, and coordinated access to promising oncological drugs that are not yet eligible for health insurance coverage in the Netherlands. Measurement and observational data on a drug's effectiveness and safety is simultaneously collected from patients, shortening the timeline to assessing the drug's eligibility for inclusion in the insured standard healthcare benefit package. This means that, beyond non-randomised registration-enabling trials, real-world data – for example on rare diseases, such as the data on cemiplimab for treating squamous cell carcinoma of the skin – can also offer Dutch patients with the same condition valuable information.[23]

2.3.2 Access to drugs within the healthcare system

One of the challenges in the delivery of appropriate care is ease of access to medicines. Ease of access involves three aspects: the physical availability of a drug, for example scarcity due to drug shortages; financial access, including the costs and reimbursements; and practical access, which may be affected by policies on prescriptions and by bureaucratic barriers.

When it comes to access to drugs within the healthcare system itself, we see various decision points, opportunities, obstacles, and decision points that science can help improve:

- appropriate use and efficiency
- uncertainty following (provisional) marketing authorisation and cyclical review
- curbing the trend towards medicalisation
- price trends
- therapeutic substitution
- environmental sustainability and personnel utilisation as criteria in the assessment framework for insured care.

We look at each of these points in greater detail below.

23 https://medischeoncologie.nl/nieuws/cemiplimab-beschikbaar-in-basispakket.

Appropriate use and efficiency

Once a medicine has been approved for inclusion in the insured standard healthcare benefit package, it is up to medical professionals to decide how to use it most efficiently with their own patients. When considering a drug's eligibility for reimbursement, the National Health Care Institute increasingly asks professional associations whether they see a need for research on appropriate use or efficiency. Such research is meant to determine whether the medicine can be used more cost-effectively and/or in a more targeted manner, for example by lowering the dose, extending the dose interval, or tightening up the criteria for commencing treatment and treatment duration. Sound criteria for research into appropriate care and efficiency must not only address the costs involved but also personnel utilisation, the influence of social media and pharmaceutical companies, and environmental impact.

Medicines are included in the insured benefits package following clinical trials that have demonstrated their efficacy and safety in treating the indication in question. Nevertheless, medical practitioners may still have questions about how to use the medicine as effectively and cost-effectively as possible. For example, does a lower dose produce the same effects? What about a longer dose interval? When is the right time to start or stop administering the drug? A good example of research addressing effectiveness, efficiency, and combination therapy is the SONIA trial (see Box 7).

Trials examining the effect of tapering doses or discontinuing a medication are fewer in number than those investigating the effect of commencing treatment. A 2023 study showed that only 1% of clinical trials were 'drug discontinuation trials', i.e. trials evaluating whether an existing treatment had remained necessary or effective, or whether patients would fare just as well or even better if they stopped taking it (Kampman, 2023). Analysis of the Cochrane database, which contains approximately 7,500 systematic reviews of drug trials, unearthed only 31 reviews on the effects of tapering or discontinuation, whereas the number of reviews evaluating the effectiveness of new treatments ran to the thousands. The right point at which to discontinue treatment is therefore a neglected aspect of drug research.

Non-inferiority trials, designed to show whether a new treatment is no less effective than a standard treatment, including 'no care', play a crucial role in this regard. Such trials are often undertaken by not-for-profit organisations. Unfortunately, a traditional non-inferiority trial requires a larger group of patients than a superiority trial, making them more difficult to perform for not-for-profits. Encouraging non-inferiority trials based on innovative designs would promote significant health benefits. For example, they can show that a new treatment administered at a lower dose is at least as effective as the standard treatment, resulting in more efficient care. In 2022, the Ministry of Health, Welfare and Sport and thirteen parties in the

healthcare sector signed the Integrated Care Agreement (IZA).[24] The signatories agreed that, where relevant, they would make appropriate care or efficiency trials a standard component when adding new, expensive medicines to the insured benefits package. A specific procedure will be developed for this purpose in consultation with the parties active in specialist medical care and the National Health Care Institute, and with supervision being provided under the Care Evaluation and Appropriate Use programme (ZE&GG).[25] For impact purposes, non-inferiority trials should ideally be international in setup, and EU-based researchers and EMA should discuss in advance what is required to make any drug label changes.

Efficiency research should provide a transparent quantitative comparison of the safety and effectiveness of different drug therapies. Relevant examples of research methods that examine a drug's benefits for patients are the PASKWIL criteria (palliative, adjuvant, specific side effects, quality of life, impact of treatment, and level of evidence), developed by oncologists in the Netherlands, and the Magnitude of Clinical Benefit Scale (ESMO-MCBS scale)[26] developed by the European Society of Medical Oncology (see Box 8). The fact that professional associations themselves articulate their views of scientific evidence and lay down requirements for what is and is not effective helps promote appropriate use and efficiency.

In addition to research on efficient use, the opinions of patients and the public are also important. They may react strongly to reimbursement decisions (for example negative decisions based on cost-effectiveness assessments). This is in part why it is important not to lose sight of core values when making difficult decisions about the allocation of scarce resources in healthcare. Solidarity, for example is a common theme throughout the history of the Dutch healthcare system. It is expressed , first and foremost, in the broad coverage offered by the insured standard healthcare benefit package. To maintain a healthcare system based on solidarity, however, we also need to impose limits. It is the task of government to ensure that this happens fairly, without solidarity being compromised too much. Independent scientific evaluation helps test whether policy aligns with society's values, leading to well-considered and legitimate decisions (Scheijmans, 2022). Questions that arise in this context are 'What is acceptable for the patient and for society?' Discussions of this kind are complex but necessary (see Box 9). Research has also shown that the Dutch public recognises the importance of making tough choices in healthcare, and broadly agrees on the reimbursement of certain types of expensive medicines (Scheijmans, 2025).

24 https://www.rijksoverheid.nl/documenten/rapporten/2022/09/16/integraal-zorgakkoord-samen-werken-aan-gezonde-zorg.

25 See for example the call for impactful efficiency questions: https://zorgevaluatiegepastgebruik.nl/wat-we-doen/agenderen/systematisch-agenderen/gerichte-procedure-dgm-ronde-2-1.

26 https://www.esmo.org/guidelines/esmo-mcbs/about-the-esmo-mcbs.

Input from the humanities and social sciences is needed to understand what society thinks about appropriate care and how choices in care are made.[27] Examples are: how do we do this for smaller groups? And should we only look at quality of life or do we include other factors? The humanities can also help us consider what we mean by such values as solidarity and fairness (ethics and philosophy), and how these values have evolved and continue to evolve over time.

Scientific research contributes to appropriate pharmaceutical care by studying appropriate use and efficiency to determine whether a medicine can be used more cost-effectively and/or in a more targeted manner, for example by lowering the dose, extending the dose interval, or tightening up the criteria for commencing treatment and treatment duration. In the case of both new and existing drugs, evidence of this kind may make it possible to lower the intensity of the treatment or shorten its duration. Such evidence can be obtained from non-inferiority trials, designed to show whether a new treatment is no less effective than a standard treatment.

Developing quantitative methods to compare the safety and effectiveness of different drug therapies openly and transparently also promotes appropriate use and efficiency. Researchers or professional associations can themselves articulate their views of scientific evidence and set criteria for what is and is not effective. Independent scientific evaluation helps test whether policy aligns with society's values and in doing so promotes well-considered and legitimate decisions. Input from the humanities and social sciences is needed to understand what society thinks about appropriate care and how choices in care are related.

Cyclical medication review

To fast-track the availability of a drug, EMA sometimes recommends admitting it to the market, despite uncertainty about its effectiveness, subject to the proviso that additional scientific data on its efficacy and/or side effects is provided later. This is what is known as Conditional Marketing Authorisation (CMA) and Accelerated Assessment (AA), such as within EMA's PRIME (PRIority MEdicines) scheme.[28] For example, a conditional marketing authorisation can be granted for a new drug that fulfils an unmet medical need (see section 2.2.1). The number of medicines granted a CMA has risen sharply in recent years, with EMA approving 51 drugs in the past five years, compared with 40 in the previous thirteen years (Lasch, 2025). In other words, the burden of proof for these drugs is more limited. One such example is

27 See for example the public consultation on expensive medicines: https://www.radboudumc.nl/projecten/burgerraadpleging.

28 https://www.ema.europa.eu/en/human-regulatory-overview/research-development/prime-priority-medicines .

the CMA for the coronavirus (COVID-19) vaccines.[29] In recommending registration, EMA accepts that there is uncertainty about the precise effectiveness of these drugs. It requires new data to be reported and analysed as soon as it becomes available; failure to do so may result in the authorisation being revoked. Nevertheless, this arrangement does give rise to a number of concerns, specifically of an ethical nature (Maksimova, 2024).

Even after a 'standard' registration by EMA, new evidence regarding the effectiveness and safety of a medicine may become available, requiring a review. That may be the case if a drug is found not to improve users' survival rate, or if safety rules have become tighter over the years. It may also occur following appropriate care or healthcare efficiency research by the National Health Care Institute.

Decision-making on medicines is often a one-off process generating either a positive or negative assessment, whereas a cyclical review offers a deeper understanding of a medicine's actual benefits and its efficient use. When a medicine is included in the insured standard healthcare benefit package, then, it would be best to specify the additional studies and evaluations needed to clarify its optimal use, and to see that the results of such studies lead to a review or update of the package decision.

One way to do this would be to conduct an additional healthcare efficiency trial examining how effective and cost-efficient the drug is in a real-world setting. A similar situation arises when inclusion in the insured standard package is conditional. Then too, it is important to make relevant information available as quickly as possible to inform decision-making about pharmaceutical reimbursements. This is certainly the case when medicines are registered based solely on surrogate outcome measures or limited evidence.

Scientists, clinicians, and other stakeholders, including patients, can participate actively in drug reviews and help identify necessary additional tests once a drug has been registered. Their participation can be facilitated by checking whether any new data has been reported and analysed, so that marketing authorisation for the relevant drug can, if necessary, be revoked after registration or inclusion in the insured standard healthcare benefit package (Liu, 2024). Specialists in the regulatory sciences have expertise on how best to organise cyclical reviews.

Curbing the trend towards medicalisation

One key question when introducing a medicine is whether it is more cost-effective than non-drug interventions (see, for example, Box 10). One of the main purposes

29 https://www.ema.europa.eu/en/human-regulatory-overview/marketing-authorisation/conditional-marketing-authorisation.

of the Integrated Care Agreement (IZA) is to curb medicalisation: 'not every request for help is a care need, and not every care need requires a medical response'. When referring to medicines, it means that not every care need can be met with a medicine, and that a medicine is not always the best solution.

Non-drug interventions, such as lifestyle changes, may often be equally effective and less expensive than a drug.[30,31] There are also diseases, such as Type 2 diabetes, that can be avoided or deferred (at least in part) by preventive measures (Pot, 2020).

Scientific research offers valuable guidance for determining whether a drug is the appropriate course of treatment, for example by investigating its cost-effectiveness compared with other interventions. In addition, scientific research provides tools for identifying health conditions for which drugs are not useful, and medicalisation should be curbed. Ethics can be helpful in analysing such concepts as sickness and health and the effects of widening the diagnostic criteria for medical conditions.

Price trends

The Netherlands Authority for Consumers and Markets (ACM) monitors whether suppliers of medicines comply with fair competition rules. Along with the Dutch Healthcare Authority, the National Health Care Institute and the Ministry of Health, Welfare and Sport, it seeks to exercise more control over drug prices and healthcare expenditure relative to other public services. The proposal is to do so by establishing a budget for routine interventions and innovations with a view to optimising health gains at any given time. The proposal stems from the Socially Acceptable Spending on Medicines (MAUG) programme.[32]

A patent expiration is a crucial moment in the life cycle of a medicine, as it often leads to a significant drop in its price. The price of an interchangeable medicine that still enjoys patent protection will remain the same, however. Once the patent on the first product has expired, it is no longer cost-effective to prescribe the interchangeable drug in many cases; it may, in fact, be cheaper to prescribe the off-patent drug at that point. And yet we see that the relative market shares of comparable drugs remain the same. One reason for this is that healthcare providers have the latitude to prescribe their preferred drugs, without considering whether all comparable medicines are still under patent. Additionally, price negotiations between pharmaceutical companies and hospitals are often not transparent to the health insurers that pay for

30 https://leefstijlcoalitie.nl/.
31 https://www.zorginstituutnederland.nl/actueel/nieuws/2021/10/19/looptraining-voorkomt-operatie-bij-etalagebenen.
32 https://www.nza.nl/zorgsectoren/geneesmiddelenzorg/programma-maug-samenwerking-nza-acm-en-zorginstituut-nederland.

the care. As a result, price reductions may be limited due to other factors, for example the fact that hospitals can then spend part of the discount themselves.

Scientific research can contribute to appropriate pharmaceutical care by offering transparency regarding the advantages and disadvantages of various market structures, so that policymakers understand how specific institutional arrangements in the various pharmaceutical markets impact innovation, accessibility, and affordability. A key factor is to update package management when a drug transitions from one market structure to the next in the course of its life cycle.

Therapeutic substitution

Substituting a drug with an alternative from the same pharmacological class is called class or therapeutic substitution. Treating patients with a less expensive alternative may represent a cost savings (De Smet, 2002; Goldstein, 2024). Understanding which drugs can substitute for others is important in this regard, but it is a question also triggered by the large and possibly rising number of drug shortages.

In certain cases, therapeutic substitution carries risks.[33] Doses are not always interchangeable, patients must be well informed to prevent incorrect use, practitioners and patients must be aware of the substitute's possible side effects, not least because they may be undesirable for some patients, and the drug should preferably also be registered as a therapy for the relevant indication, as otherwise it would be considered off-label use. To guarantee quality of care, it is therefore essential to collect enough data about drug interchangeability (see Box 11).

Equivalence trials, which examine and compare the effectiveness of multiple drugs, can improve our knowledge of interchangeability. Because such trials place an additional burden on researchers and participants, they should ideally form part of clinical care, ensuring that the resulting findings are readily available and can be applied immediately in clinical practice.

Scientists can help improve our knowledge of drug interchangeability and provide flowcharts with information on rankings, proposed substances, contraindications, costs per month, and dose (and dosing methods).

Environmental sustainability and personnel utilisation as criteria in the assessment framework for insured care

When assessing whether a drug should be included in the insured standard healthcare benefit package, the National Health Care Institute tests the drug against the four package criteria: effectiveness, cost-effectiveness, necessity, and feasibility. With regard to effectiveness, the National Health Care Institute's Scientific Advisory

33 https://www.ge-bu.nl/artikel/therapeutische-substitutie.

Board determines whether the drug meets the 'established medical science and medical practice' criterion. If so, then the following step is to determine whether the effect of the treatment outweighs its costs. That assessment is carried out by the Insured Package Advisory Committee (ACP). The National Health Care Institute makes its recommendation to the minister based on the findings of these two committees. If the drug is effective but too expensive, the recommendation in many cases is to include it in the insured package only after successful price negotiations with the pharmaceutical company. The National Health Care Institute is currently considering whether to include other factors, such as the impact of the relevant therapy on personnel utilisation and the environment, in its assessment. If a certain treatment makes a relatively heavy demand on the capacity of care personnel, deploying them in other ways may, in fact, produce more health gains. A committee established by the Health Care Institute looked into how best to include environmental sustainability and personnel utilisation in the assessment framework for the insured standard package. Some of the research questions that arise in this context address the development of standardised and practical methods for quantifying other aspects of environmental impact in care interventions. The committee has established a research agenda in this area (Zorginstituut Nederland, 2025).

Scientific research contributes to appropriate pharmaceutical care by filling in knowledge gaps relating to the environmental impact of pharmaceuticals (and drug development), the effects of prescription and use patterns on the environment, and the potential for alternatives. The resulting evidence can be used in the assessment framework for insured care.

BOX 7. DELAYING START OF BREAST CANCER DRUG AS EFFECTIVE AS FIRST-LINE TREATMENT WITH FEWER SIDE EFFECTS

The SONIA study is a good example of a trial examining the real-world effectiveness of a treatment (Sonke, 2024). The trial investigated whether women with metastatic hormone-receptor positive breast cancer should be given a cyclin-dependent kinase (CDK)4/6 inhibitor upfront in addition to hormone therapy, or whether administering it as a second-line treatment would be just as effective. The trial revealed that patients who received a CDK4/6 inhibitor as first-line treatment along with hormone therapy used the drug an average of 16.5 months longer than patients who received a CDK4/6 inhibitor only as a second-line treatment after the initial hormone therapy had failed. The 16.5 additional months the inhibitor was used produced no benefit in terms of disease control (progression-free survival) and survival, but did result in 74% more side effects and more hospital visits than patients who used a CDK4/6 inhibitor as a second-line treatment. Delaying treatment with CDK4/6 inhibitors also represents a substantial cost reduction of over 45 million euros annually in the Netherlands alone.

BOX 8. SCIENTIFIC METHODS FOR QUANTITATIVE COMPARISON OF THE SAFETY AND EFFECTIVENESS OF DIFFERENT DRUG THERAPIES

The PASKWIL criteria, developed by oncologists in the Netherlands, and the ESMO-MCBS scale,[34] developed by the European Society of Medical Oncology, are good examples of scientific methods that allow an unbiased, quantitative comparison of the safety and effectiveness of different drug therapies without being dependent on the pharmaceutical industry. The fact that professional associations themselves articulate their views of scientific evidence and lay down requirements for what is and is not effective thus helps promote appropriate use and efficiency.

That has so far been particularly the case in oncology, motivated in part by the huge number of new, expensive medicines that have become available. In 1999, the Dutch Society of Medical Oncology (NVMO) established CieBOM, the Dutch Committee for the Evaluation of Oncological Agents. The committee assesses new oncological drugs after research results are published in a peer-reviewed journal and the drug has been registered by EMA. The outcome measures must be assessed against the PASKWIL criteria.

BOX 9: EXPENSIVE DRUGS IN PRIMARY CARE

Primary care is focused mainly on commonplace health issues and makes only limited use of very expensive medicines. The development of expensive therapeutic innovations for common disorders can consume a significant portion of the total healthcare budget, however. If these innovations offer marked added value because they are considerably safer and more effective than existing treatments, they will benefit many people. Nevertheless, not everything that can be done, needs to be done. Recent examples of new, expensive drugs are those targeting such widespread conditions as diabetes mellitus, obesity and dementia. These include glucagon-like peptide-1 (GLP-1) receptor agonists, meant to treat Type 2 diabetes mellitus, which are much more expensive than the usual treatments recommended. The updated guidelines limit the indication to patients with a very high risk of cardiovascular diseases. But the beneficial effects of these drugs also make them attractive for treating overweight or obese patients who do not have diabetes mellitus, significantly increasing the size of the group eligible to receive them. In 2023, 50% of Dutch people aged 18 and older were overweight, with 15% of these being obese.[35] Treating all these people with a GLP-1 receptor agonist would compromise the affordability of care. That is why the Health Care Institute has drafted a set of reimbursement conditions

34 https://www.esmo.org/guidelines/esmo-mcbs/about-the-esmo-mcbs.
35 https://www.voedingscentrum.nl/encyclopedie/overgewicht.aspx.

for these drugs.[36] The role of GLP-1 receptor agonists in treating obesity in general practice is specified in Obesity Treatment Guidelines revised by the Dutch College of General Practitioners (NHG).[37] Other considerations include long-term effects and possible consequences for the accessibility and availability of primary care. With several drugs due to be added in the same class, however, they may well become affordable.

BOX 10. REEVALUATING THE ADDED VALUE OF ICDS FOR PATIENTS UNDERGOING OPTIMAL DRUG THERAPY FOR HEART FAILURE

New developments in care may make certain innovative interventions obsolete. Sudden Cardiac Death from severe arrhythmias is a leading cause of premature death in heart failure patients. Implantable cardioverter defibrillators (ICDs) can end arrhythmias and improve the prognosis for patients with heart failure. However, it is an expensive therapy and can produce side effects, including being wrongly given an electric shock. Evidence of the beneficial effect of ICDs was obtained in clinical trials conducted between 1997 and 2005. Research in the decade thereafter focused on various new drugs, leading to a distinct improvement in heart failure patient survival and lowering the risk of sudden cardiac death from arrhythmias. The question at the moment is, however, whether the advantages of ICDs still outweigh the disadvantages. Studies are currently underway examining the effects of ICDs in heart failure patients who are on an optimal regime of current (evidence-based) drug therapy.[38]

BOX 11. THERAPEUTIC SUBSTITUTION AND DRUG SHORTAGES

Drug shortages have become more frequent in recent years. Although the absolute number of shortages fell in 2024 (from 2,292 in 2023 to 1,563), they still entail unnecessary costs and cause considerable anxiety among patients and their physicians. The Royal Dutch Pharmacists Association (KNMP) estimates that the shortages cost pharmacy teams more than 220 million euros annually.[39] Other costs come on top of this, including the expense of consulting other care providers, such the physician issuing the prescription,

36 www.zorginstituutnederland.nl/publicaties/adviezen/2022/02/24/gvs-advies-liraglutide-saxenda.

37 https://richtlijnen.nhg.org/standaarden/obesitas.

38 https://zorgevaluatiegepastgebruik.nl/aan-de-slag/evaluatieagenda/onderwerpen/10330052310001/icd/index.

39 Based on the calculation that, on average, there is one full-time employee in every pharmacy managing shortages every day. That translates to 2,000 pharmacy team members, for a total of 220 million euros annually www.knmp.nl/actueel/nieuws/10-jaar-geneesmiddelentekorten-enorme-impact.

nurses and district nurses. Pharmacists resolve shortages by dispensing limited quantities of drugs to patients (e.g. for one month instead of three), by importing them from abroad or by preparing them themselves.
The KNMP's impact analysis shows that 4.5 million people in the Netherlands are affected by drug shortages. A pharmacotherapeutic alternative was needed for one in seven cases, with patients possibly receiving suboptimal treatment. In some instances, therapeutic substitution is not possible or not without certain risks. One example is prednisolone, used to prevent organ rejection after transplantation. It is not possible to switch patients to another corticosteroid for this indication. Research into drug interchangeability mitigates this problem significantly. International collaboration in such research speeds up the discovery of solutions.

2.3.3 Guidelines: aiming for appropriate drug use

Guidelines inform Dutch healthcare policy by making recommendations for a host of conditions with a view to improving quality of care. Their target group consists of healthcare professionals and existing and potential care recipients, who can use the guidelines as a decision-making tool in their own situation.

New data and new findings make it necessary to update existing guidelines regularly, placing demands on many different parties. There is a standard procedure to assess the quality of the drug research on which guidelines are based. The Netherlands, for example, applies an international standard known as the GRADE method (for Grading of Recommendations Assessment, Development and Evaluation) (Boluyt, 2012; Langendam, 2022). Guideline methodologists conduct systematic reviews and design the process through which a research question is formulated based on PICO, i.e. population (P), intervention (I), comparison (C), and outcome (O). The quality criteria for guidelines are laid down in the Quality Standards Guidelines, better known as the AQUA Guidelines,[40] and are based on the Appraisal of Guidelines for Research & Evaluation (AGREE II), the international standard.[41]

Because guidelines are widely used by healthcare professionals, they can only be updated if a new drug demonstrates added value over recommended existing drugs. Guideline developers focus primarily on the clinical relevance of patient-reported outcome measures or PROMs, with a minimum relevant difference being established. Patients (or their representatives) are preferably involved in selecting the PROMs. In

40 AQUA leidraad (2021). https://www.zorginzicht.nl/ontwikkeltools/aqua-leidraad-voorheen-leidraad-voor-kwaliteitsstandaarden.
41 https://www.agreetrust.org.

addition, the Dutch College of General Practitioners (NHG) prefers generic and low-cost drugs. The environmental impact of the drug is also considered. For example, the NHG prefers inhalation powders over inhalation sprays because powders produce significantly lower carbon dioxide emissions than propellant-containing sprays, as long as the patient has sufficient inhalation strength to use the drug properly.

Guideline organisations and methodologists participate in the Netherlands Guidelines Network, whose aims are to promote guideline development and use and to improve the quality, efficiency and safety of care. Guideline development and revision are and remain the responsibility of medical professional associations, as they possess the relevant expertise. They have ownership of and bear responsibility for the validity and timeliness of guidelines.

The process of developing or revising a guideline usually takes from nine months to more than two years. Even in the event of only a partial revision based on new scientific evidence, the preparations and approval procedure often take at least nine months. In urgent situations, such as the COVID-19 pandemic, development can be accelerated, but that may be at the expense of quality and public support. Certain parts of the process can be accelerated during routine guideline revisions, such as the literature review.[42]

Scientific research contributes to this phase of the drug life cycle by improving our knowledge of how best to speed up the development (or revision) of guidelines. Scientists can also assist in the prioritisation of questions that should be at the top of the agenda in guideline development and revision, but also in the collection of evidence, for example by developing novel literature search methods.

2.3.4 Appropriate medicine use in real-world settings

Whether medicines are actually used appropriately in the real world depends, among other things, on how the physician prescribes a drug and how the patient uses it. Both the physician and the patient may have many questions about this, for example whether the drug interacts with other medicines or with certain foods. The extent to which it is even practical or feasible to use a particular medicine, for example whether the dose and ingestion schedule are manageable and the patient can stick to the treatment, also determines the impact of that use. This calls for research involving patients, carers, and healthcare professionals and aimed at better understanding which aspects of drug use patients consider valuable and which factors contribute to successful use in real life (Garfield, 2022).

42 https://projecten.zonmw.nl/nl/project/versnelde-ontwikkeling-van-aanbevelingen-richtlijnen-rapid.

Opportunities, obstacles, and decision points to which scientific research can contribute in this phase include the off-label use of medicines, artificial intelligence (AI) for drug development, trial design and data analysis, public communication, and the environmental impact of medicines. We look more closely at these topics below.

Off-label use of medicines

Off-label use means that a drug is being used for a different indication, in a different dose, for a different patient group, or in a different form than those for which it has been approved, and that it is relevant for a special population, such as children. Many medicines that are also relevant for children are not registered to be used by them. In other words, there has been no rigorous risk-benefit assessment for this population (Van der Zanden, 2021). One example is the absence of research and approved treatments for psychiatric disorders in children, such as depression or bipolar disorder. In such situations, drugs are therefore prescribed off-label, i.e. for a patient group other than the one for which they have been approved. Evidence regarding their safety and effectiveness is usually limited in such cases.

Administering or dosing a drug in a manner other than that described in the Summary of Product Characteristics (SmPC) document also constitutes off-label use. Off-label use of medicines is useful in certain cases, but marketing authorisation holders are often not interested in expanding the indication, reducing the dose, or adding or omitting safety measures, such as a complete blood count.[43] Nevertheless, careful off-label use supported by evidence and clinical judgement is obviously preferable.[44] Sometimes we need more information to repurpose a medicine, i.e. use it for an indication for which it is not registered. Such studies are challenging, for example because they concern small populations (orphan indications). Even so, they are of immense value and worth conducting in international teams, for example within the EU.

> *Scientific research supports appropriate pharmaceutical care by making quality healthcare data available in a Learning Healthcare System to evaluate the effectiveness of off-label drug use. The supply of such data fills the gap that arises when a randomised controlled trial (RCT) is no longer feasible but information is still necessary to ensure appropriate use. Scientists can do this by producing more evidence regarding the use of a medicine to treat an indication for which it is not authorised (repurposing) and by collaborating internationally on research into small populations (orphan indications).*

43 A study by journalists form a combined NOS and Nieuwsuur research editorial team. https://nos.nl/artikel/2525444-farmaceut-uit-vs-in-de-clinch-met-nederlandse-artsen-over-duur-kankermedicijn.

44 https://www.zorginstituutnederland.nl/publicaties/publicatie/2024/10/08/notitie-off-labelgebruik-bij-doelmatigheidsinitiatieven-dure-geneesmiddelen.

AI for drug development, trial design, and data analysis

Artificial intelligence (AI) is playing a growing role in healthcare, fuelling research into its opportunities, risks, and effects throughout the entire drug life cycle. AI offers new opportunities to develop pharmaceuticals in a more targeted manner, design clinical trials more efficiently, and analyse large amounts of heterogeneous data, potentially facilitating early detection of unintended side effects, for example. It can also help model benefit-risk profiles for HTA. At the same time, the deployment of AI raises new medical, social, and ethical issues, for example concerning the reliability, transparency, and explainability of algorithms, requiring scientific research.

Scientific research contributes to appropriate pharmaceutical care by advancing our knowledge of the opportunities, threats, and effects of AI in this area.

Public communication

The task of public communication is, first of all, to share reliable information on what drugs do and how to use them. Its second task is to explain the choices made in pharmaceutical care, for example about tapering and off-label use. Public communication is delivered through a variety of channels. Reliable Dutch websites include Thuisarts.nl and Apotheek.nl, which base the information they provide on established guidelines and the literature. These websites are not sponsored by private parties and attract many visitors. It is not necessarily scientific evidence that drives the public's acceptance or rejection of a drug, however. Another important influence is social media. One example is semaglutide, known under the brand name Ozempic. It was developed and registered to treat diabetes, but was hyped by social media as a weight-loss drug, even though there was limited information regarding its safety and long-term effects. The global demand for the drug grew to such proportions that shortages arose – and may well persist – complicating the supply to the primary target group. Social media platforms can also have the opposite effect, for example by producing a flood of contradictory information that leads parents to question whether they should vaccinate their children.

Scientific research can contribute to appropriate pharmaceutical care by encouraging the use of independent channels for public communication and by promoting and monitoring innovations, such as AI applications. In doing so, it is important to take a nuanced approach to reporting scientific findings and evidence. Research examining optimal and novel information channels for educating patients about drug use (including vaccines) supports this process. Outreach to groups facing health inequalities merits particular attention.

Environmental impact of drugs

Healthcare has an enormous impact on the environment (Lenzen, 2020). In the Netherlands, the healthcare sector accounts for 7% of national greenhouse gas emissions and 4% of waste (Steenmeijer, 2022; KNAW, 2023). Drugs generate high levels of greenhouse gas emissions throughout their life cycle, contain substances that harm living organisms in the aquatic environment, and often end up as waste before they are even used.

Several parties have committed to working with the Ministry of Health, Welfare and Sport to promote sustainable healthcare.[45] One of their aims is to reduce the level of drug use, in particular with a view to environmental and surface water pollution. For example, the Dutch Federation of Medical Specialists is preparing a strategic sustainability agenda, and the National Health Care Institute has commissioned an advisory report on how best to develop and assign weights to personnel utilisation and environmental sustainability as criteria for decision-making in healthcare (Zorginstituut Nederland, 2025).

Sustainability will remain an important issue because transgressing planetary boundaries poses a serious threat to human wellbeing[46] and therefore demands that the Netherlands join other countries in adopting appropriate laws and regulations. Adopting more sustainable operations requires a multi-pronged approach. This includes prescribing and dispensing medicines responsibly, collecting drug waste properly, and educating healthcare providers and patients about how to limit environmental damage. When developing new interventions, it is important to also consider, at the earliest possible stage, how to maximise the value for patients while minimising the impact on the environment, as well as any trade-offs between affordability and reduced environmental impact. Sustainability may have additional benefits for patients and care providers (Luykx, 2025) (see Box 12). Sustainability criteria will also influence which treatment is chosen. One example is diclofenac, considered the worst environmental contaminant among anti-inflammatory drugs (see Box 13).

Scientific research contributes to more sustainable pharmaceutical care by improving our knowledge of sustainable drug development, manufacturing and use, and by endeavouring to minimise environmental impact during R&D.

45 https://www.greendealduurzamezorg.nl/.
46 https://www.ipcc.ch/report/ar6/wg2/.

BOX 12. LONGER-DURATION TREATMENT NOT ALWAYS BENEFICIAL FOR PATIENTS

It is important to understand what treatment duration is best. Benzodiazepines are a good example. Often prescribed for anxiety disorders and insomnia, their long-term use can lead to addiction, tolerance and cognitive side effects. Research emphasises that short-duration treatment (e.g. a few weeks) is more effective and safer for many patients than long-term use (Vinkers, 2024). This is especially true for sleep disorders, where short-term use is often all it takes to relieve acute complaints. Chronic insomnia calls for alternative treatments, such as cognitive behavioural therapy, that have proven effective without exposing patients to the risks associated with drug use (Edinger, 2021; Furukawa, 2024). Long-term use of benzodiazepine increases the risk of traffic accidents and falls. The large number of long-term users in the Netherlands is a problem that must be addressed. In addition to benefits for patients, shortening treatment duration may also have advantages for the environment. One example is psychotropic drugs, which are found in high concentrations in surface waters and pose a threat to aquatic life.

BOX 13. DICLOFENAC, THE WORST ENVIRONMENTAL CONTAMINANT AMONG ANTI-INFLAMMATORY DRUGS

The analgesic diclofenac is harmful to the environment and can easily be replaced by a more environmentally friendly alternative, such as paracetamol. Wastewater treatment plants are largely ineffective at removing diclofenac, with residues then being discharged to surface waters. The residues are harmful to fish, other aquatic organisms, and, ultimately, the food chain. When diclofenac is applied as a topical gel, the residue is rinsed off and ends up in the sewage system, causing concentrations in surface waters to exceed environmental quality standards.

3. EVIDENCE-BASED KNOWLEDGE: CHALLENGES AND CONDITIONS

Chapter 2 showed at which points in the different phases of drug development there are opportunities, obstacles, and critical decision points where the scientific basis of appropriate pharmaceutical care can - and must - be improved. The work of the advisory committee has shown, however, that the Netherlands has the basic mindset, experience, and systems in place to accomplish this and that it could assume an even more prominent role as a standard-bearer, for instance with respect to proper access to medicines, cost efficiency and a focus on appropriate use (Hofmarcher, 2024).[47] We can also find examples of successful academia-driven drug development here (see Box 14). Nevertheless, there are also challenges and conditions that dictate the extent to which scientific research can capture and deliver the necessary evidence in a manner that allows it to be utilised. The COVID-19 pandemic further showed that the Netherlands and Europe must not depend too heavily on others. The present chapter examines a number of these challenges and conditions.

Laws and regulations

It has become more difficult for scientists at academic institutions to conduct drug research. Laws and regulations governing both public and private development of complex therapies are no longer always adequate, according to a study, titled

47 OECD Health Statistics 2024. https://www.oecd.org/content/dam/oecd/en/publications/reports/2024/11/health-at-a-glance-europe-2024_bb301b77/b3704e14-en.pdf.

Academic drug development, carried out by the healthcare consultancy firm Strategies in Regulated Markets (SiRM) on behalf of the Ministry of Health, Welfare and Sport and FAST (SiRM, 2024). The study identifies two obstacles. The first is the strict criteria in the Netherlands for patient participation in scientific research, especially for children. This prevents the Netherlands from collaborating internationally and places restrictions on trial populations. Second, medicines must be compositionally consistent and reproducible to meet dossier requirements. This is a major challenge in the case of Advanced Therapy Medicinal Products (ATMPs), for example gene therapies, cell therapies, and tissue-engineered products. Producing consistent and safe ATMPs on a large scale is a technically complex undertaking. Laws and regulations should therefore be more closely aligned with drug research practices. This is especially crucial in the case of ultra-orphan drugs for treating extremely rare diseases, so that they are more readily available.

Rise in the cost of drug research

The costs associated with clinical trials have a significant impact on the overall cost of drug development. There has been a disproportional inflation of trial costs, and this has driven up the price of novel drugs (Hijma, 2024). One major factor is the larger number of endpoints being measured and measured more often. Another is that more money is being spent on clinical contract research organisations (CROs).[48] In addition, the development of more complex innovative medicines, such as drugs that target the molecular properties of diseased cells (targeted therapies), requires well-equipped research centres with advanced infrastructure and clinical testing capabilities. The market for CROs has grown by approximately 50% since 2018,[49] in part because of the demand for more technology, but also because CROs often devote a great deal of time and effort to less essential details, which is time-consuming and places an unnecessary burden on patients, researchers, and the budget (Verified Market Research, 2025). More than half of the global R&D budget is outsourced to CROs (52% in 2022). Heightened awareness of these trends is fuelling a demand for pragmatic research. Such research usually consists of academic post-registration studies, for example investigating optimal dose, treatment duration and real-world effectiveness.

Academia and drug development

One of the biggest obstacles identified in SiRM's *Academic drug development* study is that research is not always organised in a manner that aligns closely with the requirements of drug development (SiRM, 2024). Researchers' motivations differ from those of product developers, and drug development within academic

48 https://www.statista.com/statistics/1085601/global-pharmaceutical-cro-market-size-by-segment/.

49 See https://www.statista.com/statistics/1085601/global-pharmaceutical-cro-market-size-by-segment/ and Fortune Business Insights, 2025.

institutions is often fragmented. In addition, academic institutions often lack the knowledge and experience necessary for effective and efficient drug development (KNAW, 2021). SiRM has detected a hopeful trend, however: scientists at academic institutions are slowly beginning to appreciate the value of turning knowledge into practical applications. Knowledge platforms have been an investment target in recent years, and their utilisation should yield benefits in the time ahead. The consultancy firm recommends centralising academic research facilities to improve the level of effectiveness and efficiency. It also notes the importance of public funding in the phase following basic research. A good example is ZonMw's Proper Use of Medicines (GGG) programme, which seeks to ensure that existing medicines are used more safely, effectively, and efficiently. An evaluation of that programme showed that it has recouped its costs at least nine times over.[50]

Diversity in research populations

To establish the effectiveness of a medicine, trials must cover all of the populations that will be using it. Unfortunately, the number of drug trials conducted by the pharmaceutical industry in Europe is falling dramatically.[51] One of the causes is the slow roll-out of trials, for example by the EU's Clinical Trials Information System, which was meant to promote clinical research in Europe but has, at least so far, had the opposite effect. The ecosystem for clinical trials remains fragmented in several EU Member States. The COVID-19 pandemic and relocation of trials to Asia have also played a role. To ensure diversity when selecting participants for clinical trials, researchers should prioritise the following: (i) filling in knowledge gaps about groups, and (ii) including underrepresented groups in the trial where appropriate, given its objectives, risks and benefits (Van Rijssel, 2025).

One major obstacle to research in the Netherlands is the restricted access to data. Gaining access to Statistics Netherlands' registries comes at a high price for researchers, while strict privacy laws make some registries virtually inaccessible. These limitations stand in stark contrast to the situation in Scandinavia, where access is contractually regulated but generally free of charge. As a result, the body of knowledge about the effects of medicines on Scandinavian populations is disproportionately large.

Robust academic research culture

The development and use of novel drugs is of immense value to vulnerable patient groups, and in that sense, it has a major impact on society. But there are also financial interests at stake, with a lot of money circulating in the pharmaceutical market. Given

50 https://www.zonmw-geneesmiddelenmagazines.nl/magazine/tien-jaar-ggg/feiten-en-cijfers/.

51 https://www.efpia.eu/media/3edpooqp/assessing-the-clinical-trial-ecosystem-in-europe.pdf.

this tension between public and industry interests, independent research is crucial precisely because trials examining a drug's appropriate use or efficiency can often be financially disadvantageous to industry.

University administrators, funding bodies, policymakers, and academics can contribute to a strong academic culture by taking action in the following areas:

- *Open Science:* share methods and data, open access publishing, and comply with authors' guidelines.[52]
- *Research independence*: make sources of funding transparent and avoid conflicts of interest (KNAW, 2018; De Jonge Akademie, 2023).
- *Positive and inclusive academic culture:* create a safe environment for working and learning, promote mentoring, and prevent performance pressure leading to unethical behaviour.
- *Recognition and rewards:* do away with the 'publish or perish' ethos and focus more on the quality of research; in addition, expand the scope of staff performance reviews to include achievements in teaching, mentoring, and social impact.[53]

BOX 14. DRUG RESEARCH INITIATED BY RESEARCHERS IN AN ACADEMIC SETTING

In the past fifteen years, new treatments have become available for patients with metastatic melanoma. Consisting of immune checkpoint inhibitors and BRAF/MEK inhibitors, these treatments have resulted in a significant improvement in survival rates, with half of the patients still alive after ten years (Wolchock, 2025). The prognosis for patients who do not respond well to these treatments remains poor but may improve when they receive Tumour-Infiltrating Lymphocyte (TIL) therapy. TIL therapy is a complex, highly personalised form of treatment consisting of four phases. A randomised phase 3 trial conducted by the Netherlands Cancer Institute and Antonie van Leeuwenhoek Hospital in collaboration with the Centre for Cancer Immune Therapy in Copenhagen demonstrated that patients who showed progression under the immune checkpoint inhibitor anti-PD-1 treatment had significantly better progression-free survival and response rates after TIL therapy compared with treatment with ipilimumab, another immune checkpoint inhibitor (Rohaan, 2022).

This demonstrates that it is possible to conduct a phase 3 trial for an ATMP produced in academia using public funds; in this case, public funding of the Dutch portion of the trial came from the ZonMw programme for meaningful care and the Ministry of Health, Welfare and Sport. Because TIL therapy

52 https://publicationethics.org.
53 https://recognitionrewards.nl/.

proved superior to the standard treatment on multiple endpoints, including the primary endpoint, and also turned out to be cost-effective, it was included in the insured standard healthcare benefit package, even though it is not registered with EMA. Because it lacks marketing authorisation, the Dutch Health and Youth Care Inspectorate had to approve a 'hospital exemption' that would allow patients to receive treatment.[54] The therapy is cost-effective only because academic institutions produce ATMPs without seeking to generate profit. This is very good news for the Dutch research landscape and shows that such programmes can be undertaken with public funding. To secure the future of TIL therapy and avoid cancellation of the hospital exemption when a commercial TIL product enters the EU market, researchers at the Netherlands Cancer Institute –Antonie van Leeuwenhoek (NKI-AVL) have applied to EMA for a marketing authorisation based on the phase 3 trial conducted there. This is an expensive move, but made possible with the support of the Dutch Cancer Society. The complete dossier has been submitted to EMA. It should subsequently become clear whether EMA will recommend granting a marketing authorisation for an academic TIL product.

54 In certain situations, an exception may be made to the requirement that an ATMP must be granted a marketing authorisation through the centralised procedure. This exception is referred to as the 'hospital exemption'.

4. CONCLUSIONS AND RECOMMENDATIONS

Appropriate pharmaceutical care is care that optimises outcomes for patients and makes appropriate use of scarce human and material resources. The pursuit of appropriate pharmaceutical care should be based on thorough scientific research into effectiveness, costs, personnel utilisation, and environmental sustainability. Treatment decisions should be taken in consultation with the patient, their loved ones, and other healthcare providers, with the focus being on personal needs and preferences. Medicines should be used where they are most effective, and the priority should be to prevent sickness and promote health rather than treat illness reactively.

Appropriate pharmaceutical care is becoming increasingly difficult to guarantee owing to the rising cost of healthcare, drug shortages, growing staff shortages, and the negative impact of drugs on the environment.

In Chapter 2, the committee used the various phases of the drug life cycle to explore the opportunities, obstacles, and decision points where scientific underpinnings must be improved, so that research can do even more to advance appropriate pharmaceutical care. Science is the prescription.

Below is a summary of the committee's findings and corresponding recommendations.

4.1 Conclusions

The committee's five main conclusions are as follows:

1. **Better use can be made of scientific research in certain components of the pre-registration phase of drug development.** Scientific research has traditionally played an important role in the research and development phase, prior to the registration of a new medicine. This role can and should be expanded to include: a) the use of objective clinically relevant outcome measures wherever possible; b) the development and validation of relevant biomarkers; c) preparation of research agendas addressing questions that are in the public interest but frequently ignored by investors; d) the development of innovative methods for relevant and efficient research, and e) assistance in defining firm agreements and well-defined boundary conditions for the quality of evidence.

2. **Targeted follow-up research in the post-registration phase should boost the 'learning capacity' of the healthcare system, thereby improving patient care and the use of medicines and reducing unnecessary costs and environmental impact.** Scientific research should play a greater role in the phase after a medicine is introduced in clinical practice. Marketing authorisation is still regularly granted to drugs that offer limited value to patients compared with other options. Whenever gaps in relevant knowledge are identified immediately after a medicine has been registered, scientific research can help reduce such uncertainties. Targeted, pragmatic post-registration trials – which the pharmaceutical industry often finds less interesting – can then help bridge the gap between efficacy under ideal conditions and real-world effectiveness, known as the *'efficacy-effectiveness gap'*. Follow-up research into effectiveness, appropriate use, and efficiency offers further opportunities to boost the effectiveness, cost-effectiveness, and targeted use of drugs, for example by lowering the dose, extending the dose interval, or establishing explicit criteria for commencing treatment and treatment duration. Such adjustments are not only important for improving patient care but can also reduce side effects in patients, lower costs, optimise healthcare staff utilisation, and reduce the burden on the environment. Equally important is understanding which drugs can substitute for others, particularly given the frequent shortages that we are currently experiencing.

3. **Scientific research can be utilised more effectively to ensure that investments are better aligned with public needs.** Scientific research can offer policymakers even greater support in drafting rational policies and establishing productive partnerships for appropriate pharmaceutical care. Doing so will improve the likelihood that investments are more closely aligned with public needs. As public investment in drug research and development

entails considerable expenditure for the Netherlands, it is vital that we continue examining whether such investment is aligned with public preferences and whether the country's medicine reimbursement policy stimulates the intended level of innovation, in particular in the private sector.

4. **Scientific evidence is essential for making fair, socially responsible, and sustainable choices.** Solidarity is one of the pillars of the Dutch healthcare system. This means that we must make choices in healthcare, for example whether or not to reimburse certain types of expensive medicines. Given the prospect of long-term scarcity, making informed decisions of this kind will require policy frameworks that go beyond medical criteria. The humanities and social sciences (including economics, sociology, ethics and law) can offer valuable knowledge in support of fair, socially responsible and sustainable choices in healthcare. This will require further research into the underlying rationale and effects of policy and other choices.

5. **Collaboration is vital.** Such ambitious aims can only be attained through close cooperation between scientists and relevant parties, including patient and civic organisations, regulators, medical professionals, and, where appropriate, the pharmaceutical industry. The Netherlands cannot do this alone, given that many obstacles, including drug shortages, involvement in decision-making on drug registration, the changing pharmaceutical research landscape in Europe, and the need for post-registration research and clinical trials – specifically but not exclusively for rare diseases – require international action.

This report emphasises the importance of having sound evidence-based knowledge for informed decision-making about the use of medicines. The Netherlands has the basic mindset, experience, and systems in place for this. The Academy calls on the relevant parties to capitalise on the available opportunities and to do more to position the Netherlands as an international standard-bearer in this field.

4.2 Recommendations

Specific recommendations for improving scientific underpinnings for appropriate pharmaceutical care can be found at the end of each sub-section of Chapter 2. The main recommendations are as follows:

1. **Increase the level of scientific input in the pre-registration phase.** Doing so will help improve trial design and research outcomes. Science can also ensure that drug development is more closely aligned with public needs and priorities by identifying knowledge gaps and initiating or facilitating relevant research. Scientific research can also contribute by establishing core principles and by

applying new methodologies to improve endpoints and biomarkers in drug development. In addition, research findings can be used to develop strategies for optimising the Netherlands' support for private-sector innovation.

2. **Continue building a Learning Healthcare System for appropriate pharmaceutical care**, with scientific research as a vital component and with the involvement of relevant healthcare stakeholders. Encourage knowledge generation in relation to appropriate pharmaceutical care with a view to improving quality of life, drug affordability, and access to care and to reducing environmental impact. Targeted follow-up research into the most effective dose and duration of treatment will help optimise care and facilitate cyclical review, ensuring that relevant evidence is available for decision-making. In the long run, independent scientific research into appropriate pharmaceutical care is worthwhile for patients and society.

3. **Define explicit criteria for data exchange**, prioritising patient interests, establishing well-defined research questions and roles, preferably centralising data collection, specifying how stakeholders should collaborate, and minimising the burden on care providers, with the aim of supporting cyclical medication reviews and a Learning Healthcare System, among other objectives. When the authorities are faced with decisions that affect society as a whole – for example, during a pandemic – they must have quick access to sound data on how the disease will impact various vulnerable population groups. International cooperation has added value in this context, especially when dealing with rare diseases.

4. **Harness Dutch and international partnerships to conduct joint drug trials and pragmatic clinical trials.** Provided they are well designed, internationally organised and coordinated with EMA, such trials may also lead to new registrations and can be used in drug Health Technology Assessments. In addition, by harmonising procedures where possible, delivering outstanding quality and making use of leading-edge technologies, European researchers and relevant partners can once again make the European Union a more attractive place for conducting innovative trials in cooperation with the pharmaceutical industry, thus reversing the downward trend in such research.

5. **Organise meaningful patient and public involvement** during the pre-registration and post-registration phases, for example when prioritising and evaluating studies and drafting and assessing benefit-risk analyses of medicines. Utilise good practices when measuring patient perceptions.

The Academy calls on the Dutch government and relevant parties to join forces in bolstering scientific underpinnings for drug development and pharmaceutical care,

and to do more to position the Netherlands as an international standard-bearer in this field. To do this will require making smart choices about when scientific research should contribute and in what manner, how to protect and encourage independent research, and how best to collaborate internationally to avoid fragmentation. Only in this way can the promise of appropriate pharmaceutical care become reality – care that is effective, patient-centred, affordable and sustainable.

In addition to the above recommendations, which address science in general, the Academy has the following recommendations for specific target groups:

Central government, National Health Care Institute, ZonMw

- Utilise scientific research to promote appropriate pharmaceutical care and avoid unnecessary costs. Do this to promote quality of life and the affordability of pharmaceutical care. In the long run, independent scientific research into appropriate pharmaceutical care is worthwhile.
- Encourage a Learning Healthcare System in which scientific evidence is embedded in every phase of the drug life cycle and the entire spectrum of healthcare stakeholders is engaged.
- Use evidence-based knowledge to develop strategies for optimising the Netherlands' support for private-sector innovation in pharmaceuticals.
- Encourage the use of independent channels for public communication and the monitoring and evaluation of innovations in public communication.
- Encourage drug development within academic institutions by making it easier to organise the necessary research into the appropriate use of new and existing drugs.
- Support research agendas addressing appropriate use and efficiency, for example research examining whether a medicine can be used more cost-effectively and/or in a more targeted manner by lowering the dose, extending the dose interval, or tightening up the criteria for commencing treatment and treatment duration, or research on the environmental sustainability of and personnel utilisation involved in drug therapies.
- Promote the involvement of the public, patients and society in research and ensure that their input is utilised. This is particularly relevant when the research concerns building public support for tough choices, public perceptions of appropriate care and the associated care choices, and the development of transparent assessment frameworks.

Care providers and care institutions

- Have professional associations articulate what care providers think about evidence, for example by specifying requirements for research that establishes which treatments are and are not effective, as this will support appropriate use and efficiency.
- Collaborate with scientists, regulators, other medical professionals, and, where appropriate, the pharmaceutical industry. Do so prior to registration as well,

so that pertinent information becomes available on such aspects as relevant outcome measures and doses.
- Use practical knowledge in a Learning Healthcare System where a steady stream of clinical data serves to generate new research findings that support clinical decision-making. This ensures that scientific evidence becomes available in a cyclical, accessible, and transparent manner.
- Participate in clinical trials. Ensure that staff are properly trained in conducting such trials and make human and other resources available to facilitate participation.
- Improve the availability of data collected in clinical practice. Advocate for well-structured registries, combined with observational studies and randomised trials. That contribution is needed to fully understand the real-world impact of treatments.

Pharmaceutical industry
- Establish long-term collaborative relationships with scientists at academic institutions to support high-calibre, independent scientific research into innovative and creative concepts and to facilitate their valorisation. Collaborating with academic researchers, regulators, patients, and medical professionals prior to registration ensures that more pertinent evidence becomes available on such aspects as relevant outcome measures and doses.
- Help make drug use, development, and production more sustainable and promote knowledge-building in this area. Work to limit the environmental impact of research and development and make agreements with other stakeholders in that context.
- Cooperate with all of the relevant parties in the Netherlands on organising an annual, open-access study day featuring presentations on research into innovative and appropriate pharmaceutical care by various parties involved in this care sector.
- Use biomarkers in clinical trials that can aid in the development of new precision medicines and personalised care for individual patients.
- Continue conducting pre-registration trials in the Netherlands in which the clinical researchers are also involved in designing the trial, wherever possible.

Regulators, EMA, Medicines Evaluation Board
- Collaborate with academic researchers, medical professionals, and the pharmaceutical industry prior to registration to ensure that more evidence on such aspects as relevant outcome measures and doses is already available in that phase.
- Promote cyclical reviews of medicines to gain a better understanding of their real-world effectiveness. When registering a drug, state which supplementary trials and evaluations are required to optimise its use.

- Develop, validate, and apply new methods, including those using AI, to facilitate cyclical reviews in pharmaceutical care.

Health insurers
- Leverage the expertise of Dutch practitioners and researchers to optimise decision-making between different pharmaceutical options.
- Participate in conducting post-registration trials that can lead to more appropriate drug use.
- Encourage care providers to participate in clinical trials and to take on board findings that are confirmed by medical professionals.

Patient organisations
- Help build consensus on measurement methods and optimised collection of patient-reported experiences.
- Train members of as many patient organisations as possible to issue independent opinions on drug research and to be capable of assessing the results of such research.

Guideline organisations
- Work on producing innovative methods to develop living guidelines in a validated way.
- Develop knowledge on how to accelerate guideline development (and revision).
- Prioritise the questions that should take precedence in guideline development and revision.
- Consider new ways of obtaining evidence, including novel literature search methods.

International partners
- Collaborate on issues where Member States have similar needs, such as conducting joint pragmatic trials that, if properly designed and coordinated with EMA, may be used in drug evaluations, result in an updated registration, or support the HTA process.
- Collaborate on obtaining and utilising real-world data, especially for rare diseases.
- Join sister academies in the EU in pursuing evidence-based objectives, for example undertaking joint post-registration trials to support appropriate pharmaceutical care, coordinating with EMA on outcome measures, and delivering scientific evidence to support strategies for addressing drug shortages. Whether a national measure is successful also depends on the international context.
- Take advantage of EMA's free consultation service for academic scientists.
- Develop plans to make the conditions for conducting clinical trials in Europe more attractive. The Federation of European Medical Academies (FEAM) can help to achieve this.

4.3 Which recommendations apply specifically to pharmaceuticals and which are more generally applicable?

This report examined the contribution that scientific research can make to appropriate pharmaceutical care, from the early stages of drug discovery and development to clinical trials examining their efficiency and real-world effectiveness. Pharmaceutical care is well suited to this type of analysis because it involves a clearly defined and largely controlled system, thanks in part to the assessments carried out by EMA and the Netherlands' National Health Care Institute. In addition, Dutch researchers are very interested in the appropriate use of pharmaceuticals. In researching and drafting this report, the advisory committee found it essential to have a clear understanding of and to gather input from a variety of different fields of scientific endeavour before arriving at a reasoned set of recommendations. The committee was fortunate in that its members represented a wide variety of fields, allowing us to draw on one another's expertise as well as the insights gained from our conversations with numerous experts. The approach pursued here can be extended to other areas of healthcare.

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DEFINITIONS

Appropriate care *(according to the Appropriate Care Framework defined by the Zorginstituut Nederland*, 2022*)*: care that works, is affordable, where possible arranged close to the patient, and based on joint decision-making by the patient and the care provider.[55]

Appropriate care is based on four principles: 1. Appropriate care is value-driven; 2. Appropriate care involves shared decision-making between patients and healthcare providers; 3. Appropriate care is the right care in the right place; 4. Appropriate care is about health rather than illness.

Value-driven means that care adds value to people's health and quality of life at a reasonable cost in terms of funding, personnel, and natural resources. This principle is first applied at group level by assessing 'established medical science and medical practice'. Both new and existing forms of care must be shown to make an effective and efficient contribution to improving people's lives (population perspective). If they do, then the following question is whether that care has also been shown to improve the health and quality of life of a unique patient/client in their own setting (individual perspective), where such care is available and how it is organised.

Appropriate use: providing only that care that adds value for the patient.

Benefit-risk ratio: an assessment of whether the benefits of a treatment or medicine outweigh the potential risks and side effects.

55 https://english.zorginstituutnederland.nl/about-us/healthcare-in-the-netherlands/appropriate-care/infographic-what-is-appropriate-care.

Biomarker: quantifiable indicator of a biological state or condition often used to assess a person's health, detect disease, or monitor the effect of treatment.

Burden of disease: a measure of the amount of health loss in a population caused by a disorder. It consists of two components: years lost due to disability (YLD) with disease and years of life lost due to premature mortality (YLL) (Murray, 1996). The burden of disease is expressed in DALYs (*Disability-Adjusted Life Years*), with one DALY being regarded as one year of a 'healthy' life lost. The burden of disease can be quantified using data from healthcare registries, although not every disorder has a registry.

Cost-effectiveness: assessing the effects of care on patient-relevant outcomes (how much value the care adds) relative to the costs of that care to society (how much the care costs).

Drug Access Protocol (DAP): protocol developed by the Dutch Society of Medical Oncology (NVMO), the Dutch Association of Physicians in Chest Medicine and Tuberculosis (NVALT), Netherlands Cancer Institute (AVL) and Zorgverzekeraars Nederland (the representative body for Dutch health insurers) for the coordinated and controlled use of promising oncological drugs in *compassionate-use* and *named-patient* programmes for rare diseases even before official reimbursement approval, and for the simultaneous collection of patient data.

Effectiveness: how well a treatment works in the real world, when it is widely available.

Efficacy: how well a treatment works in clinical trials or laboratory research.

Endpoint: the targeted outcome of a clinical trial.

Established medical science and medical practice (SWP): criterion used to determine which care is and is not eligible for reimbursement under the insured standard healthcare benefit package. As described by the National Health Care Institute[56]: 'It is a criterion that all insurable care must in any case meet. In short, care complies with the criterion when its effectiveness can be deemed sufficiently well proven. An assessment against the established medical science and medical practice criterion is based on the principles of evidence-based medicine.'

The wording used by the National Health Care Institute indicates that the criterion is a single integrated legal standard in which both science and practice are united. An assessment against the criterion is therefore not only concerned with scientific

56 https://www.zorginstituutnederland.nl/publicaties/publicatie/2023/04/11/beoordeling-swp-2023.

evidence but also assigns an important role to practical application. This means that the expertise and experience of healthcare providers and healthcare users are taken into account in various components of the assessment, including the wording of the question and clarification of the contextual factors that may play a role in the final evaluation. In other words, it is a *single* criterion, and not two criteria ('established medical science' and 'established medical practice') that must each be assessed separately. Nor does it mean that 'practice' determines whether a treatment satisfies the criterion if scientific evidence is missing.'

EU HTA: The European Union's Health Technology Assessment, a procedure for systematically evaluating health care technologies, including drugs, medical equipment, diagnostic tests, and therapies. The purpose of the EU HTA is to deliver evidence-based data on the added clinical value of new and existing health care technologies. It was established following EU health technology assessment legislation that became applicable in 2025, i.e. Regulation (EU) 2021/2282 of the European Parliament and of the Council of 15 December 2021 on HTA.

Expensive medicines: medicines administered in hospital and costing more than €1,000 per patient per year. Sometimes referred to as add-on medicines.

Generic drug: a drug that satisfies three requirements: 1) the dossier for the original drug is no longer protected by data exclusivity, 2) the patent for the original drug has expired, and 3) the generic drug must be bioequivalent to the original drug.

Health technology assessment (HTA): the systematic evaluation of the properties, effects, or impact of a health technology as compared to another technology. HTA summarises information on medical, economic, social, and ethical issues related to the use of a health technology. Examples of such technologies include drugs, medical devices for diagnosis and treatment, and prevention methods.

Healthcare efficiency research: research in which treatment is provided that is equally effective but less expensive and less of a burden on the patient.

Inpatient and outpatient medicines: inpatient medicines are medicines prescribed in a hospital. Outpatient medicines are prescription medicines available from a public pharmacy, a dispensing general practitioner, or an outpatient pharmacy.

Lock procedure: the Minister of Health, Welfare and Sport may temporarily exclude new, expensive medicines prescribed in hospitals from the insured standard healthcare benefit package. The medicine is then said to be in the 'lock procedure' for expensive medicinal products. The National Health Care Institute subsequently advises the minister on whether to make the medicinal product reimbursable. The minister can also negotiate the price with the manufacturer.

Medical guideline: document presenting recommendations to support healthcare professionals and healthcare users, aimed at improving the quality of care, based on systematic summaries of scientific research and considerations of the advantages and disadvantages of the various care options, supplemented by the expertise and experiences of healthcare professionals and healthcare users.

Medicine (EMA definition): a substance or combination of substances intended to treat or prevent diseases in humans.

Medicine (Geneesmiddelenwet, 2024): a substance or combination of substances intended to be administered or used for, or in any way presented as being suitable for:

1. curing or preventing a disease, disability, wound or pain in humans,
2. establishing a medical diagnosis in humans, or
3. restoring, improving, or otherwise altering human physiological functions by producing a pharmacological, immunological, or metabolic effect.

Morbidity: the rate of a disease or health condition within a particular population or group. It indicates how often a particular disease or disorder occurs and is expressed in absolute figures, as a percentage, or as an incidence or prevalence figure.

Off-label use: prescribing drugs for diseases or groups of patients other than those for which they were approved by regulatory authorities such as EMA in the European Union. This is permitted by law under certain conditions, usually when there are no other suitable treatment options.

Open Science (as defined by the Dutch Research Council): movement promoting more open and collaborative research practices in which publications, data, software and other types of academic output are shared at the earliest possible stage and made available for reuse.

Orphan drugs: drugs used to treat rare, often serious diseases. See also 'Rare diseases'.

Outcome measure: the way in which an outcome is measured. It refers to the instrument, tool, or method used to measure or to the operationalisation of the endpoint in a trial.

Pragmatic clinical trials: trials designed to evaluate the effectiveness of medical interventions in real-world, everyday settings. Unlike traditional *randomised controlled trials*, which often take place in strictly controlled environments, pragmatic studies focus on how a treatment works in everyday clinical practice.

Quality of life: a person's ability to function physically, mentally, and socially, and their subjective perception of the same.

Rare diseases: diseases affecting a small portion of the population; the EU regards a disease as rare if it affects 'less than 5 per 10,000 people in the Community'.[57]

Survival: time from the start of diagnosis/treatment until death. Often expressed in terms of survival rates (i.e. percentages).

Unmet medical need: health-related issues or diseases for which there is currently no effective or adequate treatment available.

57 https://health.ec.europa.eu/medicinal-products/medicines-children/evaluation-medicines-rare-diseases-and-children-legislation_en.

ABBREVIATIONS

AGREE	Appraisal of guidelines for research & evaluation
AI	Artificial intelligence
ATMPs	Advanced Therapy Medicinal Products, i.e., somatic cell therapy, gene therapy and tissue-engineered medicines.
AQUA	Quality Standards Guidelines
AVL	Netherlands Cancer Institute – Antonie van Leeuwenhoek Hospital
CBG-MEB	In Dutch, stands for the Medicines Evaluation Board
CDK	Cyclin-dependent kinase
CHMP	Committee for Medicinal Products for Human Use
CieBOM	In Dutch, it stands for the Dutch Committee for the Evaluation of Oncological Agents, established by the Dutch Society of Medical Oncology (NVMO)
COVID-19	Coronavirus disease
CRO	Contract research organisation
DAP	Drug Access Protocol
DNA	Deoxyribonucleic acid
EC	European Commission
EFPIA	European Federation of Pharmaceutical Industries and Associations
EMA	European Medicines Agency
ESMO-MCBS	European Society For Medical Oncology – Magnitude of Clinical Benefit Scale
EU	European Union
EUPATI	European Patients' Academy on Therapeutic Innovation
FAST	Centre for Future Affordable Sustainable Therapy Development
FDA	US Food & Drug Administration
FEAM	Federation of European Medical Academies

GGG	In Dutch, stands for ZonMw's Proper Use of Medicines (GGG) programme
GGz	In Dutch, stands for mental healthcare
GLP-1	Glucagon-Like Peptide-1
GRADE	Grading of Recommendations Assessment, Development and Evaluation
GVS	In Dutch, stands for the Netherlands' Medicine Reimbursement System
Health-RI	Health Research Infrastructure
HTA	Health Technology Assessment
HMA	Heads of Medicines Agencies
ICDs	Implantable cardioverter defibrillators
INVOLV	Dutch foundation that provides advice and training for patient involvement in care, wellbeing and research
IZA	In Dutch, it stands for the Integrated Care Agreement concluded between the Dutch Ministry of Health, Welfare and Sport and thirteen parties in the healthcare sector
LODG	In Dutch, stands for National Consultation on Expensive Medicines
KNAW	In Dutch, stands for the Royal Netherlands Academy of Arts and Sciences
KNMP	In Dutch, stands for the Royal Dutch Pharmacists Association
KWF	Koningin Wilhelmina Fonds
MAUG	In Dutch, stands for Socially Acceptable Spending on Medicines
NHG	In Dutch, stands for the Dutch College of General Practitioners
NKI	In Dutch, stands for Netherlands Cancer Institute
NVMO	In Dutch, stands for Dutch Society of Medical Oncology
NWO	In Dutch, stands for the Dutch Research Council
NZa	In Dutch, stands for the Dutch Healthcare Authority
OECD	Organisation for Economic Co-operation and Development
PASKWIL criteria	In Dutch, stands for the criteria palliative, adjuvant, specific side effects, quality of life, impact of treatment and level of evidence
PD-1	Programmed cell death protein 1
PICO	Population, Intervention, Comparison, Outcome
PREMs	Patient-reported experience measures
PRIME	Priority Medicines
PROMs	Patient-reported outcome measures
RCT	Randomised controlled trial
R&D	Research and Development
SmPC	Summary of Product Characteristics
SWP	In Dutch, stands for 'Established medical science and medical practice criterion'
TIL	Tumour-Infiltrating Lymphocytes
VOI	Value of Information

VWS	In Dutch, refers to the Ministry of Health, Welfare and Sport
WRR	In Dutch, refers to The Netherlands Scientific Council for Government Policy
Zorginstituut Nederland	In Dutch, refers to National Health Care Institute
ZE&GG	In Dutch, stands for the Care Evaluation and Appropriate Use programme
ZonMw	In Dutch, stands for the Netherlands Organisation for Health Research and Development

ANNEX 1.
RESOLUTION ESTABLISHING THE COMMITTEE

RESOLUTION ESTABLISHING A COMMITTEE TO EXAMINE SCIENTIFIC UNDERPINNINGS FOR APPROPRIATE CARE: THE EXAMPLE OF PHARMACEUTICALS

The Academy Board of the Royal Netherlands Academy of Arts and Sciences, having regard to Article 5.1 of the Academy Rules and Regulations, has resolved to establish a Committee to Examine Scientific Underpinnings for Appropriate Care: The Example of Pharmaceuticals, hereinafter referred to as 'the Committee'.

Article 1. Assigned task

Which care has added value for which patient and at what point in time? This challenging question plays out across the entire spectrum of healthcare, a field subject to constant change and struggling with a variety of different ethical issues related to equity and fairness. Decisions and choices that affect patients should be informed by scientific evidence, but that evidence can and must be improved.

The Committee's task is to identify what is required to establish broad, ethical, and evidence-based (science-driven) underpinnings for healthcare. To this end, it will:

1. identify obstacles in the current system;
2. survey how science can contribute to a 'Learning Healthcare System' in which a steady stream of clinical data serves to generate new research findings that can, in turn, be used in clinical decision-making;

3. present case studies on pharmaceutical drugs (and their use) as an example:
4. propose actions based on items 1 and 2;
5. draft an advisory report in Dutch with a translation into English of the same.

Framework
The need for broad, ethical, and evidence-based underpinnings for healthcare is greater than ever: there is intense pressure on healthcare costs today, with consequences for public spending in other areas. One obstacle in the current system is that a therapy is only tested against the 'established medical science and medical practice' criterion upon inclusion in the insured standard healthcare benefit package. Because re-evaluation does not take place systematically when additional information becomes available, cyclical control based on scientific evidence is absent.

In the Netherlands, a strategic vision on scientific evidence for relevant care would benefit a very wide range of parties, encompassing policymakers in the Ministry of Health, Welfare and Sport, health insurers, physicians, researchers, and patients. This advisory report can help them manage their work based on scientific evidence. Unlike the health benefits package manager, the Academy is able to take a purely scientific approach, independent of other interests.

To arrive at a coherent and comprehensible advisory report, the Committee has chosen to present case studies on pharmaceutical drugs (and their use) as examples in this advisory report. It has selected this focus because:

- the Netherlands has considerable expertise when it comes to avoiding unnecessary costs and waste in relation to medicines;
- it aligns well with the Academy's advisory report *Efficiency gains through innovation in medicine development: how can science contribute?* of October 2021.

Lessons that can be learned from case studies on pharmaceuticals may also be applicable to other areas of healthcare.

Article 2. Composition and appointment period

The following individuals will be appointed as members of the Committee in a personal capacity:

Chairperson

- Liesbeth de Vries (professor of Medical Oncology, University Medical Center Groningen)

Members

- Jako Burgers (GP and endowed professor of 'Personalised Care in Clinical Practice Guidelines', Maastricht University)
- Marleen Kemper (managing director of Apotheek A15, compounding pharmacy for products that are not commercially available and products for clinical research; a non-profit joint venture between the medical centres of Erasmus University, the University of Groningen, Radboud University and Utrecht University)
- Xander Koolman (professor of Health Economics, VU Amsterdam)
- Rob van Marum (endowed professor of Geriatric Pharmacotherapy, Amsterdam University Medical Centre; clinical pharmacologist and clinical geriatrician, Jeroen Bosch Ziekenhuis)
- Sjoerd Repping (professor of Sensible Care, Amsterdam University Medical Centre; chair of the Care Evaluation and Appropriate Use [ZE&GG] programme)
- Ghislaine van Thiel (associate professor of Medical Ethics, Utrecht University Medical Centre)
- Christiaan Vinkers (professor of Stress and Resilience at Amsterdam University Medical Centre, and psychiatrist at inGeest Mental Health Care)
- Adriaan Voors (professor of Cardiology, University Medical Center Groningen)

After the Committee's installation, the following individual stepped down from his seat:

- Jos Beijnen (professor in Analytical Drug Toxicology, Utrecht University; researcher at the Netherlands Cancer Institute)

The Committee has been appointed for the duration of the advisory process. The Committee will offer a draft of its report to the Board before 1 May 2024.

Sjaak Neefjes will act on behalf of the Academy Board. Dr Eva Naninck of the Academy Bureau served as the official secretary to the Committee. On 1 August 2024, Dr Maartje Aukes succeeded her in this role.

Article 3. Quality and integrity

Prior to the Committee's first meeting, the Committee members familiarised themselves with the Code of conduct to prevent inappropriate influence owing to conflicts of interest (https://www.knaw.nl/publicaties/code-ter-voorkoming-van-oneigenlijke-beinvloeding-door-belangenverstrengeling) and submitted a written statement as confirmation. The Committee members have familiarised themselves with the Manual for Academy advisory opinions [Handleiding adviezen

en verkenningen van de KNAW] as adopted by the Academy Board on 18 September 2017. The policy set out in this manual will be adhered to when assessing the draft advisory report.

Article 4. Work plan

The Committee will draw up a work plan specifying its working methods and its communication and implementation strategy.

Article 5. Expenses and allowances

The Academy will cover the travel costs of the Committee members, but it will not make any other allowances available.

Article 6. Confidentiality

The Committee members will treat as confidential any information that can be construed as such to which they become privy while implementing this resolution.

Adopted in Amsterdam on 29 November 2022 by the Board of the Royal Netherlands Academy of Arts and Sciences.

On behalf of the Academy Board,

Wilma de Koning-Martens
Director General of the Academy

ANNEX 2. LIST OF INDIVIDUALS CONSULTED

Individuals consulted during the various expert meetings organised to address the main questions:

1. When can and should scientific evidence be used to provide meaningful guidance during the life cycle of a drug?
2. What methodological obstacles arise in the assessment of medicines?
3. Where and how can scientific research support decision-making and policy, with a view to serving the public interest vested in appropriate pharmaceutical care?
4. How can patients play a role in making scientific research meaningful for appropriate care?
5. Specific questions for EMA:
   a. How can scientific research in the early stages of drug development be stimulated or supported by EMA, especially when performed outside the pharmaceutical industry?
   b. What new information does EMA hope relevant investigator-driven studies will generate post-registration, and how can this influence re-evaluation by EMA?
   c. How can EMA support setting up (international) RCTs outside the pharmaceutical industry, given the different regulatory requirements within and outside the EU?
   d. How can EMA use scientific methods not only to monitor the safety and efficacy of drugs post-approval but also to identify and act on knowledge gaps?

e. What information is currently lacking that hinders EMA from making an informed decision about drug approval, and how does EMA believe science can contribute to this?
f. What role does EMA see in decision-making about new (and often expensive) drugs in maintaining the overall list of available drugs, and is consideration being given to ensuring that the availability of essential drugs on the EML is not compromised?
g. Recently, an EMA scientific committee approved administering half a vaccination dose (Mpox vaccines) due to shortages. When good data is available, is the same possible for other medications (like immune checkpoint inhibitors)?
h. Will the initiation of the EU HTA regulation in 2025 change anything regarding EMA drug registrations, and what does this mean for countries like the Netherlands?
i. In what way and at what point does patient involvement have the most impact on the assessment process?

Name, affiliation (expert meeting, if applicable):

- Marieke Bakker, Physician, METC representative and expert by experience (4)
- Liese Barbier, Regulatory Science and Academia workstream, EMA (5)
- Jan Benedictus, Programme Manager for the Dutch Patient Federation (4)
- Marcel Canoy, Endowed Professor in Health Economics at VU Amsterdam, member of the Healthcare Benefits Package Advisory Committee for the National Health Care Institute, Adviser at the Netherlands Authority for Consumers and Markets (ACM) (3)
- Giacomo Capone, Clinical Trials Transformation workstream, EMA (5)
- Lucia Caporuscio, Regulatory Science and Academia workstream, EMA (5)
- Francesca Cerreta, Scientific Evidence Generation Department, EMA (5)
- Marloes Dankers, Pharmacist and Adviser at the Institute for Responsible Medicine Use (IVM) (2)
- Mariette Driessens, Policy Officer for the Patient Alliance for Rare and Genetic Diseases (VSOP) (4)
- Joop MA van Gerven, Emeritus Professor of Clinical Neuropsychopharmacology, Chair of the Central Committee on Research Involving Human Subjects (CCMO) (1)
- Iordanis Gravanis, Head of Scientific Advice Office, EMA (5)
- Ralf Herold, Head of Regulatory Science and Academia workstream, EMA (5)
- Hans Hillige, Professor of Cardiology and Dutch alternate representative on behalf of the Dutch Medicines Evaluation Board in EMA's Committee for Medicinal Products for Human Use (CHMP)
- David Ikkersheim, Consultant, KPMG
- Astrid Janssens, Professor of Patient and Public Involvement
- Catherijne Knibbe, Professor of Individualized Drug Treatment, Clinical

Pharmacologist-Hospital Pharmacist at Leiden University Medical Center (1)
- Renate Okhuijsen-Kos, Researcher specialising in cystic fibrosis (1) at the Dutch Cystic Fibrosis Foundation (NCFS) (1)
- Bert Leufkens, Emeritus Professor of Pharmaceutical Policy and Regulatory Science at Utrecht University, Medicines Evaluation Board (3)
- Jet van Lierop, Test Subject member of the CCMO (4)
- Johan Mackenbach, Emeritus Professor of Public Health, Erasmus Medical Center, Chair of the National Health Care Institute's 'Personnel Utilisation and Environmental Sustainability in healthcare package decisions' committee
- Peter GM Mol, Professor of Drug Regulatory Science at University Medical Center Groningen, EMA, Medicines Evaluation Board (1)
- Pierpaolo Moscariello, Regulatory Science and Academia workstream, EMA (5)
- Marieke Perry, General Practitioner and Senior Researcher in Primary Care and Geriatrics at Radboud UMC (1)
- Ludo van der Pol, Professor of Neurology, Head of the SMA Expertise Center (3)
- Annemiek van Rensen, Adviser on patient involvement in care and research at INVOLV and EUPATI-NL, Board member of FAST (4)
- Maribel Rico-Salas, Academia Liaison, Regulatory Science and Academia workstream, EMA (5)
- Philip Scheltens, Emeritus Professor of Neurology, Amsterdam University Medical Center (1)
- Ivana Silva, Healthcare Professionals and Learned Societies Liaison, Public and Stakeholders Engagement Department, EMA (5)
- Gabe Sonke, Professor of Clinical Oncology, University of Amsterdam, Medical Oncologist and Head of the Medical Oncology Division at the Netherlands Cancer Institute (2)
- Elly Stolk, Professor of Measurement and Valuation of Health, Erasmus University Rotterdam (3)
- Steffen Thirstrup, Chief Medical Officer, EMA (5)
- Ly Tran, Pharmacist, Senior Policy Adviser at the Ministry of Health, Welfare and Sport (2)
- Spiros Vamvakas, Scientific Adviser on Human Medicines, EMA (5)
- Martine de Vries, Professor of Normative Aspects of Medicine, Leiden University Medical Center (3)
- Ana Zanoletty Perez, Head of Clinical Trials Transformation workstream, EMA (5)

ANNEX 3. REVIEW PROCEDURE

The following individuals reviewed a draft of this report in accordance with the *Manual for Academy advisory opinions* (2017):

- Johan Mackenbach, Emeritus Professor of Public Health, Erasmus Medical Center
- Carla Hollak, Professor of Medicines and Society, Amsterdam University Medical Center
- Ferry Breedveld, Emeritus Professor of Internal Medicine, Leiden University

The draft version was also reviewed by the Academy's four advisory councils.

The Academy is grateful to the reviewers for their efforts. The reviewers bear no responsibility for the contents of this report.