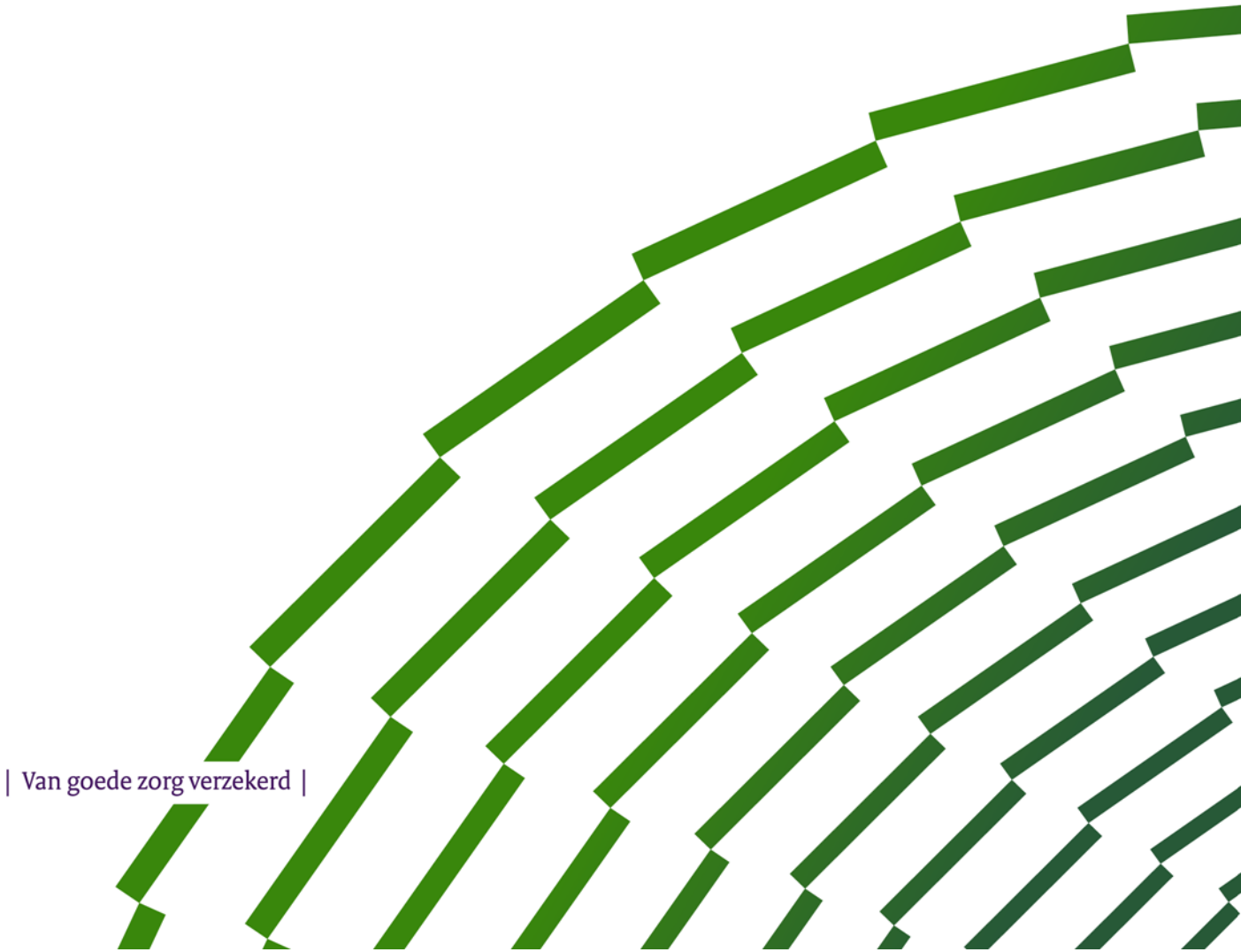
Zorginstituut Nederland

Final report
Case study phase

Programme Managing Registries for Expensive Medicinal Products
(Regie op Registers voor Dure Geneesmiddelen, ROR DGM)

Final 30 November 2023



| Van goede zorg verzekerd |

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Acknowledgements

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Foreword

Healthcare data from daily practice is becoming more important than ever. In a time when our society and the healthcare system are facing major changes and challenges, using good data from practice is essential for future-proofing the Dutch healthcare system, and a condition for appropriate care.

The quality and accessibility of healthcare are under great pressure. The number of people who want to work in healthcare is shrinking. Healthcare costs have been rising for years. This is because more and more people are needing care, more often and for longer. More and more expensive medicinal products and new technology are being put on the market. To keep care both healthy and accessible, we need to start organising care differently together. There is a realisation in the field that something needs to happen. Together, we are moving towards more appropriate care.

Good health data from clinical practice is necessary to let us focus on appropriate care, including information about the use of expensive medicinal products. Physicians learn which medicinal products really work for which patients and can target medication more effectively. Patients can use healthcare data better to help decide what available treatment suits their needs. This enables researchers to analyse how medication can be used effectively, health insurers to use this information to buy medication at fair prices, and manufacturers to get more information about safety and how medicines work. The government can manage the content of the basic insured package better so that care remains good in terms of quality and accessibility. The available care budget can also be used for the correct care at a reasonable price. Healthcare data from practice is hugely important.

We are excited to release this report with our vision on data availability about expensive medicinal products in a wide-ranging registry of disorders. The report also aims to encourage people to work together to accelerate the road to data availability and it provides concrete tools for doing so. Our vision is the result of a close collaboration with various stakeholders. We would like to thank everyone who has contributed!

Peter Siebers
Member of the Board of Directors

Hans Paalvast
Programme manager, Managing Registries for Expensive Medicinal Products

Summary

In this final report, the National Health Care Institute presents the conclusions and findings of the closed case study phase of the programme called Managing Registries for Expensive Medicinal Products (Regie op Registers voor Dure Geneesmiddelen, ROR DGM). Our vision is that data about the effects in clinical practice of expensive medicinal products should be available to all stakeholders with a legitimate need for that information. This vision is the result of extensive practice-based research, dozens of conversations with stakeholders, plus a public consultation. In this report, we clarify what the conditions and preconditions are for data availability about expensive medicinal products in the medical specialist care sector, and what steps must be taken to reach a suitable healthcare data landscape.

Objective: learning from practical effects of expensive medicines

The aim of ROR DGM is to take control of data registrations of expensive medicines. So that the practical effects of medicines are clearly registered, are interchangeable and are suitable for different purposes.

Vision: data availability for a wide-ranging disease-specific registry

ROR DGM has developed a vision of the ideal final situation regarding data availability for disease-specific registry. Ideally, healthcare data from practice is available to all stakeholders with a legitimate need for such information, and at the very least for managing the insured package. This includes data from clinical practice about expensive medicinal products. This will allow the stakeholders involved to focus on appropriate care. To avoid extra administrative burden, healthcare data is recorded in the regular care process, depending on the disease/disorder, using supporting software systems. Additionally, there is an information desk centralising knowledge associated with a specific condition and regulating access to data, so that people's privacy can be ensured.

The availability of healthcare data from daily practice is also very important for realising appropriate care. To achieve the goals of the Integral Care Agreement (Integraal Zorgakkoord, IZA), healthcare parties must work together to make data available more quickly in healthcare. This needs to be controlled by the authorities to create a good data landscape that healthcare parties can use to learn and improve real-world data (RWD). Existing programmes and initiatives for better data availability in healthcare should join forces and share knowledge, working towards a national vision on data availability.

Appropriate care as a result of data availability

Healthcare professionals will need information from clinical practice to make better decisions, tailor treatments to the patient's needs and ensure quality of care. Researchers can carry out further studies into the causes and consequences of diseases and the effects of medication and treatments. Policymakers in government and within healthcare stakeholders can make decisions based on information from clinical practice to keep healthcare and the contents of the basic healthcare package at a good level in terms of quality and accessibility for everyone.

Conditions and preconditions for the healthcare data landscape

In our vision, a good healthcare data space meets at least the following conditions:

- Information about medicinal products is an integral part of the treatment information and is collected within the patient's clinical pathway;
- Healthcare data from clinical practice is also available for the improvement goals of various stakeholders (both primary and secondary goals).

- The content of the minimum dataset required is determined jointly, with at least physician and patient representation involved . The dataset contains both clinical data and information about the effects of treatment (or refraining from treatment), side effects and the quality of life. This can be used to determine the effectiveness and cost-effectiveness, as well as being used for management of the insured package.
- Data collections are managed with the disorders/diseases as the basis. The governance must at least include representation of scientific associations and patients.
- Multiple usage of data requires agreements about standards and the inclusion of datasets in electronic medical records (EMR) and other software systems. One precondition is reliable linking of various information sources. This makes it possible to follow patients both longitudinally and across multiple healthcare providers and care institutions.
- Special care is needed for orphan drugs because registries for rare diseases always require an international approach. Joining existing national and international initiatives through, e.g. the European Reference Networks (ERNs) is recommended.

Maturity model helps data registries develop

The ROR DGM maturity model reveals how mature a data registry is and what development is desired. The maturity model includes all aspects that, in ROR DGM's view, are important for a good and functional disorder registry. The model describes the preconditions that a registry must comply with and gives a development path for data registries.

Case studies expose bottlenecks in the current situation

In the past 2 years, ROR DGM has done extensive research in collaboration with stakeholders into recording and analysing the effects of medicinal products for colorectal cancer, haemophilia, metachromatic leukodystrophy (MLD) and multiple myeloma (MM). In all the case studies, a minimum dataset is determined for each condition that will answer the research questions of the National Health Care Institute about management of the insured package. We conclude from the experience with the case studies that it is not possible to meet the information needs for the various information goals of healthcare parties using individual registries without links from other sources. This is due to organisational, legal and technical issues:

- **Legal framework**: In the current situation, clinical practice data is spread over many different sources. It is not possible to link this data reliably due to a lack of an unambiguous identification code and a lack of clarity about the principles. Scaling up the use of practical data is also hindered by various legislative and regulatory aspects about research goals and other goals.
- **Nationwide management**: To make clinical practice data available for the primary and secondary goals of the healthcare parties, good national governance and structural funding are essential. Currently, registries rely on uncertain and often temporary project-based funding, making continuity and continued development of registries a complex issue.
- **Technical implementation**: To keep the administrative burdens for care professionals low, it would be desirable to restrict the recording of clinical data and subsequent retrieval of those data to the EMR. However, the utilisation of EMR for this purpose is currently not possible because data is usually not recorded in a structured and standardised way and because healthcare providers make their own EMR design choices. Direction and stamina are needed to accelerate the standardisation of data.
- **Data quality**: Clinical practice data must be of good quality for the desirable applications. The data quality of various registries is still fluctuating and often insufficient for the goal. Within the case studies, the REQueST tool was used to evaluate and improve the quality of data.

The ROR DGM expertise group (see Annex 1) supports the programme's findings and has additional ideas about it. These have been expressed in the second formal plea calling for a concrete Healthcare Data Action Plan. The expertise group suggests bundling the governance of all existing projects, programmes and registries into a newly created Dutch Health Data Authority. This could accelerate the realisation of standardised healthcare data and improve the efficiency.

Vision and collaboration come together in harmonisation project

The colorectal cancer harmonisation project is a collaboration of Health-RI, governance quality registries and the ROR DGM and Outcome-Oriented Care (Uitkomstgerichte Zorg) programmes. At the request of the stakeholders, they are working together with various healthcare organisations to take control of the healthcare data of people with colorectal cancer. In this harmonisation project, a complete dataset that can serve all the primary and secondary purposes of the healthcare stakeholders is specified by a multidisciplinary group of experts. A recommendation about the control and implementation of the dataset follows, which links in with existing initiatives such as Health-RI's Obstacle Removal Process. This harmonisation project is a test of the ROR DGM vision and can be used as an example for other oncological disorders.

Advice: extend the programme for supporting Integral Care Agreement goals

ROR DGM's case study phase has provided new and useful insights and results for the future of data availability in healthcare. It is important to follow up on these gains. This can be done in an extension of the programme for 2024 and beyond, or the gains can also be improved upon elsewhere.

The National Health Care Institute advises the Minister of Health, Welfare and Sport (VWS) to extend the programme until the following goals have been achieved:

- Ensure the governance and funding of data availability through disease-specific registries for all purposes through connections to the governance quality registries;
- ROR DGM's vision is included in the long-term perspective of the National Vision and Strategy for the Healthcare Information System;
- Good results and learning experiences have been realised in the ongoing processes to strengthen disease-specific registries in prioritised target groups (oncology, haematology and rare diseases);
- Real-world data in several urgent National Health Care Institute cases is used for cyclic management of the insured package for expensive medicinal products, including molecular diagnostics.

We expect that an extension of the programme will help make care appropriate and will provide support for achieving the Integral Care Agreement objectives for data availability specifically for expensive medicinal products. Ending the programme would remove the control and urgency for availability of this data, making it less likely that these Integral Care Agreement goals will be met.

Introduction

This is the final report of the Managing Registries of Expensive Medicinal Products programme (ROR DGM) covering the definition and case study phases. Closing this phase marks the end of the vision development and case study research phases.

This report describes what results the programme has yielded so far, and what actions are still planned. The results fall into three blocks:

- Products and results of the programme – Section 2;
- Results and understandings gained from the case studies – Section 3;
- Vision and results in relation to the original assignment – Section 4;
- Section 5 includes a reflection on the programme;
- Section 6 describes the possible follow-up steps that are needed.

For the duration of the programme, ROR DGM worked frequently and intensively with the expert group, steering group, stakeholders, various adjoining programmes and organisations. They have made a key contribution to the programme. However, the work of ROR DGM is not finished yet; the intended goals of data availability for the patient, healthcare provider, researcher, government and other stakeholders have not yet been achieved.

The programme continued in what has been referred to as a "bridging phase" from 1 January 2023. In its letter of instruction, the Ministry of Health, Welfare and Sport has indicated that the prime objective in this phase is alignment to the governance of Quality Registries and supporting the current case studies (i.e. registries) within this context. This link is also mentioned in the Integral Care Agreement. It means that the findings, vision and objectives of both ROR DGM and Quality Registries will have to be taken into account in this phase.

In addition to this final report, ROR DGM published the "Consultative Document" with the vision in March 2023 on the website. This includes the document that was sent to all stakeholders in July 2022, together with the results of the consultation. A brochure was also published in April 2023 that outlines ROR DGM's vision.

This and the other sub-products mentioned in this report can be found under www.zorginstituutnederland.nl/werkagenda/regie-op-registers-voor-dure-geneesmiddelen

1 A retrospective

Managing Registries of Expensive Medicinal Products (ROR DGM) started its management activities in November 2019 at the request of the Dutch Ministry of Health, Welfare and Sport, with the objective of making the necessary information about the use of expensive medicinal products available in clinical practice, defining the conditions for registries and setting priorities. The information about practical use of medicinal products is often called 'real-world evidence' (RWE). This is information that cannot be found in practice because it is spread out over various systems, sources and organisations and cannot be shared or linked due to technical, organisational or legal reasons. Certain data needed for making good analyses is not (or not yet) recorded. This makes it difficult to use registers to understand the actual effectiveness and cost-effectiveness of the medicinal products used.

In 2019, the minister indicated – and recently reaffirmed (see Parliamentary Letter of 16 June 2023, Ref. 3599950-1049053-GMT, 'Naar een toekomstig stelsel voor de vergoeding van nieuwe dure geneesmiddelen uit het basispakket') – that at least data answering information needs for insured package management should be made available. The problem with licensing for care packages is that the literature and practice-based data are often still not available shortly after registration of a new medicinal product, resulting in insufficient understanding of the effectiveness and cost-effectiveness of that product. The National Health Care Institute's current working method of assessment, which only involves selection 'at the gate' (time of entry), does not therefore provide sufficient guarantee that these medicinal products are used effectively and efficiently in practice. There is also an increased number of medicinal products approved by the EMA via the central procedure.
Additionally, intramural specialist medicinal products automatically enter the insured package if they meet the established medical science and medical practice. After automatic entry, evaluation information about e.g. the optimum dosage and the criteria for starting and stopping are lacking in many cases. This involves information about appropriateness with the intent to correctly determine the status and refine the starting criteria for a medicinal product.

To find a structural solution to this problem, the minister has given instructions to improve control of the registries to achieve greater uniformity.
The following tasks are connected to this role:

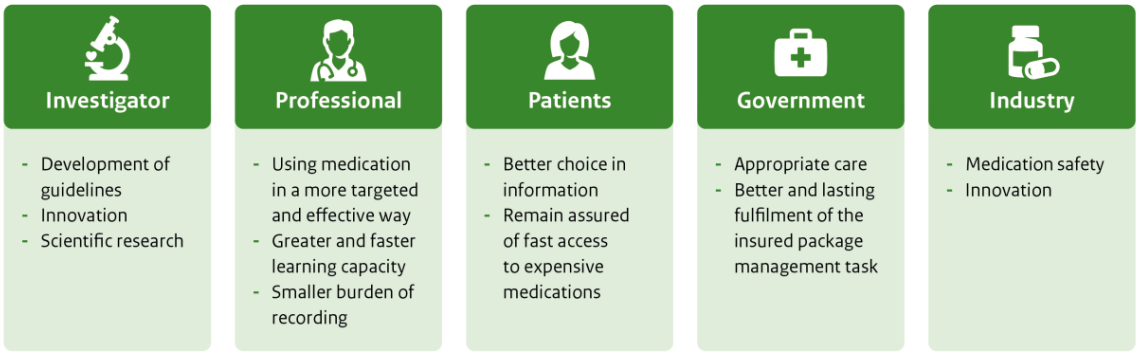
a. Determining and developing the standard conditions of the framework for the uniformity of registries.
b. Prioritising those registries related to disorders where new and/or expensive medicinal products are or will be on the market, which require an understanding of the effects and the use in daily practice. This particularly relates to medicines in the insured package that have a relatively high cost impact which requires further research into their effectiveness, appropriateness and/or more meaningful use.

The outcomes envisioned by the ROR DGM programme when launched were:

- Availability of good data:
  - availability of unambiguous and reliable data for everyone (patient, healthcare provider, health insurer, researcher, pharmaceutical companies, supervisory bodies and government).
- Registries that provide clarity, equal access and transparency:
  - for use in research into effects on effectiveness and cost-effectiveness, side effects and appropriateness;
  - to give treating physicians starting points for patient selection, determining the dosage and the moments that a treatment should be started and stopped;
  - treating physicians and patients can use the information from registries for 'shared decision-making';
  - to give reliable information to health insurers for healthcare procurement;
  - to give hospitals information about expensive medicinal products for optimising operational processes;

- to give the government the information needed for insured package assessments – sometimes with conditional inclusion – for the basic health insurance package;
- to give researchers and pharmaceutical companies information about the clinical relevance of a medicinal product in practice.

Figure 1. Intended effects



To achieve this, ROR DGM has worked with stakeholders from the start in 2019 on a common vision of the content, data and IT subdomains, and on governance & funding of the healthcare information landscape. Additionally, various products have been developed and delivered. An inventory has also been published of disease-specific patient registries for monitoring expensive medicinal products (e.g. medical specialist products) that were known at that time.

This report lists several types of registries. As a clarification, note that we use the following definition:

– **Patient registry**: a file in which medical and other data about patients is recorded structurally. This can include personal details, medical indication and treatment, and also data generated by patients e.g. about their experiences.
– **Quality registry**: collection, storage and further processing of data (including personal details) of a client population that is carried out with the intention of measuring and improving the quality of care given to the client population.

At the end of 2020, four registry holders were selected to play a role as case studies in different subdomains. The disorders included in the registries are intestinal cancer, haemophilia, metachromatic leukodystrophy (MLD) and multiple myeloma (MM). The overarching goal of the case studies was the development of a protocol to make registries suitable for monitoring the effectiveness and cost-effectiveness of expensive medicinal products. The visions and products developed have been tested and refined within the case studies, which had an intended term of 24 months. This is done partly on the basis of several research assignments carried out by the case study parties during the case study phase.

In parallel with the case studies, ROR DGM worked on drafting a vision of the desired healthcare data landscape for expensive medicinal products, in line with other ongoing programmes and initiatives. The learning experiences from the case studies have been included in that vision. The vision document was sent to the stakeholders, the expertise group (see Annex 1 for further explanation) and related programmes for consultation in July 2022. During the period that followed, conversations were had with stakeholders to test the vision; this included 'umbrella' stakeholders with a good overview. This consultation and the feedback have led to further clarification and refinement of the vision and formulation of the conditions that registries must meet.

ROR DGM formally closed the case study phase on 31 December 2022. This final report contains all the findings and lessons learned. What should be noted here is that the case study holders (plus underlying registers) are well on the way to making information available about the disorders they manage. At the same time, ROR DGM notes that the data needed for monitoring

expensive medicinal products is not usually available in a single register. This will require multiple sources, which are currently difficult or impossible to link together. Additionally, third-party access to the data in the various sources is usually impossible.

With the publication of the Integrated Care Agreement in 2022, it can be argued that agreements and good real-world evidence are also needed to meet the Integral Care Agreement goals relating to expensive medicinal products and appropriate care. Many steps still need to be taken to achieve the final goals set out at the start of ROR DGM.

See Integral Care Agreement: 'Working together on healthy care' | Report | Ministry of Health, Welfare and Sports

2 Results

2.1 Vision on information about the use of expensive medicinal products

As an all-encompassing result, ROR DGM has developed a *Vision on information about the use of expensive medicinal products* with input from the expertise group, various stakeholders and the learning points from the case studies. This vision has been addressed in what is referred to as the "Consultative Document". The results of the consultation were published in March 2023 on the National Health Care Institute website. This publication includes the original consultation document, all responses and questions with our answers, plus a summary response of the ROR DGM.

See Consultatiedocument visie Regie op Registers voor Dure Geneesmiddelen | Rapport | Zorginstituut Nederland

In addition to this vision and the learning experiences from the case studies (see Section 4), the ROR DGM programme has produced several sub-products. These are listed briefly in this chapter. In Section 5, we use the key points from the vision to give recommendations for the follow-up based on the original assignment, the sub-products described and the learning points from the case studies.

Conditions and data availability brochure

Using the responses and recommendations collected, ROR DGM's vision was refined and a sketch was made of the ideal final situation, where the various projects fit together coherently. The similarity between the different projects is that they all use healthcare data. ROR DGM included the findings in the "Data availability brochure" where the vision on data availability for expensive medicinal products is given for all primary and secondary applications. Using the current situation as the starting point, given the various programmes and their objectives, ongoing development towards data availability for all applications is needed. We have called the ideal final situation the 'Dutch Health Data Space' (DHDS), as a nod to the European Health Data Space (EHDS), but a different name is also possible. The *Data availability brochure* can help in the discussion and refinement and recognition of the overlap in the objectives of the various programmes.

DHDS Maturity Model

The data availability brochure also includes the *DHDS Maturity Model*. The maturity model indicates what aspects are important for good provision of information, what conditions or preconditions are needed and what the level of development is. The elements identified were stakeholders, governance, funding, application of and access to healthcare data, datasets and data collection, data quality, legal and privacy aspects, IT standardisation, IT implementation and public participation. The model distinguishes between five levels of development varying from 'unaware' to 'mature'. The elements will have to develop cohesively towards a higher level.

The current version of the maturity model was developed using the learning experiences from the ROR DGM case study phase and input from the expertise group. ROR DGM has expressed the wish to develop the maturity model further together with other programmes and stakeholders, so as to create greater coherence in the various objectives and actions. For quality registries, the Content and Data Governance Committees have already set up criteria that will be compared against the maturity model. Additionally, it would be desirable to align with the visions of other programmes.

Our expectation is that the maturity model can be a tool for helping to realise the development of the current registry landscape and its evolution into an ideal healthcare data landscape. The maturity model can be used as a tool that lets registries and organisations assess themselves. This will give them a grasp of how they score on specific elements and what that signifies. From there, we can focus on finding solutions for concrete issues and for providing guidance, letting

registries attain maturity step by step. The model also helps address ownership of specific components and bottlenecks in the healthcare data landscape.

The vision on data availability and the DHDS maturity model were compiled into a single brochure that was published on the National Health Care Institute website in April 2023.

See Data availability brochure | National Health Care Institute

2.2 Subsidiary results

The ROR DGM programme resulted in various sub-products (numbered 1 to 7) during the programme from 2020, some of which are no longer current. Additionally, various activities were started from the programme that produced partial results or will be followed up in the future (numbers 8 to 15).

1 *Report entitled 'Prioritisation of Disease-Specific Patient Registries' (Deliverable 1) including the 'Proposal for Selection of Case Studies' (Deliverable 6) – Managing Registries for Expensive Medicinal Products*

In this document, we have described the selection criteria that should determine the prioritisation of disease areas for which patient registries are considered important for monitoring expensive medicinal products. The selection criteria were divided into substantive and non-substantive criteria. The substantive criteria relate in particular to the uncertainty surrounding the effectiveness and safety of expensive medicinal products. Non-substantive criteria are related to the types of medicinal products. Criteria have also been defined for selecting case studies.

See Deliverables 1 & 6 Managing Registries of Expensive Medicinal Products | Report | National Health Care Institute

2 *Report entitled 'Overview of International Collaboration – Managing Registries of Expensive Medicinal Products (Deliverable 2)*

This document describes what areas in international collaboration have added value for registries relating to the use of expensive medicinal products. To that end, the ROR DGM programme is studying international disease-specific patient registries and the methods for using and analysing data from such registries. Additionally, this memorandum serves as input for Deliverable 3 (Framework for analysis methods) and Deliverable 4 (Dataset). Finally, the overview will be used to determine which international initiatives offer added value for collaboration during the case study and implementation phases.

See Deliverable 2 Managing Registries of Expensive Medicinal Products | Report | National Health Care Institute

3 *Report entitled 'Frameworks for Analysis of Observational Data from Patient Registries – Managing Registries of Expensive Medicinal Products' (Deliverable 3)*

This document describes the frameworks for determining a guideline for analysing observational data from patient registries. These are based on the existing relevant literature and reports plus an inventory of the possible methodological gaps that may need to be addressed.

See Deliverable 3 Managing Registries of Expensive Medicinal Products | Report | National Health Care Institute

4 *Report entitled 'Determining Datasets, Managing Registries of Expensive Medicinal Products' (Deliverable 4)*

This document describes the step-by-step plan to arrive at a disease-specific dataset that can be used to answer questions about cost-effectiveness, effectiveness and appropriateness. The criteria and methods described for achieving this disease-specific dataset have been tested in various case studies.

See Deliverable 4 Managing Registries of Expensive Medicinal Products | Report | National Health Care Institute

5 *Advice on Governance & Funding*

In collaboration with various care stakeholders, the National Health Care Institute has drafted a recommendation about setting up a national governance and funding structure for recording and using data about expensive medicinal products. The advice was presented to the Ministry of Health, Welfare and Sport on 15 June 2021.

See Advice on Governance & Funding from the 'Managing Registries of Expensive Medicinal Products' project | Advice | National Health Care Institute

6 *Report entitled 'Inventory of Disease-Specific Patient Registries for Monitoring Expensive Medical Specialist Drugs'*

ROR DGM has compiled an inventory of disease-specific patient registries with information about expensive medicinal products used in medical specialist care. The purpose of this inventory was to create a clear picture of the organisation and design of these registries, as well as gathering suggestions about which issues are important for the programme. The inventory reveals various important variations in the type, objective, organisation and funding of registries with expensive medicinal products. An important point is that data collection is often – inevitably – done manually and only a few marketing authorisation holders use Care Information Building blocks (Zorg Informatie Bouwstenen, ZIB) or standard coding systems. It emphasises the need for management of the healthcare information landscape and central coordination and management to achieve the basic infrastructure for multiple uses of healthcare data.

In 2022, ROR DGM transferred the findings from the inventory to the RIVM so that they could be included in the national metadatabase on the website www.Zorggegevens.nl.It is important for ROR DGM that all specific registries/cohorts etc. remain findable and including them in this metadatabase ensures that. The European Medicines Agency (EMA) is currently also working on an overview of qualified or almost-qualified registries.

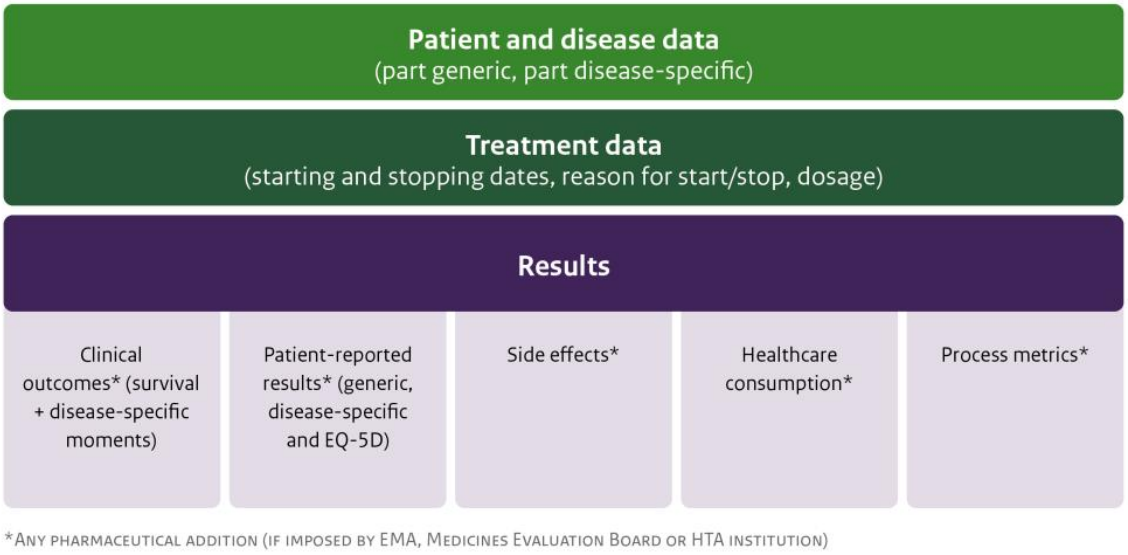
See Inventory of Patient Registries for Monitoring Expensive Medical Specialist Drugs | Report | National Health Care Institute

7 *Disease-specific dataset*

Within a well-functioning disease-specific registry, reliable data is collected about the patient's treatment, including data about the use of expensive medicinal products and their health effects. The consultation document includes a generic dataset (see Figure 2) that indicates what data or type of data is needed for monitoring the course of the disease in daily practice, and of the use of expensive medicinal products for that disease. This dataset can be supplemented with disease-specific characteristics for each disorder to form a disease-specific dataset. This process is aligned with the description of the determination of the dataset (Deliverable 4). The details of the dataset are included in Annex 2.

It is primarily about healthcare data about all medical specialist care and, in the longer term, about patient data such as individual healthcare environments (IHE), care in primary healthcare, and care given by other healthcare institutions.

Figure 2: Datasets for each disorder



8 Expertise groups call

At the end of 2021, the expertise group made an urgent appeal to the Dutch Ministry of Health, Welfare and Sport, healthcare professionals, patients and care insurers for central management of the healthcare information landscape to eliminate the current fragmentation.

See Managing Registries – call for central management of the healthcare information landscape | Publication | National Health Care Institute

9 Standard for data quality/REQueST

The ROR DGM programme attaches great importance to the subject of data quality because it is an essential precondition for the use and reuse of data. However, confidence in the results and the information obtained from healthcare data is also determined by the data quality. The REQueST tool, or in full the 'Registry Evaluation and Quality Standards Tool' is a potential instrument for assessing the quality of data in registries used for HTA purposes. The tool was developed by EUnetHTA. This is a European network of HTA organisations, of which the National Health Care Institute is a member. This tool was tested in the HTA environment and many international stakeholders – including the European Medicines Agency (EMA) – have given commentary on this tool in the public consultation. The usability of the REQueST tool will have to be investigated further, including in the international context. The REQueST tool is currently being tested in Canada. We hope that the tool can be tested in more countries in the future and that this will lead to further development and actual use.

To test the data quality in the case studies, the tool was used in ROR DGM. These experiences were used to draft a memo with further explanation about the REQueST tool and lessons for the future (see Annex 3).

10 Harmonisation Project on Colorectal Cancer

As an extension of Case Study 1 (PLCRC), the CRC harmonisation project was created in 2022. In this project, Outcome-Oriented Care, Health-RI, governance for quality registrations and ROR DGM work together to achieve a harmonised dataset for colorectal carcinoma (CRC) that is usable for primary and secondary use. The added value of this dataset is that an advantage can be gained from the one-time implementation in the IT systems and the ability to use the data multiple times.

Activities to achieve a dataset that will be backed by care professionals and patient associations were started in January 2023. The development process was carefully crafted

and layered, with continuous efforts to achieve good communication and collaboration between the core team and the working group members. The core team provided the basis with a design for the care process and the dataset. Through an iterative process, the working group and feedback group gave input and feedback in four sessions.

The guiding principle of the CRC Harmonisation Project was to use existing initiatives and datasets that have already been developed for colorectal cancer. Reusing the technical specifications of other projects allows quicker and more long-lasting progress to be made and aligns the project better with ongoing initiatives.

Our approach can count on plenty of support from the stakeholders involved. Consensus about the harmonised dataset was reached in September 2023. The final report, which includes a recommendation about the governance and implementation, is expected to be published in December 2023.

11 *Road map for "Use of Real-World Data for Cyclic Package Management"*

The National Health Care Institute, in particular in the role of insured package manager, is one of the stakeholders that has an interest in the availability of data about the use of expensive medicinal products in practice (the real-world data, RWD). The ROR DGM programme has helped refine the role and positioning of the use of RWD by the National Health Care Institute. The discussions about this and the developments have not yet been completed and the ROR DGM programme will remain involved.

For cyclic management of the insured package, it is important that sufficient good and reliable RWD is available. This has not been the case enough until now, except for the rare disease case, where the case led to the legal and procedural establishment of a registry, the MLDi. This collects validated measures of outcome internationally that can be used for cyclic package management. A successful link was made with the independent database set up for the Libmeldy manufacturer's mandatory post-marketing data collection. In the future, this infrastructure can be used for other uncertain and expensive treatments for MLD. There are additional obstacles for the larger indication areas: it is for instance not always clear what RWD must be collected. That means it is necessary for responsibility to be taken for scheduling and prioritising making RWD available and that this is aligned with the agenda for cyclic management of the insured package.

As an extension of this, the National Health Care Institute should give high priority to the topic of data availability and use of RWD. Good and reliable healthcare data is indispensable for its core tasks – both now and in the future.
This should for instance be seen in relation to the reassessment of the National Health Care Institute's quality tasks, which must include current developments: the framework for appropriate care and the link that is then desired to the quality tasks for insured package management and the agreements in the Integral Care Agreement. There is also the desire that the stakeholders have for expensive medicinal products to be reassessed periodically after licensing in the insured care packages. This will be developed further in 2023 together with the stakeholders, the VWS and the National Health Care Institute as part of the process of improving and expanding the basic health insurance package testing. The availability of healthcare data is essential for this and requires prioritisation.
In 2023, the National Health Care Institute will also publish an established medical science and medical practice roadmap for the practical implementation of cyclic package management, including the use of real-world data in assessments and reassessments. This will use (inter alia) the results of Deliverable 3.

12 *Vision entitled "Use of Real-World Data by Pharmaceutical Companies"*

In addition to the National Health Care Institute, ROR DGM has also asked the pharmaceutical companies (via the VIG, the Association for Innovative Medicines), as stakeholders with a unique role in medicinal products, for their vision on the use of RWD. For which legitimate objectives would the VIG want to use healthcare data, and RWD in particular? ROR DGM's opinion is that concreteness and transparency about this help the

discussion and improve trust. In June 2023, the VIG published a white paper about this on its website.

See VIG Healthcare Data White Paper | Publication | Vereniging Innovatie Geneesmiddelen (Association for Innovative Medicines)

13 *Expertise group call follow-up*
In June 2023, the RORDGM expertise group (Annex 1) made an additional call to the Ministry of Health, Welfare and Sport (VWS) asking them to accelerate central management of healthcare information. The members do see that there are various good initiatives, but they argue that there should be more central orchestration. They also plead for building upon standardised healthcare data and for a Dutch Health Data Authority (DHDA) to be established.

See Managing Registries plea for central management of healthcare information; not dreaming but acting | Publication | National Health Care Institute

14 *Approach for making a rare disease registry FAIR*
To improve interoperability of the MLDi database (Case Study 3) with other databases, a 'FAIRification' process was started in 2023. The goal was to create complete interoperability for a selected amount of data through a web-based semantic model for which an ontology was made.

In July 2023, a webinar was organised together with Health-RI to actively share the knowledge gained. Additionally, it was presented on the Health-RI website as a FAIR demonstrator.

See Demonstrator portfolio | Publication | Health-RI

15 *Conceptual information model for a disease-specific registry*
Within the ROR DGM programme, experience was gained with the conceptual information model for a 'disorder registry'. This can be seen as a potential solution for embodying knowledge of how healthcare works in a human-readable information model. The reasoning behind this is to create an understanding of the relevant information elements (concepts) and how they are related to each other. The conceptual information model offers healthcare organisations a communication tool and reference model for what information it would be desirable (in the longer term) to make available in a standardised and structured way from the operational healthcare and business processes. The information model can be used for the metadata definition of datasets so that healthcare providers can make their data available to the various disorder registries with a clear and uniform meaning.

For a good description of the information elements (concepts), we looked at the process models and definitions of the Hospital Reference Architecture (ZiRa: Ziekenhuis Referentie Architectuur) and the information elements were then linked to definitions in the healthcare and welfare thesaurus and the national terminology thesaurus. This was done in consultation with Nictiz. The relationships between the dataset for colorectal cancer, the care information building blocks (ZIBs) and the OMOP model were also established. This is planned for OpenEHR. The publication of the first version of the information model is expected to take place in December 2023. Further discussion on applicability is taking place with the data governance committee, Health-RI and Nictiz.

3 Case studies

3.1 General

The ROR DGM programme started with four case studies at the end of 2020, with a term of two years. The overarching goal of the case studies was to develop a protocol to make registries suitable for monitoring the cost-effectiveness and effectiveness of expensive medicinal products. The case studies include two oncological case studies, on colorectal carcinoma and multiple myeloma. The other two case studies are non-oncological orphan diseases, haemophilia and metachromatic leukodystrophy (MLD).

The case studies have provided valuable information about the technical, administrative and legal aspects of data collection and the desired governance and funding. In that context, the case studies gave important input for ROR DGM's vision. Bottlenecks were also exposed and requirements for the preconditions were specified to align disease-specific registries with the future healthcare data landscape.

Annex 4 includes templates of the case studies that briefly show the context, assignment and stakeholders involved. The final reports by the case study holders will be published separately on the National Health Care Institute website. Section 4.3 includes the most important insights and recommendations from the case study phase. This gives a picture of the current status of data availability on a disorder.

3.2 Selection of case studies and progress

3.2.1 Selection procedure

The procedure for selecting case studies was prepared in close collaboration with the expertise group and was described in the above-mentioned 'Deliverables 1 & 6 – Managing Registries of Expensive Medicinal Products'.

Several general selection criteria were determined that a case study must at least meet (for more details see the document mentioned above):

- The case study must be performed in a disease-specific patient registry.
- It must be for a clinical picture or indication for which at least one new medicinal specialist product was included in the basic health insurance package in the period between January 2019 and January 2022.
- Sufficient data from patients must be collected in a period of two years after the start of the case study in order to test the effects of the standards and methods, as established during the first year of the ROR DGM programme.
- Stakeholders must be involved or must show commitment to this patient registry.
- Access to individual patient data for the implementation of package management for expensive medicinal products and for scientific research should be possible for the National Health Care Institute through the appropriate informed consent, including the possibility of linking the data (using pseudonyms) from other sources.
- There must be a willingness to implement in the patient registry a set of agreements on information standards (and FAIR principles), principles of IT systems and the use of analysis at source, as are being developed in the ROR DGM project.
- There must be a willingness to achieve nationwide coverage of the patient registry per medical condition.
- There should be a willingness to collect additional data if necessary for a proper assessment of the effectiveness (in terms of cost and otherwise) and appropriateness.

Additionally, several specific selection and award criteria have been defined. A distinction was made between the type of disorder and the phase that the patient registry was in when a case study was started. The guiding principle was to select at least two oncology case studies, one non-oncological orphan drug case study and one case study on other disorders (excluding

oncology). In all cases, they had to involve disorders where expensive medicinal products are used.

Tendering processes were carried out via the dynamic purchasing system (dynamisch aankoopsysteem, DAS) for selecting the case studies. The registry holders felt that this procedure was one-sided: it gave them no option to jointly decide on a shared project proposal. For that reason, a new work plan was set up for all four case studies after the procedure was finished. This new plan, based on the submitted project proposal, did provide an option for developing and specifying objectives, results and preconditions together.

3.2.2 Initial and adjusted objectives for case studies

The first steps in the case studies focused on formulating a research question focusing on the expensive medicinal product that became available for the disorder (or that was expected soon). The primary focus in the case studies at the start was management of the insured package, and more specifically package assessment. Initially, the research question was formulated in such a way that answering this question could be used for an assessment or reassessment of the expensive medicinal product.

The research question was formulated based on the PICO method (population, intervention, comparator and outcome). The research question had a broad scope, with different outcome measures to look at both the favourable and unfavourable effects of the expensive medicinal product and to make it possible to assess the cost-effectiveness.

The research question was formulated in consultation with the secretary of the Scientific Advisory Council's Medical Products Committee (WAR-CG) of the National Health Care Institute. However, in the period between the start of the selection procedure and the actual start of the case study, some medicinal products had already been assessed and other products were found to have less impact on the budget and were therefore not placed in the lock procedure. In the end, one of the four case studies had a current demand from insured package management.

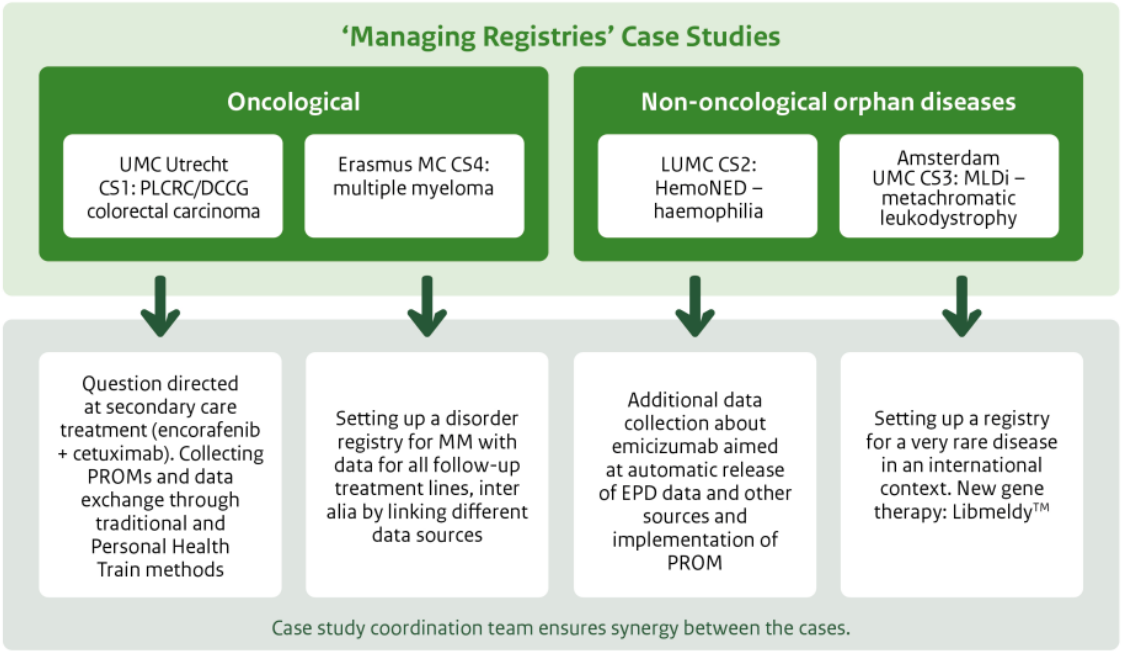
In the case study about colorectal cancer (PLCRC, CS 1), a treatment for metastasised carcinoma – encorafenib (in combination with cetuximab) – was included based on the list of possible candidates for the lock procedure. The estimated budget impact turned out to be lower than initially expected, and in the end this product was not assessed by the National Health Care Institute. However, the case study did look at the use of encorafenib, in particular at the results of the combination therapy compared to the results from the initial clinical trial.

In the end, there was no direct package question for the case study about clotting disorders (HemoNED, CS 2); the appropriateness of emicizumab was followed actively on the recommendation of the National Health Care Institute. HemoNED provided reports for that, although this has not yet led to further action by the National Health Care Institute. The case study did look more closely at patients who were treated with emicizumab, and also at how these patients differed from the patients who were treated with Factor VIII.

In CS 4 (multiple myeloma), there was ultimately no immediate package question. The data from the case study may possibly help the multiple myeloma working group in the future in terms of indication-wide assessment, within the frameworks set up by the National Health Care Institute.

The only case study that did have a current package question was the MLDi registry (CS 3). It involved an assessment of the gene therapy Libmeldy® as part of the collaboration in the Beneluxa initiative. In particular, natural history data from the registry was used in the package assessment.

Figure 3: Research questions for the case studies



3.2.3 Defining a dataset

In all case studies, a dataset is determined to answer the questions of the National Health Care Institute. For two case studies, PLCRC (CS 1) and HemoNED (CS 2), the procedure 'Deliverable 4 Managing Registries of Expensive Medicinal Products' was used. In Case Study 3 (MLDi), the dataset was determined with an international Delphi procedure, which the representatives of the National Health Care Institute and the Medicines Evaluation Board provided input for. This dataset has been described in an international publication. For multiple myeloma (CS 4), a dataset for 5 Dutch hospitals had already been determined in the pilot project 'Value-Driven Care for Multiple Myeloma' (WGZ-MM).

3.2.4 Data and IT

The selection criteria and objectives for the individual case study holders/registries on data and IT appeared difficult to realise in practice. This was because the data needed for monitoring expensive medicinal products is not collected in any single registry and is not recorded fully and/or in a standardised form in the EPD either. As a result, additional actions were needed (by care professionals, data managers or algorithms) to convert the necessary data from the EPDs into a standardised format.
Additionally, other datasets are also needed for data that is currently not fully recorded in the EPD (such as PROMs and side effects) or for data that is already being collected centrally – such as national basic hospital care registry (LBZ) data by the hospital data service (DHD), or the Vektis database.

Partly for this reason, it proved difficult for the National Health Care Institute to have access to the necessary data for the implementation of package management of expensive medicinal products in the setting of the case studies. There were also legal limitations: the informed consent for each registry was regulated for a specific objective and amending it for a different objective proved difficult in practice. It was also not possible to link reliable data from different sources based on the BSN (the 'citizen service number' in the Netherlands) in actual or pseudonymised form because registries are not allowed to process the BSN. The latter made identification of patients and/or the data of patients in the various sources difficult. Various case studies were examined for solutions for these bottlenecks, but this was time-consuming and costly. It also does not offer lasting solutions that can be implemented widely.

The programme therefore chose to focus the Data and IT subprojects on the information layer of the Nictiz interoperability model. This does not cover the application and infrastructure layers. As mentioned before, the legal, organisational and technical bottlenecks around setting up a

national healthcare data infrastructure should be regulated nationally under the management of VWS (wider than just the information policy Executive Board), from the Care Information Council (Informatieberaad Zorg, IBZ) and the obstacle removal process of Health-RI.

3.2.5 Quality of data

The REQueST tool mentioned earlier was applied to the case studies. Both the case studies/marketing authorisation holders and a reviewer completed the tool independently from ROR DGM. After that, the key findings and differences were discussed. The conversations were illuminating and led to better mutual understanding. The marketing authorisation holders stated that the tool, and an evaluation of it with an HTA organisation, clarifies where they can further improve the quality and transparency of their registries. This shows that the REQueST tool can be valuable in identifying the quality status of registries. This allows HTA organisations to consider whether data that registries already collect is suitable for insured package management and appropriate care. Marketing authorisation holders also gain insights into what items might need to be developed more. For additional information, see Annex 3.

3.3 Insights and learning experiences

Experience was gained in the case studies with the possibilities and limitations of (real-world evidence) registries for evaluating medicinal products in daily practice. This section gives the key insights and recommendations of the case study/registry holders.

3.3.1 Defining a dataset

In recent years, the ROR DGM programme has worked on conditions, preconditions and methods for defining a dataset. Every case study uses a different system for defining the disease-specific dataset. This is because the case studies differed in the development phase that the patient registry was in and a pragmatic approach was sometimes chosen.

Together with members of the expertise group, ROR DGM developed the D4 procedure, which describes the step-by-step plan for defining a disease-specific dataset. The D4 procedure was applied and evaluated in the two case studies. The D4 procedure was followed in Case Study 1 (PLCRC), but a pragmatic approach was chosen. A dataset was compiled with 24 items from the research cohort, which was able to answer the National Health Care Institute's package question. This limited dataset was submitted to stakeholders for commentary.

In Case Study 2 (HemoNED) a pragmatic approach was also chosen for the composition of the dataset. The dataset of the registry as previously specified in a wide group was tested with stakeholders in two rounds of discussion based on the D4 procedures.

Case Study 3 (MLDi) chose a structured and standardised consensus procedure, the Delphi method, for determining the dataset. This is an international procedure where physicians and patient representation are involved as 'experts'. A caveat here is that not all stakeholders were included in this process.

In Case Study 4 (MM), the decision was taken to reuse an existing dataset from a previous pilot study (Value-Driven Care for MM) and to enhance it. The D4 procedure was not followed, which did not safeguard the input from the National Health Care Institute, Medicines Evaluation Board and other stakeholders. In a later phase, input was requested from international projects such as H2O and ICHOM.

As an extension of Case Study 1 (PLCRC), the CRC Harmonisation Project was started in January 2023. The basic starting point for defining the dataset in this project was the CRC care process. Care professionals determined – jointly and in a multidisciplinary approach – what the care process for patients with colorectal cancer looks like generically. It was then decided what items are needed as a minimum and at what moments to help care professionals provide the optimum oncological care for making the diagnosis, setting up a treatment plan and the follow-up.

Other lessons learned about defining the dataset:

- To be able to collect information associated with daily practice for a specific disorder, it is essential that disease-specific datasets are specified nationally by multidisciplinary committees. Governance agreements should prevent different datasets from being developed in new projects and initiatives.

- Multi-stakeholder involvement in defining a dataset is important to get input other than just from the perspective of the 'physician/researcher'.

- In rare disorders, where guidelines or other high-quality justification are not available (or not to a sufficient extent), the opinions of national and international experts are key. A consensus-based procedure with international experts is a good way of determining the dataset carefully.

- A consensus-based procedure in which many potential data items are considered is time-consuming: in Case Study 3 (MLDi), this took one year in total. Instead of a Delphi procedure (modified if necessary), a real-time Delphi procedure is a simpler and more efficient method.

- When determining the data required for research questions, continuous coordination is needed between the content-level experts and the information experts. This is to determine whether the desired dataset can be populated with data that is recorded in the primary care process. Early coordination can (a) prevent research questions from being formulated that cannot be answered with the available real-world data at that time and (b) allow the conversion from research question to the required queries to go smoothly and ensure the results are clinically relevant.

- This means a switch in the thought process when determining the dataset: the starting point should be the care process and the data that is already being recorded, including data definitions of care information building blocks (ZIBs) and information standards, instead of what it would be desirable to record.

3.3.2 Collecting the required data

A lot of data collections or registries were set up with a single goal or a specific research question in mind, making it difficult to use them for multiple purposes. Answering the research question for package management using the case studies and the associated underlying registries made it necessary to expand or adjust the dataset, and collecting the data in practice also proved difficult. The use of PROMs is still in its infancy and is an example of a potential expansion of the dataset.

Lessons learned about collecting the required data:

- In all case studies, collecting the required data was impossible from just a single source or single registry. Clinical data is usually available from a single source but sometimes needs to be supplemented from other sources. Additionally, a lot of clinical data is not recorded in a structured way. The PROMs/quality-of-life data and data about healthcare consumption/costs are usually recorded in separate sources.

- With the introduction of molecular diagnostics and the associated personalised medicinal products, treatments are now being created for increasingly smaller patient populations. This has consequences for collecting data (including research data), namely selecting a sufficient number of patients and selecting the correct patients.

- There are a lot of challenges in collecting PROMs:
  - Including patients for PROMs still has numerous limitations: most hospitals do not have a structural demand for PROMs. Additionally, not every patient wants to participate or will not always complete a PROM questionnaire.
  - Patients are only willing to complete PROMs regularly when participating in research projects with clear purposes. Important criteria here are that the patient must benefit from

their own individual treatment, and that the PROM results must be discussed during an outpatient consultation.
    - There is insufficient support among healthcare professionals to invest in a broad implementation of PROMs in the consulting room. There are concerns about the logistics and time required at the outpatient clinic.
    - Using PROMs is not yet well-embedded in daily patient care. PROMs are currently rarely used for shared decision-making in the consulting room.
    - Hospitals make their own choices about PROMs – independently of the developments in PROMs – and then start implementing them.
    - Although incorporating digital PROMs is possible in all EMRs in principle, the implementation of PROMs is being slowed down by a lack of capacity in IT departments.
    - Health insurers are not taking many measures to actively facilitate the implementation of PROMs in daily practice through healthcare procurement.
    - The frequency of PROM surveys should be more in line with the research questions. Basing this on a generic frequency does not always result in useful data because health effects can become manifest earlier or later.
    - PROM questionnaires for the regular care process are different from the questionnaires for clinical trials. In order not to burden patients with double the number of questionnaires, regular questionnaires are paused for the duration of the clinical trial; this does not help the collection of PROMs data.

- For rare diseases, data usually needs to be collected internationally in order to obtain enough data. In the national registries with very small numbers of patients, such as MLDi, the data is usually found in a single source (the EMR), but most data is recorded as unstructured text. In rare diseases there are often no uniform definitions that are used in a consistent way internationally. This makes one-time registration for multiple uses difficult.

- An existing registry can act as the infrastructure for the study and data collection for a conditional inclusion process or a managed entry agreement through a pay-for-performance regulation. The MLDi registry has shown that valuable data can be collected quickly this way, and existing initiatives can be used in the longer term.

3.3.3 Availability, completeness and quality of data

A defined dataset is the starting point for identifying which sources these data items are stored in and what it will take to collect these data items at the national scale. Important principles for this analysis are the quality, timeliness, completeness and availability of the necessary data. The case studies show that it is not possible to meet the information needs using individual registries, and that there are many legal, organisational and technical sticking points when combining the various sources. That is why it is impossible at the moment to have all the required data items, or not with the desired levels of completeness and quality.

The following bottlenecks and learning experiences were listed by the case study holders:

- In the ideal situation, the required data items are available straight from the source system. This 'raw data' has not been processed or transformed in any way. However, current EMR systems in hospitals and the local configurations only facilitate standardised or structured data recording to a limited extent; data is therefore being recorded as free-format text. This makes it complex to extract data from local sources, especially when scaling up to nationwide coverage across all hospitals. Using regional or national sources is currently still the best option for collecting data at the national scale. Using these sources has several limitations:
    - They are restricted to a limited dataset, making it impossible to collect specific (e.g. clinical) data easily and at a large scale through this channel.
    - Data that can be extracted from the EMR relatively easily is often related to the financial handling of treatments within the EMR. A caveat here is that such information does not necessarily reflect reality: a certain oncolytic being prescribed and declared does not necessarily mean that the patient has completed this course of treatment. However, the administration of the medication (and registration of that fact) is usually not available in these national sources.

- The clinical data, which is recorded unstructured in free-format text fields, needs data managers to manually extract the information from hospital systems. This is a labour-intensive and expensive process, which also has a negative effect on the timeliness of the available information. Additionally, extracting this data is often done periodically, which also delays availability.

- For effective extraction of information from local sources in future, it is important that the defined dataset matches the implemented data definitions of the care information building blocks (ZIBs) and associated information standards, in accordance with the principles of Registration at the Source. These ZIBs and information standards are the cornerstones for recording and exchanging information within the healthcare sector. In addition to supporting regular healthcare, these information standards can also promote the use for secondary objectives.

- Case Study 2 (HemoNED) provided the first insights into the reliability of clinical outcome measures reported by the patients themselves through an app (number of bleedings). A variety of reasons led to it proving difficult to obtain enough reliable data:
  - Motivating patients to use the app is difficult;
  - Technical problems hinder data entry by patients and their willingness to use the app;
  - Patients who do use the app may possibly be a select and motivated group that does not represent the total population;
  - It is difficult to check if home-treated bleedings are sometimes forgotten, and whether bleedings that were treated in the hospital were not reported by patients in the app.

- There is currently no national source that has a complete overview of all care-related harm (adverse events). This is partly because this data is not uniformly recorded in the EMR and the extra burden of work this creates for the treating physicians in practice.

3.3.4 Linking data sources

In the current situation, data from multiple sources is needed for monitoring the effectiveness and cost-effectiveness of expensive medicinal products. This requires data about an individual patient from different data sources to be linked together. The BSN is a unique identification number per person, making it a candidate as a linking key or identifier. However, recording the BSN for (quality) registrations, research cohorts and national data collection is not permitted, so it cannot be used for matching at the patient level across multiple data sources. Several case studies looked into alternative possibilities for correlating the data.

The following findings and bottlenecks were noted by the case study holders:

- Case Study 1 (PLCRC) used probabilistic matching, with a success rate of 91.7%. The patients where this failed were linked manually afterwards, following a case-file study. This way of linking was feasible for a small population and a limited number of sources. When the number of sources and the size of the population increases, though, this method is unsuitable because the likelihood of mismatches increases.

  Case Study 4 (MM) also describes the problem with various pseudonymisations or patient identifiers and refers to the report 'Final report evaluation use of PROMs' of the Value-Driven Care for MM pilot. Without a linking key, aggregated collection of PROM data and the link to clinical data and healthcare consumption data to create a coherent outcome set are hindered. This is needed if it is to be possible to use this set for benchmarking, research into the effectiveness and cost-effectiveness of treatments (expensive ones in particular) and for improving the quality of care. Another limitation noted in the report is that certain links are not possible without consent from the individual patient.

- Case Study 1 (PLCRC) offers a possible solution by setting up a national linking service that works on the trusted third party (TTP) principle for query issues/linking. A linking key remains necessary for linking data about an individual patient across sources. This requires a legal basis.

- In the European context, research is being done on the options for linking data across various sources. The European rare disease registry platform (EU-RDR) initiated the European Patient Identity Management project (EUPID), but this was not yet completely operational at the time of the international MLDi registry's launch (Case Study 3). EUPID was designed to make secondary use of datasets easier in biomedical research and healthcare. Recently, the EU-RD Platform launched a new pseudonymisation tool called 'Spider'.

3.3.5 Analysing data

After determining the required dataset and identifying the source systems, there needs to be a check of whether this results in usable data for answering the research question.

This resulted in the following insights from the case studies:

- In Case Study 1 (PLCRC) and Case Study 2 (HemoNED), it was possible to carry out a limited data analysis based on the research question. This was because not all data items were available, due to excessively small patient numbers with specific treatments in the cohort and because supplying and linking data cost a lot of time and was partly impossible. Case Study 1 (PLCRC) made an initial analysis and came up with results that were in line with the current insights in practice.

  Even though the analyses made are not generating clear answers, obtaining this data helps to gain understanding and a picture of how well this data is already sufficient to meet the wishes of the National Health Care Institute.

- A proof of concept to set up a federative learning network was carried out in Case Study 1 (PLCRC). This shows that it is possible to use real-world evidence to answer research questions without setting up a single central registry for the purpose, instead working with decentralised sources within a secure network. There is then a requirement that the data is standardised and structured.

- Case Study 1 (PLCRC) describes the options for data analyses across multiple sources, distinguishing between horizontal and vertical analyses. When carrying out horizontal analyses in the network, the same data items are requested from each data station. This is mainly intended to increase population selections. Because that case only involves unique patients who appear in just a single data station, no link is needed across the sources for the patients.

  The power of vertical algorithms is the option of combining and analysing data items from the same patient that are stored in different data stations. This makes it possible to carry out complex analyses without first collating all the data centrally. A precondition is that the same patient's data can be identified across data stations so that it can be linked.

- When starting the analysis, it is important that there are clear definitions for all aspects in the research question. This must already be taken into account when formulating the research question and describing the data collection process. Some terms that seem clear at first sight, such as the treatment line, turn out to be very complicated to determine based on the available data items.

- Legal, technical and organisational limitations made it impossible for National Health Care Institute staff to carry out analyses. This was a requirement in the quotation process for the case studies to gain access to the pseudonymised registration data. In the Health Insurance Act, the National Health Care Institute has a legal basis for receiving personal details for carrying out its statutory duty of insured package management, but this can only be done based on pseudonymised BSNs (citizen service numbers). Registries are not allowed to process the BSN, so exchanging data was not possible.

3.3.6 Efficacy-effectiveness gap

During the marketing authorisation procedure of new medicinal products, there is often an efficacy-effectiveness gap, i.e. a difference between the homogeneous study population and the

effectiveness in the heterogeneous patient population in daily practice. Case Study 1 (PLCRC) concluded that trial outcomes for medicinal products (new ones in particular) are not – or not always – representative for predicting outcomes in daily practice too. The analyses in this case study provided proof of this efficacy-effectiveness gap.

3.3.7 IT aspects

Focusing on structured and standardised recording of care data makes it possible to share such data with other healthcare professionals and use it for secondary purposes. This is the assumption underpinning a healthcare information landscape in which data availability is key. In the case studies, experience was acquired with various IT aspects relating to recording and exchanging data.

This yielded the following insights:

- All case studies found that data is mostly stored in free-format text fields in the EMR. Additional actions were needed to make this user-generated data accessible and usable. An example of this is a data manager who manually extracts the requisite data from the EMRs and records it in a structured and standardised way in a registry. Ideally, healthcare data should be recorded in the source system in as structured and as standardised a way as possible.

- This also means that it should be enforced in the governance that scientific associations, national research groups and other stakeholders conform to the structured and standardised way of recording in the EMR.

- The transition from free-format text to more standardised and structured recording of data must be widely backed by healthcare professionals and hospitals. This process takes time, money and resources, for which a pragmatic approach is therefore fitting as there always needs to be scope for unstructured data. A short-reward loop for the patient and the person doing the recording, e.g. in the form of up-to-date dashboards, can be motivational.

- In rare diseases, where data from multiple countries is usually used for analyses and research, almost all data is recorded in an unstructured yet unambiguous way in the local EMR. This is because there are often no uniform definitions for rare diseases that are used in a consistent way internationally. That is why the unstructured data from the EMR is structured in the MLDi registry by recording it using an electronic data capture system with clearly defined data elements.

- To improve interoperability of the MLDi database with other databases, a 'FAIRification' process was started. The goal was to create complete interoperability for a selected amount of data through a web-based semantic model for which an ontology was made. This resulted in the following learning experiences:
  - The FAIR principles can only be implemented properly if the purpose and the application are clear. Without a clear application, randomly making things 'FAIR' is not sensible.
  - When creating a semantic model, close collaboration between the semantic modeller and the subject matter expert (physician or researcher) is needed to make the correct translation from data element to meaning and definition.

- Case Study 2 (HemoNED) completed the SKMS project Making Quality Registries Future-Proof (Verduurzamen Kwaliteitsregistraties) and was given practical tools for optimising the dataset, linking the data items to ZIBs and code lists, as well as gaining a better understanding of the care process. The principles of the SKMS project are valuable in the further development of registries. A major bottleneck is the implementation of the recommendations, because of the dependency on the hospitals and EMR suppliers that are limited in manpower and funding.

- At the moment, new technology and solutions are being developed by various commercial and other organisations that can simplify extracting data from the EMR. In the report from Case Study 1 (PLCRC), natural language processing (NLP), machine learning (ML) and

artificial intelligence (AI) were mentioned as technology that could be used for getting both system-generated and user-generated data out of the EMR in a structured way. Most products currently still focus on the quick wins achievable using system-generated data such as lab values or intervention codes.

- In Case Study 4 (multiple myeloma), there was collaboration with the RHONDA project, which aims to extract as much digital and real-time structured clinical data as possible from EMRs for the NKR. A proof of concept was carried out in the case study to investigate which parts of the clinical data from the desired dataset could be accessed digitally via RHONDA. The data was also validated by comparing it against the same dataset collected in the regular process via IKNL data managers. Acquiring experience with RHONDA makes it possible to investigate what quick wins and other results can and cannot be achieved and what preconditions are important when working with RHONDA. The dependency on a commercial data gateway party in particular came to the fore as a subject of discussion.

- INKL is also doing research together with partner organisations on extracting user-generated data, whereby free-format text notes are converted into structured data and metadata. The first outcomes of this are positive, but the underlying models need to be trained more to deal with false positive and false negative outcomes as much as possible. Independently of the design choices, there is a chance that these models will still need to be fine-tuned and adjusted to work properly at the level of an individual hospital. This may potentially limit the scalability of the models. This limitation can partly be removed by transforming EMR data from hospitals into e.g. a local OpenEHR or OHDSI OMOP data model node and then having the models run on this. This benefits both the scalability and the efficiency. The transition from EMR data to these data models (and the corresponding maintenance) does require efforts from the hospitals. The question is whether hospitals have the time and resources for this.

- Case Study 2 (HemoNED) developed an improved technical data extraction method for two EMR suppliers. Data extraction through FHIR standards was developed for the hospital that worked with Chipsoft HIX, and a batch delivery method was developed for the EPIC centre. Further research needs to show whether these methods are scalable.

- The principle of having a single central database in which information from multiple sources is collected is not desirable, in part due to stricter privacy legislation and the presence of alternative solutions. In Case Study 1 (PLCRC), research was done into a federated learning model based on the privacy-by-design principle, in which data remains decentralised, stored at the source, and only single or aggregated outcomes are shared with the – duly authorised – requester/researcher. The proof of concept carried out in the case study shows that the federated learning model makes it possible to use real-world evidence to answer the research question without setting up a single central databank for the purpose, working instead with decentralised sources within a secure network.

- The European Medicines Agency has also been involved for several years now in extracting real-world evidence. DARWIN-EU has launched a large-scale project for federative analysis of the use of medicinal products using OHDSI-OMOP data from clinical practice. At the moment there is ongoing research into MM, which IKNL is involved in from the Netherlands and for which the National Health Care Institute provides input through a Stakeholder Advisory Board. The results of the MM project are expected at the end of 2023.

3.3.8 Legal aspects

All organisations involved in the case studies had to deal with legal obstacles around collecting, linking and exchanging the data. Existing agreements did not offer sufficient options and had to be adjusted and/or new contracts had to be drawn up. This is a very time-consuming and burdensome process. In addition to explicit restrictions in privacy legislation, there are also differences in interpretation about the scope that the exceptions in the law appear to offer. Because it is often unclear who is responsible for the final legal test and who makes a decision based on that, a lot of time can be lost in each case on discussing and realising legal possibilities.

The lengthy throughput times in the legal departments at hospitals can hinder international cooperation and data exchange projects.

The case studies resulted in the following experience being acquired:

- Patients in Case Study 1 (PLCRC) and Case Study 3 (MLDi) were explicitly asked for permission to share their data with various parties and for multiple purposes. This offers a solution for some of the limitations. Contracts are still needed for data exchange with e.g. pharmaceutical companies and governmental authorities.

- In the case of Case Study 4 (MM), the issues involved linking clinical data, PROMs and LBZ data (Landelijke Basisregistratie Ziekenhuiszorg – National Basic Registry of Hospital Care). Hospitals and hospital data services (DHD) had to make additional agreements about supplying PROMs and linking different datasets. An additional agreement was also needed with the hospitals which made it possible for IKNL to carry out and supply additional registrations to DHD. This was time-consuming and delaying for the case study party, and a considerable burden for the individual hospitals.

- In Case Study 1 (PLCRC), using data about care products fell outside the scope of the existing processing agreements between DHD, IKNL and the hospitals. The legal complexity and throughput time for changing this meant that it could not be done within the duration of the case study, and the decision was made – of necessity – to use DHD data only for signalling that there were patients (which did fall within the agreement). The data about care products could not be used.

- In Case Study 3 (MLDi), a joint data registry agreement was chosen as the contract form for realising a legal basis for exchanging data within an international multi-centre patient registry. A contract in which partners are jointly responsible (Joint Controllers) for the registry and for ensuring privacy has both advantages and disadvantages.
  - The advantage is that no other contracts are necessary for data entry or data release between all the partners. Additionally, the responsibility and control over the data remain regulated close to the patient, namely with the local hospital. The same contract applies between partners; this is good for the uniformity and consistency. Finally, shared responsibility and ownership of the data mean that the continuity, impact and accessibility of the registry are better safeguarded.
  - A disadvantage is that a time-consuming negotiation period (about 2 years for the MLDi) must be taken into account. The shared responsibility makes hospitals reluctant. It is more common for many hospitals to transfer data plus the associated responsibilities through e.g. a data transfer/sharing agreement.

3.3.9 Governance

In the case study phase of ROR DGM, we worked on recommendations about the design and governance to achieve data availability at the level of the disorders. Healthcare data is important for multi-stakeholder setups, in ROR DGM's vision, and can serve multiple purposes. Based on the governance of quality registries, a design was chosen that ROR DGM would prefer alignment with. The experiences from ROR DGM's case study phase will help in the further development of the governance of quality registries to ensure data availability for primary and secondary purposes.

- The governance has already been determined in both Case Study 1 (PLCRC) and Case Study 2 (HemoNED). There is multi-stakeholder involvement: the relevant scientific associations and the patient organisation have active roles, but pharmaceutical companies are also involved.

- A proposal for a new governance model was developed in Case Study 4 (MM) which has been aligned as far as possible with the governance models of comparable registry initiatives. The goal is national recognition of this new governance model to combat the fragmentation of initiatives and the inefficient use of resources to collect data for haematological disorders.

- Several governance issues are defined in the above-mentioned joint data registry agreement from Case Study 3 (MLDi):
  - The role of stakeholders in the collaboration;
  - The structure of the organisation;
  - How privacy is safeguarded;
  - What conditions apply to the data sharing?

  The governance is gradually taking shape through an iterative process. Currently, 22 physicians from 13 centres and 10 countries are participating in this partnership, with meetings every two months.

- MLDi, in collaboration with the ERN-RND and the Clinical Patient Management System (CPMS), has also established an official international indication committee for current and future therapies (e.g. stem cell transplants, gene therapy, enzyme replacement therapy) to improve the appropriateness of use in Europe.

- Case Study 3 (MLDi) has carried out additional research into alternative contractual and organisational forms for international registries. An example of this is an International mono-centre registry in which a single centre acts as the controller and processor. Amsterdam UMC has experience with this structure in a different very rare disease, Vanishing White Matter. In this registry, patients and families throughout the world give informed consent to Amsterdam UMC and share patients' medical data with Amsterdam UMC. Legally, this is a simple construction without complex contracts at multiple centres. In addition, recruiting through patient organisations and colleagues can be done relatively quickly and easily. Disadvantages are that the success and quality of the data rely on the willingness and motivation of patients and families to participate (including selection bias) and share their medical information. Another possible disadvantage is that one centre owns the data. This can be less than optimal for the continuity of the registry (suppose that the physician or researcher involved quits) and the impact (suppose that the data is not shared with other researchers).

- In Case Study 3 (MLDi), the dataset was tested against the criteria for compliance with the EMA guidelines. However, this proved to be a complicated procedure. The case study party therefore recommends including the EMA guidelines in the design and creation of a registry at an early stage.

3.3.10 Funding

All case study holders currently rely on project funding, which is often short-term. Without the prospect of structural funding, the project organisations struggle for continuity. The survival of various registries is under threat. Inclusion in the registry of the governance of quality registrations is considered the only option that is eligible for structural funding, and currently only HemoNED has signed up.

In Case Study 2 (HemoNED, a public-private partnership has been set up with the pharmaceutical companies. However, they say that all the parties would prefer the public purse to bear the costs. Raising private funding annually is a labour-intensive process, requiring work by the registry's employees and board members. Additionally, pharmaceutical companies are becoming bound by increasingly strict regulations, making offering financial support even more complex. Moreover, the willingness of pharmaceutical companies to help pay for monitoring the use of medicinal products depends on the phase their medicinal products are in. This makes long-term registry funding impossible.

Case Study 4 (MM) indicates that an independent and lasting funding model must be set up to offer long-term funding. The guiding principles of this funding model are based on the social perspective that:

1. Healthcare must be available to all patients in a long-lasting, affordable way;
2. Conflicts of interest between researchers, marketing authorisation holders, regulators and insurers must be avoided;

3. For collaboration with private parties, new models of public-private partnerships should ideally be investigated, where a direct financial relationship between the private partner and the data supplier (the registry) is avoided

3.3.11 Other learning experiences

- Case Study 3 (MLDi) described all the lessons learned from setting up an international multi-centre patient registry for rare neurogenic disorders in an international framework. The framework is a practical manual for registries that are useful for research, medicinal product development and policy. It is based on five core themes: interests, data, IT infrastructure, governance and funding. The ideal situation is outlined for all subjects and practical solutions are provided to achieve the ideal situation (or alternatives where the ideal situation is impossible).

- Additional research is needed to assess whether and how the criteria for the governance of quality registries are applicable to organisations that provide data availability structurally for a disorder or across a domain of disorders for all stakeholders. A specific focus on rare diseases is needed here. Due to the international cooperation, tailored solutions and/or new legislation may be necessary, especially as these national registries – like all other registries – need structural funding. The international context brings additional complexity to this.

- The link with European initiatives was investigated in three case studies, such as ERNs, the Data Analysis and Real World Interrogation Network (DARWIN EU) and the H2O project. Joining forces with centres of expertise for rare disorders in the European context is seen as an important step forward.

- The maturity model developed by ROR DGM is a suitable tool for objectively assessing various elements of the development of a registry. The model provides concrete steps for improving specific areas. All the case study parties have now self-assessed a score using the maturity model (see Appendix 6). Afterwards, ROR DGM discussed the results in a consultation. Feedback was also given on the model's usability.

- The maturity model's usability for registries of rare diseases is inadequate in certain areas. It is worth considering developing a modified model for rare diseases.

- The case study parties had to do pioneering work in several areas. Point solutions were often designed for this and it is not yet possible to extrapolate these to scalable solutions. Nevertheless, the enthusiasm and drive of these healthcare professionals are needed for the development of new initiatives.

3.4 Key recommendations

The final reports of the case studies give a nice picture of what is and is not possible with the current registries within a short period. In summary, the case studies give the following urgent recommendations to allow real-world data from registries to be used for cyclic insured package management and appropriateness of use of medicinal products:

Key recommendations:

- Make data linking between different sources possible: resolve the legal and contractual limitations. Use a unique identification number such as the BSN to make it possible to identify patients and link data. Simplify the links between the NKR, PALGA, DHD and hospitals in the short term for monitoring oncological medicinal products.
- More progress and cohesion to achieve automatic extraction of data from the EMRs: structured and standardised recording at the source, in particular for data that is recorded as free-format text. Remove limitations caused by different IT systems and design choices at hospitals.
- Explore setting up a data gateway at DHD so that LBZ data from hospitals (Landelijke Basisregistratie Ziekenhuiszorg – National Basic Registry of Hospital Care) can be collected more in real time.

- Invest in structured recording of missing data and completeness of data: PROMs, toxicity, side effects, numbers of patients/participating hospitals.
- Set up a multi-stakeholder governance structure in which agreements are made about determining and managing the dataset for each domain and about the release of data.
- Set up an independent and long-term funding model based on the social perspective that healthcare should be available to all patients affordably in the longer term. Preconditions are structural data availability (and structural funding for it) and monitoring of the effectiveness and cost-effectiveness of healthcare at socially acceptable costs.

4 ROR DGM vision and outcomes

The original assignment from VWS, i.e. making the requisite information about expensive medicinal products available, has not yet been completed despite the urgency having increased. That urgency can also be seen in the Integral Care Agreement (ICA), which describes objectives for:

- improving insured package management;
- the desire for expensive medicinal products to be reassessed periodically after licensing in the insured care packages;
- improvements in scientific research, the purchasing of expensive medicinal products and agreements about appropriateness of use.

The availability of good real-world data for all applications is a precondition for the ICA objectives relating to expensive medicinal products and appropriateness of care being achieved.

In this section, a link is laid between the core elements of the ROR DGM vision, supported by the lessons learned from the case studies, and the original assignment given to the ROG DGM programme, insofar as the topic in question was mentioned in that assignment.

4.1 Information about expensive medicinal products is part of the treatment information

In the ROR DGM vision, using expensive medicinal products is part of the overall care process for the patient. This also applies to the diagnosis, an operation or another treatment. Data about medicinal products only becomes useful when it is combined with the outcomes and the clinical data. That is why data about expensive medicinal products must be an integral part of a dataset for each disorder and must not be gathered in separate registries for the drugs themselves.
The disease-specific dataset contains not only information about the medicinal products (and their use) but also about other treatments the patient is undergoing, characteristics of the disease and measures of outcome such as the clinical results, PROMs, quality of life, side effects and healthcare consumption. This information should preferably be recorded in the primary care process (for instance the EMR) in such a way that there is no additional administrative burden within the care process and that the data is also suitable for multiple uses.

Assignment: Greater control of the registries and thereby greater uniformity.

ROR DGM outcome: *The control should focus primarily on data availability instead of on the individual registries. Data about expensive medicinal products only becomes valuable when combined with other information such as the clinical data and the (treatment) outcomes. If data availability for all purposes is made the principle and disease-specific datasets are defined, this will bring all the existing projects, programmes and registries together.*

4.2 Information about expensive medicinal products is important for various stakeholders

Information about expensive medicinal products is important for various stakeholders and it is used for multiple purposes. ROR DGM distinguishes the principal stakeholders as the patients, healthcare professionals, researchers, care insurers, governmental authorities and pharmaceutical companies. All these stakeholders have a legitimate interest in having good and complete data about expensive medicinal products.

Better decision-making for the individual patients in the consulting room will only be feasible if that healthcare data is available longitudinally, both now and in the future. Additionally, this data is essential for evaluating the quality of care, and for innovations in care that are driven by

scientific research. The ultimate purpose is to improve care and achieve the best possible, accessible and affordable healthcare.

The information requirements for each stakeholder and the grounds (legally in particular) need to be expressed explicitly, depending on the question. We see two exceptional data users for medicinal products, namely the pharmaceutical companies and the National Health Care Institute (as the insured package manager). ROR DGM has asked the Association for Innovative Medicines (Vereniging Innovatieve Geneesmiddelen, VIG) and the National Health Care Institute to produce a position paper about the use of real-world data.

Assignment: Registries that are set up must at the least correspond to the information requirement for insured package management.

ROR DGM outcome: *Individual registries are not able to meet the information requirement for insured package management. Information about expensive medicinal products is important for various stakeholders and purposes. Combine all the objectives and define the information requirements and the necessary variables jointly, as they will largely be the same. Prioritise data availability for disorders for which new and/or expensive medicinal products are on the market or will be arriving soon and where research is needed into the effectiveness, appropriateness and/or more suitable use. Configure the data landscape so that high-quality data will be available as much as possible for answering the questions arising from cyclic insured package management and other objectives.*

4.3 Working together towards clear, nationwide governance

To achieve data availability for both primary and secondary use, a good nationwide governance system is needed. Within the governance for quality registries in medical specialist care, the parties are working towards a manageable and efficient landscape for quality registries. The quality data will be used by care professionals and healthcare providers for the continuous cycle of learning and improvement, as well as by patients.

Current quality registries do not envisage sufficient data availability for all the primary and secondary applications. The objectives of ROR DGM are broader than those of the quality registries and that in turn affects the governance agreements. Aligning ROR DGM with the governance of quality registries will not be possible to achieve in the short term and would in any event only resolve some of the issues. The orchestration of the implementation needs to be done by all the parties involved so that the data is genuinely made available; this is an urgent issue. In its second call for action, the ROR DGM expertise group suggests creating a concrete Healthcare Data Action Plan (Actieplan Gezondheidsdata) in the short term, in line with the national vision and strategy for a healthcare information system and the VWS's vision on secondary use of data. In addition, they are calling for the governance of all existing projects, programmes and registries to be bundled together under a newly created Dutch Health Data Authority. This will allow genuine progress to be made rapidly towards achieving data availability for both primary and secondary use. As a precursor to this, a forum set up on instructions from VWS could make preparations and tackle the urgent matters.

Assignment: Advice about the control mechanisms deemed necessary by the National Health Care Institute and how such mechanisms can be put into effect.

ROR DGM outcome: *In their recommendations of June 2021, the National Health Care Institute pleaded the case for ongoing public funding and a clear governance structure in which all the important stakeholders are represented. Merging this with the governance structure of the quality registries would be preferable, but progress and assurance of the preconditions were stated as requirements. As of yet, such progress is not happening and there is no ongoing and independent funding for disease-specific registries for the purpose*

of evaluating expensive medicinal products; this is causing acute problems with the current registries.
The ROR DGM expertise group supports the programme's findings and, in its second call for action, made the case for a concrete Healthcare Data Action Plan. They suggest bundling the governance of all existing projects, programmes and registries together under the aegis of a newly created Dutch Health Data Authority. This could accelerate the realisation of standardised healthcare data and improve the efficiency.

4.3.1 Focusing work on the disorders

In terms of both the content and the control, it is important to centre the working methods on a disorder or domain of disorders, within the context of the nationwide governance. This is because expertise is available at the level of the disorders for tackling disease-specific questions and information.

There would seem to be a prominent and leading role here for the relevant scientific associations, in close collaboration with the specific patients' representation. Their task will be to organise the subdivisions within the disorder domain and to handle the structure and orchestration. They will also take the reins in defining, optimising, managing and maintaining the disease-specific dataset. When doing so, they will take account of the minimum amount of information needed for the legitimate data requirements of all the stakeholders.

The limitations of a disorder-oriented setup were also the subject of debate during the consultative rounds. Patients sometimes have several disorders, resulting in the patient being involved with multiple healthcare professionals. It must therefore also be possible in the future to follow patients longitudinally across different healthcare providers and care institutions so that a continuous cycle of learning and improvement is created. Consensus about the data required for each disorder and standardisation of the recording is a precondition for this.

Assignment: VWS encourages disease-specific setups for patient registries, along with a sufficiently flexible design to allow for future changes.

ROR DGM outcome: *Work is currently being done on setting up a disease-specific governance structure following on from the case studies for multiple myeloma, haemophilia and colorectal cancer, as well as the colorectal cancer harmonisation project.*
The scientific associations, supported by the relevant patients' associations and the Federation of Medical Specialists (FMS), seem to us to be the obvious parties for producing a proposal for the further setup of the disorders and domains of disorders, with sub-themes and clustering where needed.

4.3.2 Information Desk

At present, healthcare data relating to patients or disorders is largely stored in a variety of source systems. Multiple sources are then needed when answering more complex questions. ROR DGM is therefore pleading the case for a virtual 'information desk' for each disorder or domain of disorders, which will provide coordination and disseminate the requested information. The information desk is part of the governance structure and it has the following functions:

- facilitating access to the data (now linked together);
- monitoring the quality of the data;
- assistance with the correct methods of analysis, interpretation and use of the data.

Making the information desk part of the nationwide governance makes it possible to guarantee the rights and responsibilities of all stakeholders. Within a disorder or domain of disorders, a review committee will be set up with experts from the field. This will allow disease-specific questions to be answered.

Assignment: One point requiring attention here is the meaning assigned to individual data items. The data is not per se usable if it cannot be placed in the correct context.

ROR DGM outcome: *The case studies have shown that experts with knowledge about the data, its meaning and the disorder concerned are indispensable in the analysis, interpretation and use of the data. It is extremely important that expertise for each disorder is given a place within the permitted access to data via such an 'information desk' as part of the nationwide governance.*

4.4 Joint agreement on the contents

Within a disorder or domain of disorders, there needs to be agreement about the minimum dataset that meets the information needs of all stakeholders. A key precondition for this is that it must be clear what legitimate objectives the stakeholders want to use this data for. The ROR DGM programme has developed a procedure (D4) jointly with the expertise group for determining a dataset for a disorder. This takes account of the information requirements of all stakeholders. The D4 procedure thereby offers a method for registries to determine the dataset for a disorder jointly. Although the D4 procedure is originally intended for national registries, it could also prove useful for international registries.

Because the stakeholders jointly determine the dataset, we expect that substantive discussions will arise about the usefulness and necessity of data items. This means that the dataset will not become disproportionate and the administrative burden for care professionals will be limited to the information that is genuinely essential.

ROR DGM outcome: *Data availability starts with a jointly defined dataset. Several procedures are possible for this. The working method used in the colorectal cancer harmonisation project uses the care process as its starting point, as is the case in many other projects. This ensures the best alignment with the data that is already being recorded in the primary care process.*
It is important that all the stakeholders for a particular disorder are involved and that there is agreement during the process between the content experts and the information experts. This avoids a situation in which the research questions (or other queries) cannot be properly answered using the defined data elements. In addition, it is important that the governance is furnished with details of the agreements about management of the dataset.

4.4.1 Generic dataset

A well-functioning disease-specific registry contains reliable data about the patient's treatment, including data about the use of expensive medicinal products (or the choice not to give treatment) and their health effects.

The ROR DGM programme drew up a generic dataset that indicates what type of data is needed for monitoring the course of the disease in daily practice, and of the use of expensive medicinal products for that disease. This dataset can be supplemented with disease-specific characteristics for each disorder. This kind of structure for datasets, with a generic part and a disease-specific part, has been suggested in the Regional Oncology Networks. Work is being done here in general on defining not only the oncology dataset but also the tumour-specific datasets and components of the care process, such as the multidisciplinary meeting.

Medicinal products and the associated diagnostics are part of the treatment along a patient's care pathway and they have a relationship with various outcome categories. We can distinguish the following elements in a dataset that sometimes require disease-specific additions:

- relevant characteristics of the patient;
- characteristics of the disorder, including those relating to diagnosis and prognosis;
- the interventions and treatments, including dosage, administration route and administration location (at home or in the care institution setting);

- measures of outcome:
  - clinical results;
  - patient-reported outcome measures (PROMs);
  - quality of life measurement (EQ-5D) for cost-effectiveness calculations;
  - side effects, new ones in particular, serious adverse events (CIOMS) and side effects for which policy changes are needed;
  - healthcare consumption, such as the number of days in hospital or intensive care, outpatient consultations or A&E visits;
  - process results.

This data has already been included partly in the basic healthcare dataset (BGZ). It is emphatically about healthcare data for all medical-specialist care and, in the longer term, about data (self-reported by patients) such as individual healthcare environments (IHE), care from primary healthcare and from other healthcare institutions.

4.4.2 Disease-specific dataset

In addition to the items in the generic dataset, disease-specific data is also essential, such as the disease-specific clinical outcomes. Progression-free survival is for instance an important outcome measure for colorectal cancer, whereas the number of bleeds per year is relevant for haemophilia. Joint agreement among the stakeholders is therefore important; this includes the care professionals, in both a multidisciplinary approach and at the disorder or domain level. It is the intention that the care providers should be able to record the items in the defined dataset once only for multiple uses, i.e. both within the primary care process (such as lab requests or discharge letters) and for secondary uses. In addition to disease-specific information, additional data can be collected (temporarily if necessary) based on the medicinal product used or a specific research question.

ROR DGM outcome: *Fit in where possible with the basic healthcare dataset (Basisgegevensset Zorg, BGZ) and the generic datasets that have already been defined for other disorders. It is moreover essential that any disease-specific dataset should be determined in consultation with the various stakeholders. Special attention should be paid to side effects and PROMs. The Dutch Health Data Authority should play a coordinating role in getting datasets defined and in that these are made generic where possible.*

4.4.3 A focus on data quality

The quality of the healthcare data that is recorded is essential if such data is to be used and reused. Confidence in the results and in other information based on healthcare data is also determined by the quality of that data. Standardising the data requires the users to reach agreements about the content of the data items and what the items signify.

The REQueST tool can be used for checking the quality of the data in registries when it is to be used for HTA purposes. The tool has a two-part goal:
- it supports consistent evaluation of the applicability and reliability of registries for HTA organisations;
- it offers those who hold patient registries an understanding of where further developments and improvements can be made in the quality of their registries.

In addition to the REQueST tool, there will also be efforts to find a fit with other resources, e.g. the test criteria that have been drawn up for quality registries. Efforts will also be made to achieve standardisation of the recording done in the primary process. This could for instance cover the parts that are relevant for the BGZ (basic healthcare dataset) and for coding the diagnoses – and other items – based on the SNOMED terminology. This data should then be made available according to the FAIR data principles for use by the registries and other secondary data users.

In addition, it is important that those using the data also start thinking about the requirements that they themselves would wish to impose in terms of actuality, availability, reliability and completeness of the data by stating explicitly what purposes they will be using it for.

ROR DGM outcome: *As of 2023, there has not been much attention paid to the quality of data in registries. In the view of ROR DGM, this should however be a regular component when setting up the healthcare data landscape, preferably ensured in the source systems. Good data quality is essential for confidence in the correctness, completeness and usability of the data and results.*

4.5 Centralised control of the Data and IT component

ROR DGM believes that the care process for the patient should be the starting point for recording healthcare data. A standardised, structured and user-friendly process for recording the data has benefits for the data quality and reduces the burden for healthcare professionals of making such records. Research in 2022 by Tom Ebbers et al. has in fact shown that structured recording improves the quality of dossier building by 20%, as well as taking up less time than unstructured recording. It was then possible to use the data automatically for a multidisciplinary quality dashboard and to pass it on to the quality registry with the same quality score as for manually checked and encoded dossiers (see the article by Tom Ebbers et al. from 2023). These studies have shown the importance of recording by the healthcare professionals in a structured and user-friendly way. The EMRs need to become supporting and facilitating in this process, for example with structured input or by automated recognition of input or speech as part of the dossier building.

If data is recorded during the primary process according to standards and the FAIR principles, it is then easier to exchange it for multiple uses. Once the variables in the dataset have been defined, the information models can be specified (e.g. ZIBS) along with the terminology systems such as SNOMED. This ensures that the meaning of the data is uniform and unambiguous.

Because healthcare data cannot mostly be gathered in a single care information system, linking datasets from different sources together at the patient level needs to be possible. To achieve such a connection, a single linking key or identifier is needed, such as the BSN (the 'citizen service number in the Netherlands), along with the justification for processing the data in question. Linking data from information sources and being able to follow patients over time are preconditions for being able to carry out monitoring in the current healthcare data landscape. Processing the BSN is permissible in the primary care process, but not for example in registries. Care providers must actively ask for permission from patients if that data is to be made available for multiple uses. This is currently inhibiting the availability of data from registries and of the linked data that is a prerequisite for answering the legitimate questions about expensive medicinal products.

There is a broadly shared and accepted need for the Ministry of Health, Welfare and Sport (VWS) to handle the centralised management of the infrastructure layers of the healthcare data landscape, across the various programmes. As part of this, concrete choices need to be made about the following aspects:

- mandatory and standardised recording of data in all layers of the primary care process;
- consistency of language use and significance, which is required if the data is to be used in multiple ways;
- a legal basis for processing the BSN or some other identifier;
- interoperability of data sources, based on the FAIR principles;
- making the necessary healthcare data available.

Centralised control of the standardised setup of EMRs in hospitals (and other healthcare providers) plus an infrastructure for exchanging data are fundamental to this.

Assignment: Various principles have been formulated.

1. Reuse of existing data according to the principle of recording at the source.
2. Application of the FAIR principle.
3. The Information Policy Directorate can provide assistance in carrying out the tasks.

ROR DGM outcome: *We support the principles of the original assignment: standardised, structured and user-friendly recording at the source, making healthcare data available along with regulation of the IT market. These developments are however proceeding too slowly. ROR DGM is fully behind the recommendations by the expertise group that were mentioned earlier, starting that a Health Date Action Plan should be produced in the short term in which concrete steps are taken on the stated topics (and others) under the aegis of the said Dutch Health Data Authority.*

This means that choices must be made at the national level about providing all patient data (clinical data, medication data, PROMs and healthcare consumption data must not be seen as separate data processes), the parties that will have to play a role in this and how it is to be funded. The solution must not focus solely on data that has already been standardised; it must be scalable and efficient as well as being applicable independently of the setup choices made by hospitals, Dependency on commercial parties for extracting data (whether standardised or not) will not lead to structural solutions and is therefore not desirable.

4.6 Orphan drugs require an international approach

Where registries are related to rare disorders and orphan drugs (especially in the most exaggerated cases), ROR DGM has observed that an international approach is needed. There are various reasons for this:

- the numbers of patients at the national scale are low;
- the numbers of hospitals offering treatment at the national scale is limited (often just one or a very few university hospitals);
- the number of available treatments or drugs is generally small;
- data collection for these patients is often highly specific: data is collected that is not part of what is routinely gathered;
- the budgets for research are generally limited;
- it is more difficult to guarantee patients' privacy.

Where orphan drugs are involved (and the extreme cases in particular), there is often already cooperation at the European level, with European reference networks (ERNs) and the associated centres of expertise. Registries for rare diseases can be organised from these ERNs, but there is inadequate funding and it is not provided structurally. On top of that, there will need to be coordinated collaboration at the national level for the specific disorder.

Experience has been acquired within ROR DGM with the extremely rare disorder metachromatic leukodystrophy (MLD) and the less prevalent diseases haemophilia and multiple myeloma.

Assignment: Orphan drugs are mentioned separately in the assignment as drugs in the insured package that have a relatively high cost, for which further research into effectiveness, appropriateness or more sensible use is needed.

ROR DGM outcome: *Orphan diseases must be given a spot within the national and international governance structure of diseases/disorders (or domains of disorders). For the European and international clustering of very rare disorders in particular, alignment with the ERN's sub-themes is a logical step. Additionally, an international inventory of the initiatives that are already available internationally will need to be made before the registries for orphan diseases are set up, in order to guarantee that this international alignment takes place.*

5 Reflection from within the programme

The ROR DGM reflected upon how things had gone after completion of the case study phase. We used the final reports from the case studies and interviews with employees and ex-employees of ROR DGM who were involved. Distinctions were made between four domains: selection procedure, research assignment, guidance and the project organisation.

5.1 The selection procedure for case studies

The selection process for the case studies was discussed in Section 4 (Learning experiences from the case studies). Initially, ROR DGM was supposed to select at least two case studies relating to topics where the Minister of VWS at the time envisaged the biggest problems. At a later stage, it was decided within the programme to expand this to four case studies. ROR DGM drew up specific selection and award criteria for the selection process, distinguishing between the type of disorder and the phase that the patient registry was in when a case study was started. Two oncology case studies were selected, one non-oncological orphan drug case study and one case study on other disorders (excluding oncology). In all cases, they had to involve disorders where expensive medicinal products are used.

Selecting parties handling registries for different disorders and in varying stages of development meant that learning experience could be gained on several fronts. The case-study setup – with sub-projects on content, data/IT and governance/funding – also looked at the problems from a broad perspective. This yielded a lot of practical information for the ROR DGM programme about the problems, differences and cohesion, as well as on the dependency on other projects and parties. This has all been translated into the ROR DGM vision.

Legislation and regulations required the National Health Care Institute to use a selection procedure. Every selection procedure has its own pros and cons. ROR DGM ultimately chose to go through the tender process via the dynamic purchasing system (DAS). This procedure was felt by some of the parties to be one-sided and not very flexible. The case studies that were selected met the selection criteria but the procedure gave them no option to decide jointly on a shared project proposal. For that reason, the objectives, results and preconditions were partially modified after the procedure had been completed and a new work plan was put together jointly.

After the subsidy criteria were issued, the number of registry parties who were interested in making a submission was lower than expected. There also turned out to be major variations in the quality and developmental level of the parties involved in the registries. Partly as a result of this, it became clear at an early stage that achieving the initial objective of the programme – using the case studies to answer questions about assessing the insured healthcare package – would be extremely complex. A pragmatic solution was therefore found in the case studies to allow the objectives of the programme to be fulfilled. Despite the limitations of the selection procedure, four registry parties were finally selected and the case study phase started.

Based on the experience acquired in the case study phase, the question remains of whether the DAS procedure was the most suitable tool for selecting the case studies for ROR DGM's objectives. On top of that, it would have been nice to reflect on things more at interim points and make adjustments within the case studies to help achieve the overall objectives and point them more at the study questions. This allows the programme to keep control of its own goals.

5.2 Research questions

The original assignment given to ZIN by VWS was to use ROR DGM to work out a data collection method that would at least correspond to the information requirements for insured package management of expensive medicinal products. To achieve a structural solution for this issue, the first instruction given by the minister was to create better

orchestration of the registries and thereby create uniformity. The stratified nature made it a complex task and dependency on other parties was high.

Learnings were gained on the case studies via the various sub-projects. This yielded general knowledge and experience on the sub-topic, as well as specific information for answering the research question looking at insured package management.

Throughout the case study phase, ROR DGM observed that responding to the initial assignment – working out a data collection method that would at least correspond to the information requirements for insured package management of expensive medicinal products – was virtually unfeasible in the case studies. This also applied for the registries, in which large amounts of data had already been collected structurally for a long time and for which the infrastructure had been set up. A key cause of this was the fact that the registries had been set up for a specific purpose and the associated data collection. Such data collection turned out not to be complete and representative enough for the questions to be answered within the case studies. Adapting the data gathering for a registry is a lengthy process. Linking registries to the other data sources that were available was also scarcely possible. Finally, access for the National Health Care Institute and other parties to the data was only possible to a very limited extent. It has already been noted at interim evaluations that it was difficult to obtain a clear picture during the selection procedure of what the initial status was for the registries. As a result, expectations beforehand may well have been too high. In addition, the conclusion may be drawn that a two-year period was too short for obtaining results. The original project plan also made allowance for an extension of the case study phase by at least two more years, so that the initial period could be used for the organisational and technical activities and the second period for generating data and processing it to create the information. This confirms the need to configure the data landscape so that high-quality data will be available as much as possible for answering the questions arising from cyclic insured package management and other objectives.

During the case study phase, the ROR DGM programme amended the vision and strategy, based on advances in understanding and other developments. The angle adopted here is that information about expensive medicinal products is part of the treatment information for a disorder and that it is important for multiple stakeholders, allowing various objectives to be addressed. During the case study phase, it transpired that these objectives are difficult to achieve with disease-specific registries that focus on narrow indications (small disorder domains). The case studies were also given a certain degree of freedom to make choices within the project as they saw fit and according to their own preferences. Strict agreements were not imposed by ROR DGM that could then be used for steering.

5.3 Supervision

The case studies let the ROR DGM programme learn valuable lessons from experience and test out new ideas in practice. That is why a choice was made from the start of the case study phase to adopt a clear control method for each case study, in the person of a case manager from ZIN. This case manager was the first point of contact for the parties in the case study, reporting directly to the project group and interacting continuously with the sub-project groups.

Throughout the case study phase, it was noted that not all case managers had the desired and necessary characteristics for leading the case studies. As a result, the case study parties were not steered sufficiently well and the opportunity to adjust the process at the interim evaluations was not utilised. This led to issues and problems not being picked up in time, so that there was no longer a proper grasp of the outcomes and results. A complicating factor in this was the changes in the ROR DGM team. In addition to knowledge and experience leaching away, this also affected the supervision of the case studies. To fill the vacancies, external staffing was widely used. This did indeed provide short-term relief in the work activities but did not structurally embed the knowledge and quality within the team.

The various sub-projects also required specialist knowledge, for instance for IT issues or substantive medical knowledge. In the tight labour market of the time, ROR DGM was not always able to provide that knowledge appropriately, again meaning that specific knowledge had to be hired in from outside.

Over the course of the programme, various members of staff from the client (VWS) were also involved in ROR DGM. This applied at all levels in the organisation. This meant that the programme did not always get the attention and supervision that would have been desirable. It was also unclear for a long time that an integral approach would be needed if the vision of ROR DGM on data availability was to be put into effect and that all departments within VWS would have to be involved. The Medical Devices and Technology Directorate (GMT) was involved because of the urgency created by the rising costs of expensive medicinal products, appropriate care and insured package management; the Patient and Care Organisation Directorate (PZo) because of the way it was intertwined with quality registries; and the Information Policy Directorate for the essential questions about the information landscape setup, including primary and secondary data use and standardisation.

The parties involved in the registries generated expectations for the case study process, based on the project plan and the agreements made. This included expectations that ROR DGM/ZIN would provide structural solutions for governance and funding. The expectations were adjusted for some of the elements because of understaffing and organisational limitations.
During the case study phase, we noted that the parties involved in the case studies often needed practical assistance, steering and supervision if they were to develop. The parties handling the registries were short-staffed and did not have enough financial resources and specific knowledge, making them dependent on ROR DGM. In the end, the pragmatic approach was adopted and ROR DGM took on a mediating and organising role. A role was also played in this by the fact that ROR DGM was able to exert a limited amount of influence on the funding, governance and setup of the information landscape.

5.4 Project organisation

Recording the course and vision in ROR DGM, as mentioned earlier in the section on the study assignment, is appropriate for a programme such as ROR DGM because a joint national vision is still subject to change. Determining the correct scope and at the same time paying sufficient attention to the sub-products and case studies does however demand an adaptive capacity on the part of all parties involved. A key gain of this is that work has been done within ROR DGM on the cohesion between programmes, projects and initiatives and on their overview/control. Awareness of the need for data availability has also increased.

The National Health Care Institute, in its role of looking after the ROR DGM programme, has a key role in expressing the ROR DGM vision of data availability within the healthcare landscape, placing it correctly and getting it on the agendas. However, there was no overall vision within the National Health Care Institute for a long time about the use of healthcare data for primary and secondary purposes, or of real-world data and data availability in the wider sense. The National Health Care Institute's own information requirements for cyclic insured package management and appropriateness of care are also still unclear. ROR DGM has suffered from this absence of concreteness and vision, particularly in the discussions with VWS.

6 Continuation

The healthcare system has various major tasks within society: care must be made more economical (in terms of labour and money), more focused on the individual and more durable. The challenge in the domain of expensive medicinal products is similar. Also, during licensing of expensive medicinal products, there are often still shortcomings in the literature and practice-based data shortly after registration of a new medicinal product, resulting in insufficient understanding of the effectiveness and cost-effectiveness of that product. In his lecture, the internist, oncologist and epidemiologist Prof. G.S. Sonke made the case for carrying out real-world studies into appropriateness of use before introducing new, expensive medicinal products. Several interventions have been mentioned in the Integral Care Agreement (IZA) that should help make the use of expensive medicinal products more effective and more individually focused (appropriateness) and control the costs and pricing better. Carrying out tests such as molecular diagnostics can also be used as a way of selecting the right patients for targeted therapy.

Data availability as a precondition

A crucial precondition for appropriate use of molecular diagnostics and expensive medicinal products is the availability of good healthcare data, as that lets the patients, care professionals, care providers, health insurance companies, scientific researchers and insured package managers answer essential questions using data from practice. Evaluation of care is not possible if the requisite data about patient characteristics, molecular diagnostics, the choice to give treatment or not and its effects is not available and cannot be linked together.

Over the last three years, the ROR DGM programme has managed the improvements in the availability of data about expensive medicinal products. This has been a voyage of exploration, undertaken jointly with the stakeholders, and it has led to a vision of the healthcare data landscape that contains the following elements:

- information about medicinal products (expensive ones in particular) is an integral part of the data on treatments and outcomes;
- healthcare data from practice must be available for all interested parties, as well as for both primary and secondary objectives. The data must at the very least be suitable for managing the insured package;
- to avoid administrative burdens as far as possible, healthcare data is recorded in the regular care process, depending on the disease/disorder. The software systems must facilitate this;
- a dataset must be set up to be multidisciplinary and with multiple stakeholders;
- control by the authorities is needed for accelerating the realisation of data availability and for creating a good data landscape. Active support of registries is effective for this;
- structural funding is needed for the continuity and further development of data availability.

In addition, the programme has signalled preconditions, bottlenecks and follow-up actions to help achieve the desired healthcare data landscape. In the form of the maturity model, ROR DGM has provided an initial impulse setting the framework for a mature healthcare data landscape. The maturity model can also be used for describing the 'dot on the horizon' and the route to the ideal healthcare data landscape. Working with other parties to flesh out the maturity model further will make it a powerful tool for addressing issues of cohesiveness, ownership and responsibility. This means that it must be managed properly, that parties act correctly and effectively as the owners, within the limits of the tasks assigned to them. The interdependencies in resolving bottlenecks (such as using a pseudonymised BSN as the linking key) will mean that this can no longer be done on a voluntary basis.

The acceleration and prioritisation that are required

To attain a future-proof system of remunerations for new medicinal products via the basic health insurance package (as stated in the Parliamentary Letter of 16 June 2023), more efforts and an acceleration are needed for achieving that data availability in reality. The ROR DGM expertise group backs the programme's vision and has additional ideas about it. These have been expressed in the second call, which asks for a Healthcare Data Action Plan (Actieplan Gezondheidsdata) to be drawn up, in line with the national vision and strategy for a healthcare

information system and the VWS's vision on secondary use of data. The expertise group also suggests bundling the governance systems of all existing projects, programmes and registries into a newly created Dutch Health Data Authority.

For the purposes of insured package management, priority should be given to data availability about disorders for which a lot of new (and expensive) medicinal products have or will appear. The National Health Care Institute's Medicinal Product Horizon Scan (Horizonscan Geneesmiddelen) is a valuable instrument that makes it possible to anticipate market developments in good time.

Recommendation for following up on the programme

ROR DGM's case study phase has provided new and useful insights and results for the future of data availability in healthcare. It is important to follow up on these gains. This can be done in an extension of the programme for 2024 and beyond, or the gains can also be improved upon elsewhere.

The National Health Care Institute advises the Minister of Health, Welfare and Sport (VWS) to extend the programme until the following goals have been achieved:

- the governance and financing of data availability has been ensured, including for rare disorders. The preferred route for doing so would be fitting in with the governance and funding of quality registries;
- the vision on data availability is sufficiently guaranteed in the long-term perspective of the National Vision and Strategy for the Healthcare Information System;
- the current projects for strengthening disease-related data availability in the prioritised domains (oncology, haematology and rare diseases) have yielded sufficient results and the learning points have been implemented;
- Real-world data in several urgent National Health Care Institute cases is used for cyclic management of the insured package for expensive medicinal products, including molecular diagnostics (where applicable).

We expect that an extension of the programme will help make care appropriate and will provide support for achieving the Integral Care Agreement objectives for data availability. Ending the programme would remove the control and urgency for availability of the linked data, making it less likely that the Integral Care Agreement goals will be met.

Annex 1: Expertise group

The ROR DGM programme is assisted by and backed by a group of experts from the field. They are referred to collectively as the expertise group. The group gives recommendations and ensures there is backing for existing initiatives and for the links to them. Participation in the expertise group is in an individual capacity. The composition can change during the course of the project (e.g. per phase). In addition, extra people can be asked to join for subprojects.

The ROR DGM expertise group aims to ensure a broad representation of the parties involved, in terms of knowledge of the content. The following elements were the determining factors when selecting the group members.

- A good representation of organisations:
  - patients' organisations;
  - registries and research infrastructures;
  - information standards (Nictiz);
  - industry.
- A broad selection of disciplines:
  - clinicians and hospital pharmacists;
  - research and methodology;
  - data (including clinical data) and IT;
  - policy (central government plus one health insurer).
- Balance between oncolytics and non-oncological orphan drugs.

A good geographical representation has also been taken into account (for the academic institutions in particular), as well as an appropriate balance between men and women.

Expertise group Regie op Registers voor Dure Geneesmiddelen | Website | Zorginstituut Nederland

As at mid-September 2022, the members of the expertise group are as follows:

Name of group member	Job position
Prof. J.G.W. (Jos) Kosterink Chair	Professor of hospital pharmacy, in particular clinical pharmacy, Universitair Medisch Centrum Groningen, University of Groningen
Prof. W. (Wim) Goettsch (secretary of the expertise group)	Special HTA adviser to the National Health Care Institute Professor of HTA of Pharmaceuticals, Utrecht University
Dr P. (Pauline) Evers	Patient representative for oncology, Federation of Dutch Cancer Patients' Organisations (NFK) Patient representative for the European Medicines Agency
Dr M. (Mariëtte) Driessens	Patient representative for orphan drugs, Association of Collaborating Parent & Patient Organisations (VSOP) Involved in setting up patient registries for haemophilia (HemoNED)
J. (Joep) Rijnierse	Physician Representative for the Association for Innovative Medicines (Vereniging Innovatieve Geneesmiddelen, VIG) Chair of the VIG Committee on patient registries
Professor. M. (Miriam) Koopman	Professor of Medical Oncology, University Medical Center (UMC) Utrecht
Prof. K.C.B. (Kit) Roes	Professor of biostatistics at Radboud UMC Member of the Medicines Evaluation Board (College ter Beoordeling van Geneesmiddelen, CBG)
Prof. C.E.M. (Carla) Hollak	Internist and professor of Metabolic Disorders, in particular hereditary metabolic diseases, Faculty of Medicine, University of Amsterdam (AMC-UvA) Member of the Insured Package Advisory Committee (Adviescommissie Pakket, ACP) National Health Care Institute
N.W.Y. (Nadine) Thé	Senior policy developer, VGZ cooperative
Prof. V.E.P.P. (Valery) Lemmens	Professor by special appointment of Cancer Surveillance, Erasmus MC Rotterdam Member of the Executive Board of IKNL
Dr M.W.J.M. (Michel) Wouters	Surgeon at the Antonie van Leeuwenhoek Hospital head of the Scientific Bureau of the Dutch Institute for Clinical Auditing (DICA)
B. (Brenda) Leeneman	Health Technology Assessment (HTA) iMTA
Prof. G. (Gerrit) Meijer	Professor of Pathology at the Netherlands Cancer Research Institute (Nederlands Kanker Instituut, NKI) Scientific director of Health-RI
Dr N.T. (Naomi) Jessurun	Hospital pharmacist Pharmacovigilance Centre LAREB
Dr E.M.W. (Ewoudt) van de Garde	Clinical pharmacologist Epidemiologist Hospital pharmacist, Sint Antonius Hospital Member of the Scientific Advisory Council (Wetenschappelijke Adviesraad, WAR), National Health Care Institute
Prof. M.A. (Manuela) Joore	Professor of Pharmacoeconomics, Maastricht University Member of the Scientific Advisory Council (Wetenschappelijke Adviesraad, WAR), National Health Care Institute
S. (Stef) Meihuizen RZA	Data collection manager for Dutch Hospital Data
Dr D. (Dennis) van Veghel	Manager and director of the Dutch Heart Registry (Nederlandse Hart Registratie)
Dr. P.H.W.M. (Paul) Oude Luttighuis	Architect and adviser at Le Blanc Advies
J. A. (Jan) Hazelzet, MD PhD	Prof. Emeritus of Care Quality and Outcomes at Erasmus MC, independent consultant
N. (Niels) Caro	Product manager at Nictiz, the knowledge organisation for digital information exchange in the healthcare sector
C.J.J. (René) Hietkamp, deputising	Enterprise Architect Reference Architecture Coordinator for the Healthcare Information System (DIZRA)
Dr P.G.M. (Peter) Mole, deputising	Senior Researcher, University of Groningen Member of the Medicines Evaluation Board (College ter Beoordeling van Geneesmiddelen, CBG) Chair of the working group on patient registries, European Medicines Agency
Dr B. (Benien) Vingerhoed Deputising	Managing Director of FAST
Dr L. (Lotte) Minnema Deputising	Policy Officer for Medicinal Products, Ministry of Health, Welfare and Sport, Medical Devices and Technology (VWS-GMT)
Dr L. (Lonneke) Timmers	Scientific Secretary to the Scientific Advisory Council (WAR), National Health Care Institute

Annex 2: Datasets for each disorder

Categorie	Gegevens	Ziekte-specifiek in te vullen?	Definitie variabele
Demografie	Geboortedatum		
	Geslacht		
	Patiëntnummer/ID/BSN		
	Inclusiedatum registratie		
Functionele status	Performance status	JA; bv WHO performance score, frailty score	
	Comorbiditeit		
	Comedicatie		
	Lengte		
	Gewicht		
Risicofactoren	Tabakgebruik		
	Alcoholgebruik		
	Drugs gebruik		
Overige	Medische hulpmiddelen		
	Voedingstoestand	ja; bv sondevoeding	
Symptomatologie	Presenterende symptomen		
	Datum manifestatie symptomen		
Diagnostiek	Diagnose		
	Datum diagnose		
	Laboratoriumonderzoek	ja (niet altijd relevant, indien relevant welke uitslagen, aantal nodig etc)	
	Moleculaire diagnostiek/biomarker	ja (niet altijd relevant, indien relevant welke uitslagen, aantal nodig etc)	
	Beeldvorming	ja (niet altijd relevant, indien relevant welke uitslagen, aantal nodig etc)	
Stadium/Ernst	Ernst/subtype/Stadium	ja	op basis van gevalideerde/geaccepteerde ernst- of event classificatie (indien beschikbaar)
Progressie/Uitbreiding	Orgaanfunctie	ja	
	Laboratoriumonderzoek	ja	
	Biomarkers	ja	
	Beeldvorming	ja	
	Anatomische lokalisatie	ja	
Operatieve ingrepen	Verrichtingen		
Geneesmiddelen	Systemische behandeling (middelen)		
	Frequentie behandeling		
	Dosering behandelingen		
	Datum behandelingen		
	Reden stop systemische behandeling		
	Plaats van toediening	ziekenhuis, dagbehandeling, thuis	
	Wijze van toediening	sc, iv, oraal	
	Datum voorbereiding behandeling	bv bij CAR-T, stamceltransplantatie, gentherapie	
Overleving	datum overlijden		
	doodsoorzaak		
Overige klinische uitkomsten	1-3 ziekte-specifieke uitkomstmaten	ja	
Gebruiksgemak	Patiëntervaring mbt gebruiksgemak	ja	
Generieke PROMS	EQ-5D-5L		
	PROMIS item banken (CAT)	ja	
Ziekte-specifieke PROMS	Ziekte-specifieke PROMs	ja	
	EQ-5D -5L		
	Aantal opnames		
	Aantal ligdagen verpleegafdeling		
	Aantal ligdagen IC		
	Aantal SEH bezoeken		
	Aantal operaties		
	Aantal dagbehandelingen		
	Overig	ja; bv	
	Ernstige bijwerkingen	ja	> graad 3
	Nieuwe bijwerkingen	ja	nieuw tov bekende bijwerkingen in SmPC
	Bijwerkingen waarvoor therapie aanpassingen	ja	ofwel uitstel in frequentie, dosisaanpassing van DGM zelf of bijstarten van andere medicatie

Annex 3: REQueST Tool

Context

The importance of recording the effects of expensive medicinal products in practice is generally acknowledged. Numerous parties are actively involved with disease-specific registries. Their quality is however variable and the information can often not be used by other parties[1]. The REQueST Tool provides a structural approach for making the information from registries useful to all parties. This means that the REQueST Tool fits well within the intended objectives of the Managing Registries of Expensive Medicinal Products (ROR DGM) programme. That programme aims to provide reliable data and unambiguous and immediate understandings for everyone.

The REQueST Tool, or in full the 'Registry Evaluation and Quality Standards Tool', has been developed by EUnetHTA, a European network of HTA bodies that includes the National Health Care Institute. This tool can be used for testing the quality of registries. The tool has a two-part goal:

- It supports consistent evaluation of the applicability and reliability of registries for HTA organisations;
- It offers those who hold patient registries an understanding of where further developments and improvements can be made in the quality of their registries.

The tool consists of three categories and 23 items against which the registries are checked: (1) methodological information, (2) essential standards and (3) additional requirements. A colour system (green, yellow, red) is used to determine whether the quality of an item is sufficient. The twelve items that fall within the category of 'essential standards' are knock-out criteria, i.e. must get a green assessment. If that is the case, it is then possible (according to the makers of the tool) to assume that the quality of the registry will be high enough that the data being collected will be usable and reliable for the purposes of HTA organisations.

Expected value of the REQueST tool for the National Health Care Institute (ZIN) and marketing authorisation holders

Expected value of the REQueST tool for HTA organisations:

- It provides a testing framework for HTA organisations (such as ZIN) for determining the usability of patient registries for HTA purposes. This tool creates a clear understanding, in a uniform way and using test criteria, of whether the registry complies with the standards that the health technology assessment (HTA) organisations require.
- If there are multiple registries within a single field of disorders, it can be used for benchmarking.
- Assigning a valuation category to each item creates an immediate overview of the points where a registry complies with the requirements and the points where further development may still be needed. This does not immediately approve or reject a registry but instead makes clear how good and relevant it is.

The expected value of the REQueST tool for marketing authorisation holders

- It provides a picture of the minimum standards demanded by an important stakeholder, e.g. an HTA organisation. Providing this picture can allow a registry to be set up in a high-quality and transparent way and/or to get it developed further where necessary so that it becomes relevant and usable for HTA purposes.

The REQueST tool can therefore offer a great deal in theory. Implementing the REQueST tool can help obtain a picture of the quality of a registry quickly and consistently. There is however little experience as yet with implementing the REQueST tool. As yet, we do not know sufficiently well how user-friendly it is and whether achieving the desired effects is feasible.

[1] See also our report entitled 'Inventarisatie patiëntenregistraties voor de monitoring van dure, medisch-specialistische geneesmiddelen'

Implementation of the tool

Because ZIN has acknowledged the potential, it has been decided to implement the REQueST tool within the four case studies. A four-stage step-by-step plan has been used for implementing the tool successfully and extracting the learning points from the exercise. These steps have been run through within each of the case studies and, taken together, that has yielded the lessons that are described later in this document.

- **Step 1**: The marketing authorisation holder and the reviewer from ZIN each complete the REQueST tool independently for the case study in question. The reviewer does this on the basis of publicly available information (websites, published material, etc.).
- **Step 2**: For each case study the reviewer compares the answers written down by themselves and by the marketing authorisation holder and assesses whether each item matches.
- **Step 3**: The marketing authorisation holder and reviewer discuss the answers they have given and attempt to find out where any possible differences may have arisen. They also share their general impressions of working with the REQueST tool and indicate where improvements might be possible or needed.
- **Step 4**: The reviewer collates all the lessons learned that came to the fore in the discussions with the marketing authorisation holder, from their own experience of working with the tool, and from the literature. The most important lessons are filtered out from that list and suggestions are made for improvements. Those are given in the next section.

Lessons for the future

The findings from the experience acquired of working with the REQueST tool, the discussions with the marketing authorisation holder and the literature have all been written down in a separate document. An attempt has been made to group the key lessons from all these findings together and make suggestions as to how improvements could be made. Those lessons and the corresponding suggestions for improvements are described below.

Lesson 1: Test criteria for each item can be interpreted in different ways; this needs to be more user-friendly.

Comparing the answers of the marketing authorisation holders against the reviewers showed that different opinions were possible as to how certain test criteria should be interpreted. This led to answers being given that were not always properly aligned with the question or expectation. This makes it difficult to bring the correct information to the fore. Differences in interpretation occurred in some of the criteria and moreover did not always occur in the same items. In short, there seems generally to be too much scope for interpretation and this yields responses that do not really answer the questions as they were intended.

Suggestion derived from Lesson 1:

The test criteria should be defined more specifically so that they will be interpreted consistently and uniformly. It is possible to find inspiration in the literature for drawing up clearer definitions and the discussions with the marketing authorisation holders showed having examples of e.g. coding systems works well. It should therefore be stated specifically for each test criterion what information should be delivered as a minimum to respond to the item in question. ZIN itself can play an active role here as the first step and – with an eye on a future national dataspace for health – state what they consider important for the Dutch context and what they would like to see. However, to make the tool genuinely interpretable in a uniform and consistent way, including at the international level, input will need to be requested from the other HTA organisations that helped develop the current version of the REQueST tool.

Lesson 2: The test criteria are not very operational: there is no clear description of when particular items should be classified as green.

A description is given for each item, though, of what you are being asked to respond to. However, this is not followed by a statement of when the answer that is given should be scored as 'sufficient' (i.e. placed in the green category). This means that the testing of the registries still remains quite subjective. If one reviewer deems the answer that was given to be sufficient, it does not necessarily mean that another will have the same opinion.

Suggestion derived from Lesson 2:
The test criteria should be operationalised better. This can be achieved for the majority of the test criteria by reading the literature about them to see what is regarded as sufficient 'in the field'. There needs to be a statement for each test criterion of when an item should be classified as green, yellow or red. This will create clear, operationalised contexts that are not subject to subjective opinions. This makes uniform and consistent testing possible. In the appendix (and this document), you can find suggestions for this type of operationalisation of the test criteria. The sequence of the items may perhaps also need examining, as well as whether some could be merged to make things clearer. Ideally, ZIN and the other HTA organisations would take a critical look at the test criteria and suggestions for more specificity in them and then use that to reach a consensus for a possible REQueST Tool 2.0.

Lesson 3: The information that is publicly available differs from the information that the marketing authorisation holders themselves have available
In all the case studies, there were significant differences between the information written down by the reviewer and that of the marketing authorisation holder. In other words, not all items are described transparently and in sufficient detail in the public domain. It is therefore not possible to have blind faith in the information that is publicly available.

Suggestion derived from Lesson 3:
The gaps in the information that could not be found in the public domain can be given as feedback to the marketing authorisation holders. After that, they themselves can modify their publicly available information in such a way that all the information that is relevant for the REQueST tool can be found online. This has in the meantime been explained to the marketing authorisation holders involved in the case studies and they all responded positively. As a follow-up step for testing the development of their various registries and to see if progress has been made in transparently representing essential information, the REQueST tool could be completed again one year later to see if there are any differences. An alternative that could be considered would be to have only the marketing authorisation holders themselves complete the tool, or provide the requested documentation in cases where they do not want to make certain items publicly available. An HTA organisation can thereafter still review the answers and assess the quality using the test criteria (which as yet still need improvements).

Lesson 4: Having the marketing authorisation holder and HTA organisation go through the answers together is useful
This created a better mutual understanding of why certain interpretations were given the way they were and why certain answers differed. In some cases, this was in fact easily explained, whereas this might not have been the case without the discussion. It turned out in several discussions to be the case, in fact, that marketing authorisation holders do not like making informed consent forms publicly available, to prevent patients from filling them in without first making a carefully considered decision. The independent reviewer was not looking for any underlying reason and merely assumed that the information was missing. This therefore helped the parties understand one another better.

Suggestion derived from Lesson 4:
A comparison exercise may perhaps not always be possible or desirable in the future, but where a marketing authorisation holder has completed the REQueST tool, it does seem useful to plan in a short discussion to tackle anything that is unclear or to cover additional questions that the HTA has as a result of the answers given. Except for the four case studies, this is however something for the more distant future. Efforts will have to be made first to improve the REQueST tool itself, to make the positioning of the tool clearer and to encourage people to complete the REQueST tool. If the REQueST tool is seen as too lightweight and is not completed, it is not possible to plan in discussions to go through the answers together.

Lesson 5: In the current situation, it may well be the case that none of the case studies complies with the knock-out criteria.

The REQueST tool is sometimes vague in how the test criteria are formulated; however, at the same time, the broad outlines are given clearly. Then again, information was not given about every single one of the requested criteria in any of the case studies. It is also possible that certain processes were present without being mentioned, but it certainly gives food for thought. Items 17 and 18 in particular, data cleaning and missing data respectively, were often not described in sufficient detail. The same pattern was also seen among our Canadian colleagues at CADTH, who looked at 25 Canadian registries.

Suggestion derived from Lesson 5:
There are two possibilities for improvement: either the tool must be less strictly defined OR it must be made clear to marketing authorisation holders that these items are important and must be in good order if the quality is to be deemed 'good' enough for HTA purposes. The latter would seem preferable. The REQueST tool is after all a product created by several HTA organisations who have looked to consult various other influential stakeholders such as patients' associations and regulators. There has therefore been proper and thorough consideration and a consensus has been reached about which aspects it is essential to have in good order. Practice has shown that the criteria within the topics themselves are sometimes too vaguely defined, but making it all less strict or excluding certain topics seems to be less appropriate. In short, it should be clearly communicated that it is important to have the quality of a register up to scratch for each of the essential items; the consequences of this need to be made clear. The last of these is a task that should be tackled by ZIN. Showing and explaining the importance of having the documentation for the knock-out criteria in order is something that ZIN must put in place, in consultation with marketing authorisation holders both within and outside the case studies, and in which doctors, patients' organisations, regulators and researchers can also play a role. After all, they all benefit from high-quality data and they all also need to have confidence in how that data is gathered. Making those interests fully clear and backing them will give weight to the essential items. Marketing authorisation holders have their own intrinsic motivation to set up their registries as well as possible, of course, but getting multiple stakeholders behind it can do no harm. It would be a good idea in future to look for support for this from the above-mentioned stakeholders.

Lesson 6: The positioning of the REQueST tool is not always clear
Discussions with the marketing authorisation holders showed that they wondered how important the tool actually is. What does it actually mean if you don't meet all the criteria? And how does this testing tool relate to other procedures from the field, such as the Qualification Procedure of the European Medicines Agency (EMA)?

Suggestion derived from Lesson 6:
Clarity on the positioning and implications of the REQueST tool needs to crystallise out further. We have not done that within this project. A good first step would be to hold up the REQueST tool against other initiatives for registries (such as the EMA's Qualification Procedure) and attempt to get a clear view of other real-world data sources, in order to see how they fit together and could perhaps be used alongside each other. It is important that ZIN expresses what role it sees for the REQueST tool and acts accordingly. If it is decided that the REQueST tool should be used systematically for checking the quality of a registry and of its data, this policy must be clarified and propagated. There must also be clear communication then about what the implications are for the results generated by the REQueST tool. Will registries in future get a quality mark if they comply with all the knock-out criteria, and/or will those that fail to comply in full not be used for HTA purposes? Such implications must be expressed clearly and acted upon accordingly. To add weight to this, an international consensus about the various initiatives may perhaps need to be found between the stakeholders as to when the tool should be used.

Conclusion

In conclusion, it can be stated that the REQueST tool is a good starting point and that it can be useful for checking the quality of registries and their data, meaning that it may be a useful tool not only for HTA organisations but also for other parties such as marketing authorisation holders and regulators. It fulfils some of our expectations. It does for instance show nicely which items the case study registries still need further development for, and that it is useful for the marketing

authorisation holder and the reviewer to hold discussions about the results of the tool. However, practice has also shown that there are still some barriers that mean an optimum implementation of the REQueST tool is not yet possible. Further development is required to improve the tool. A start can be made on this using the suggestions given. In particular, further specification of the test criteria will be needed. These cannot be interpreted sufficiently uniformly at the moment, and, on top of that, it is unclear what a registry has to be compliant with in order to be classified as green, i.e. for its quality level to be assessed as sufficient. In our view, these are two requirements if this tool – which has the potential to give a picture of the quality of registries – is genuinely to live up to that potential. Only then will a testing framework be created that can be uniformly interpreted, has test criteria for which it is clear when items should be categorised as 'good', and yields consistent evaluations – thereby meeting its own objectives. The Appendix shows suggestions for further specification of the test criteria. These are based on findings from a literature review. It would be valuable if ZIN and the other HTA organisations took a critical look at the test criteria and suggestions for more specificity in them and then used that to reach a consensus for a possible REQueST Tool 2.0.

Furthermore, the case studies have been shown to be nice examples of the potential success of the tool, and the implementation of the REQueST tool within the case studies has at the same time made clear the points where greater clarity needs to be provided. In addition to the content of the tool itself, it was noted that the positioning and the consequences of whether or not the tool has been completed are as yet too optional. With that in mind, ZIN must investigate how the tool relates to other initiatives, preferably doing so by working with the developers of such initiatives, on the international scale too. After that, ZIN must adopt a position about the position of the REQueST tool within its own policy and the implications of results generated by the REQueST tool. Finally, the implementation of the REQueST tool within the Dutch case studies is once again a good starting point, but more experience must be acquired with it (by filling in the tool in later years so that progress can be measured) if the shortcomings and successes are genuinely to be demonstrated. Testing the tool in other countries would also be beneficial. Canada is already doing this and we hope that other countries will join us in future.

Appendix: Suggestions for operationalizing the assessment criteria of items 9-20 of the REQueST Tool

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Item	Assessment criteria	Researchers suggestions to make the assessment criteria operable	Descriptive assessment or quantitative assessment of item?
9 registry aims and methodology	Registry has specified objectives, target population, exposures of interest, primary and secondary outcomes, data sources, linkage (and analysis plans if any). If the documentation is more than 5 years old, the current status should be checked with the registry coordinator or participant.	Mention that all elements should be present. Only award green if all elements are defined.	**Descriptive assessment of item:** green = all elements are defined in a complete/sufficient manner yellow = all elements are described, but description of any one of these elements are incomplete/insufficient OR one of the required elements is missing but the other elements are present and described in a complete manner red = multiple elements are missing and/or all are described in an incomplete/insufficient manner
10 governance	An independent steering committee or a governing body and a data quality team with specified responsibilities are in place. These should include patient representation. Registry governance should have an audited process for declarations of interest covering all financial contributions to the work. Employees of the relevant manufacturers, close relatives who have a position of responsibility within these manufacturing companies or close relatives with financial interests in the capital of these manufacturers could have a declared role in data analysis for the specified HTA project as long as the declared interests are considered not to affect the validity of the data.	No further comments, but only award 'green' if all elements marked in yellow are in place. What is stated below the yellow-marked part, I personally find less relevant. A registry can still be of high quality regardless of financial particular disclosures. So it might be worthwhile to assess but I don't think they should count as a knock-out criterium.	**Descriptive assessment of item:** green = An independent steering committee/governing body and a data quality team is in place and roles and COIs are defined. Patient representation is present in the governing structure. Industry stakeholder is not part of the independent steering committee/governing body yellow = An independent steering committee/governing body and a data quality team is in place but their roles or COIs are not defined, patient representation is missing OR a data quality team is not specified. red = information on the governance structure and defined roles of any teams/committees is lacking or this is present but industry is part of the independent steering committee/governing body.
11 informed consent	The informed consent document should explain to potential participants: • the nature, purpose of the registry and whether secondary analyses may be undertaken, • why they are candidates for participating in the registry, • what risks, benefits, and alternatives are associated with the participation • what rights they have as research subjects. If the documentation is more than 5 years old, the current status should be checked with the registry holder.	No further comments, but perhaps specify how confidentiality is guaranteed	**Descriptive assessment of item:** green = all listed elements are present and completely described. Ideally it is also stated that the completed informed consent document will be discussed between the patient and registry owner/physician to ensure the patient makes an informed decision. yellow = all listed elements are present but description of some elements is does not provide the required level of detail red = one or more of the listed elements are missing

12 data dictionary	The data dictionary should contain identifying attributes (name, ID), definitional attribute (definition of data element, where also the purpose of the data element is described), and representational attributes (permissible values, representation class, data type, format). The data dictionary defines terms needed to answer the registry's research questions and objectives. If the documentation is more than 5 years old, the current status should be checked with the registry coordinator or participant.		**Quantitative assessment of item:** green = data dictionary present and ≥70% of attributes are identified, defined and its purpose explained yellow = data dictionary present but <70% of attributes are identified, defined and its purpose explained red =data dictionary is missing
13 minimum data set	The registry has a defined minimum data set that is able to answer the registry's research questions and objectives. If new fields are required for a specific purpose, the registry is able and willing to make the necessary changes. If the documentation is more than 5 years old, the current status should be checked with the registry coordinator or participant.	Come up with a list of minimum data set elements from HTA perspective, to lay against the Registries' minimum data set "*The specific data elements that should be captured by a registry depend on the sponsor's intended use or uses of the registry*" – FDA guide Update: apparently there is a list for case study 1 & 2.	**Quantitative assessment of item:** green = minimum data set is present and matches for at least 70% those data elements required by HTA parties yellow = minimum data set is present and matches between 50%-70% those data elements required by HTA parties red = minimum data set is missing OR minimum data set is present but less than 50% of collected data elements match those required by HTA bodies
14 standard definitions	Name of the standard, category of data (diagnosis, procedure, medication) and usage of the standard (organising, storing, managing or protecting the data sets) should be provided.	Name of the standard, category of data (diagnosis, procedure, medication) vind ik onderdeel van item 12. Use of standard is prima hier maar noem het wellicht standard operating procedures.	**Descriptive assessment of item:** green = Standard coding systems and operating procedures are used for the categories of data that belong to the minimum data set. For instance, ICD-10 coding, ATC coding or SNOWMED coding is used. yellow = It can be derived that standard coding systems and operating procedures are used for the categories of data that belong to the minimum data set. However, these coding systems are not specified. red = Standard coding systems and operating procedures are not used for the categories of data that belong to the minimum data set OR nothing is mentioned about them.
15 data collection methods	Data collection methods are realistic (e.g. software requirements acceptable to submitters) for the proposed population and treating centres with clear access rights.	Specify that this is about data collection methods, particularly aimed to assess whether methodology on data submission into the registry is suitable.	**Descriptive assessment of item:** green = data collection procedures are clearly defined and described in a detailed manual, data entry systems are described and realistic to the user yellow = data collection procedures are in place but based from the description it cannot be assessed whether data submission is realistic to the user red = description of data collection procedures is missing

16 quality assurance	Quality assurance activities relevant for the registry need to described.	Trained staff for data curation, who follow standard operating procedures and take into consideration representativeness, completeness, accuracy, consistency and perform data acceptance tests on the above elements. Another marker of quality assurance can be audit systems.	**Descriptive assessment of item:** green = trained staff for data curation is present, their roles and responsibilities are clear and they follow standard operating procedure that test the validity of data yellow = A data quality team is present but their level of training, roles and responsibility and procedures they perform are not specified red = there is no mentioning or presence of trained staff/a data quality team nor are standard quality assurance processes described
17 data cleaning	There is a plan for cleaning the data that includes the time required for cleaning after closure to data submission.	This should be accuracy + consistency. I think a 'plan' is not strong enough. Standard operating procedures must be in place to ascertain accuracy and consistency. accuracy = correctness (please see representational attributes in item 12) consistency = uniformity of submission/collection across all data submitters e.g. hospitals	**Descriptive assessment of item:** green = a data management manual is present that identifies the data elements that are intended to be cleaned, describes the data validation rules or logical checks for out-of-range values, explains how missing values and values that are logically inconsistent will be handled, and discusses how duplicate patient records will be identified and managed yellow = there is a general description that (elements of) data cleaning are/is performed but details are missing. red = no mentioning of data cleaning
18 missing data	The percentage of missing data for the core outcomes has been provided. An explanation is given for whether missing data may potentially bias results.	Completeness is probably a better concept than missing data (considering literature). To be assessed as: - % of missing data for core data elements in most recent availability (establish acceptable level of missing) - % of data elements missing over time (establish acceptable level of missing) - in case of any (considerable/unacceptable % of) missing data, explanation is given whether it may bias results	**Quantitative assessment of item:** green = no missing data or % of missing data is acceptable (for example <20%) or % of missing sufficiently explained and accounted for. yellow = There is some missing data, but not a serious level, yet the % missing in not explained or accounted for red = % of missing data is considerable and no or insufficient explanation is provided

19 financing	Financial security to the end of the evidence development period should be demonstrated in the financial plan, solvency with a summary of income and expenditure for the previous 2 years is recommended. Also, funding sources are identified and the approx. proportions (%) of total sum from each funding source is indicated. If the documentation is more than 5 years old, the current status should be checked with registry coordinator or participant.	No further comments	**Descriptive assessment of item:** green = Financial plan gives sufficient detail and specifies all funding sources, ideally with proportions (%) of total sum from each funding source indicated yellow = There is a financial plan but with insufficient detail or there is not a complete overview of all funding sources, including their proportions of contribution to the Registry specifies all funding sources red = financial plan or specification of funding sources is lacking
20 protection, security and safeguards	The security controls specific for the registry should be specified. Risks should be identified and appropriate mitigation described.	Please state specifically whether there is a description and adherence to: - a formal data security policy (ideally ISO 27001 or similar) - in case of access by a third party are policies in place to remove or mask direct identifiers (if not applicable, because no third-party access, then no knock-out) and terms and conditions for use are stated	**Descriptive assessment of item:** green = formal data security and data access policies with defined roles are in place and terms and conditions are described in a complete manner yellow = formal data security and data access policies with defined roles are in place as well as terms and conditions, but any of these elements are incompletely described OR one of the above elements is missing but the other elements are present and described in a complete manner red = data security policy and/or data access policy is non-existent nor are the terms and conditions for access described

Annex 4: Case study templates

This annex contains what are known as the 'templates' of the case studies. These are summaries of the case studies including (inter alia) details of the context, the assignment and the people involved. The learning points and the results can be found in the final reports by the case study parties, as published on the National Health Care Institute website. ROR DGM has included the insights and learning points obtained for the programme in Section 4.3.

Case study	**1. PLCRC (Prospective Nationwide CRC Cohort)**
Date of report	June 2023
Duration of case study	January 2021 – December 2022
Contribution from ROR DGM	€100,000
Contractor	Dutch Colorectal Cancer Group (DCCG)
Person(s) involved	– Prof. M. Koopman, internal medicine specialist/oncologist at UMCU, secretary of the DCCG – Dr G.R. Vink, PLCRC programme manager, UMC Utrecht/IKNL (project leader) – H.J. van Doorne-Nagtegaal, IKNL adviser – P. Lubbers, clinical IT specialist, IKNL – Dr G. Geleijnse, Data Science Team Lead and Innovation Program Manager, IKNL
Related projects	– UGZ (Outcome-Oriented Care) – Health RI – Oncode Pact
Context	The Prospective Nationwide Colorectal Carcinoma cohort (PLCRC) of the Dutch Colorectal Cancer Group (DCCG) is a prospective cohort in which patients give informed consent for the use of their clinical data, patient-reported outcome measures, blood and tissue products, and to being approached for participation in studies in the future. There is collaboration with numerous organisations, including IKNL (Comprehensive Cancer Centres) and Profiel. PLCRC provides an infrastructure for scientific research.
Assignment (work plan)	A work plan has been drawn up jointly with the DCCG and IKNL defining the following objectives: **General**: to develop a protocol that will render the registers suitable for monitoring the effectiveness (including cost-effectiveness) of expensive medicinal products for purposes of insured package

	management (incl. cyclic) and appropriateness. The focus here is on both developing a generically applicable protocol and applying and specifying the protocol on PLCRC. **Governance** To obtain an understanding of the governance and funding structure of PLCRC and insights into the interaction between the governance and funding structure of PLCRC and the nationwide governance and funding structure that is to be developed. This will in particular pay attention to the data exchange between PLCRC and the National Health Care Institute. This will yield a model for the governance and funding, as well as further agreements. **Contents** A protocol for obtaining a generic dataset for cyclic management of the insured packs and for testing and optimising appropriateness. Applying this protocol when determining a specific and suitably supported dataset for answering the research question of the case study. **<u>Research question (PICO)</u>** P (population): patients aged ≥ 18 with metastasised BRAF-V600E-mutated colorectal carcinoma in whom progression has been seen after 1 or 2 lines of palliative systemic therapy and who have given informed consent for data collection in the PLCRC cohort. I (intervention): encorafenib + cetuximab C (comparator): standard secondary or tertiary care systemic therapy O (outcome): Effectiveness: • Overall survival (OS) • Progression-free survival (PFS) and/or time to treatment failure (TTF) Quality of life: • Generic health-related quality of life (HRQoL) • Disease-specific HRQoL (using EORTC-QLQ-CR29) Toxicity Cost-effectiveness **Data/IT:** Drawing up and implementing a system of agreements about information standards and assumptions for IT systems, as well as defining the process for reaching this point, in order to promote reuse in further registries.

Case study	**2. HemoNED**
Date of report	June 2023
Duration of case study	January 2021 – December 2022
Contribution from ROR DGM	€100,000
Contractor	Stichting HemoNED
Person(s) involved	– Dr S.C. Gouw (Samantha), board member and HemoNED project leader – Dr F.J.M van der Meer (Felix), HemoNED board member (Jan 2021–Mar 2022), replaced by Prof. K (Karina) Meijer, HemoNED board member – Dr M.H.E. (Mariette) Driessens, member of the board of Stichting HemoNED, patients' representative – Dr G. (Geertje) Goedhart, project coordinator for Stichting HemoNED; (Jan 2021–Jul 2022) replaced by C.M.E. van Veen – E.M. (Liesbeth) Taal, data manager at Stichting HemoNED
Related projects	– SKMS project (for making the quality of registries more long-lasting) – Quality registries – WFH GTR (Gene Therapy Registry) for data collection for gene therapy – Symphony consortium – Efficiency study
Context	HemoNED is the Dutch haemophilia register, listing people in the Netherlands with haemophilia and related disorders. The key aim of the register is to improve the quality of care for this group of people through continuous recording (and merging and comparison) of data about their condition, treatments and treatment outcomes. Patients who are treated at home record their medication and bleeding in a digital logbook that is directly accessible for both the patient and the treating physician.
Assignment (work plan)	A work plan has been drawn up jointly with the case study defining the following objectives: **General:** To develop a protocol that will render the registers suitable for monitoring the effectiveness (including cost-effectiveness) of expensive medicinal products for purposes of insured package management (incl. cyclic) and appropriateness. The focus here is on both developing a generically applicable protocol and applying the protocol on HemoNED. **Contents:** The procedure's dataset (D4) will be used to create a specific dataset for haemophilia that can be used for insured package management. This dataset will also be the basis for answering the case study's research question. The research question in this case study focuses on patients with haemophilia A who are being treated with the medication emicizumab. – What is the effectiveness and cost-effectiveness of emicizumab?

	– What is the dataset that is needed for answering the question above? **Data/IT:** Make agreements about information standards and assumptions for IT systems, both generic and specifically applicable to HemoNED. Additionally, the connection should be realised between the sources (EMRs, pharmacy systems, PROMs) alongside the HemoNED registry and that registry should be set up for processing such data. **Governance/funding**: Develop a national model for the governance and funding of registries for expensive medicinal products. The focus of the case study is on comparing the governance and funding structure of HemoNED against the nationwide governance and funding structure that is to be developed. In particular, attention should be paid to the governance associated with data exchange between HemoNED and the National Health Care Institute and international data exchange. Additionally, there will be studies into what effect there will be on HemoNED from the implementation of the national governance and funding structure for ROR DGM and from quality registries. **Research question (PICO)** • A PICO research question was determined with the project team: P (population) = patients with haemophilia; I (intervention) = treatment with emicizumab; C (comparator) = treatment with Factor VIII products; O (outcome) = effectiveness (incl. cost-effectiveness), safety and quality of life.

Case study	3**. MLD initiative (MLDi)**
Date of report	June 2023
Duration of case study	January 2021 – March 2023
Contribution from ROR DGM	€100,000
Contractor	Amsterdam UMC
Person(s) involved	– Professor. Nicole I. Wolf (project leader) – Prof. Carla E.M. Hollak (project leader) – D. Schoenmakers (researcher) – S. van den Berg (coordinator of Medicijn voor de Maatschappij) – S. Beerepoot (Researcher)
Related projects	– Health-RI – Medicijn voor de Maatschappij – DARWIN
Context	The MLD initiative (MLDi) focuses on a very rare disease, metachromatic leukodystrophy (MLD). This is a hereditary metabolic disorder that affects the nervous system. The data about this disease is recorded by the MLD initiative (MLDi), as part of Medicine for Society (Medicijn voor de Maatschappij). It is affiliated to the Amsterdam UMC, the centre of expertise for MLD in the Netherlands. Because MLD is a very rare disorder, international collaboration is an important element of the case study.
Assignment (work plan)	A work plan has been drawn up jointly with the case study defining the following objectives: **General:** To develop a protocol that will render the registers of rare disorders suitable for monitoring the effectiveness (including cost-effectiveness) of expensive medicinal products, at least for purposes of insured package management (incl. cyclic) and appropriateness. This protocol is being drawn up inter alia with the help of practical experience that has been accumulated within the MLDi, for instance in the context of the evaluation process for the new gene therapy for MLD and the collaboration with international centres of expertise. Experience with the practical applications will be used both for developing a generically applicable protocol and for applying that protocol to MLDi. **Contents:** Use and test the 'procedure dataset (D4)' by comparing the dataset for MLDI (determined through an international consensus procedure) against D4 and testing its applicability for (cyclic) insured package management and appropriateness. The dataset will be the basis for answering the research question from this case study, whereby the current question about inclusion in the care package from the evaluation process of Libmeldy will be a key starting point for drawing up the study question.

	Data/IT: Make agreements about national and international information standards and the assumptions for IT systems (both generic and applied) for MLDi and how those standards should be implemented. In addition, define the process for achieving this in order to encourage reuse in other registries. **Governance and funding** Develop the preconditions for the governance and funding of registries involving expensive medicinal products. In particular, attention should be paid to the governance as it relates to data exchange between MLDi and the National Health Care Institute, as well as international data exchange. Furthermore, there should be an investigation of what effect on MLDi there will be from the implementation of the nationwide governance and funding structure of ROR DGM and quality registries.

Case study	**4. Multiple myeloma**
Date of report	June 2023
Duration of case study	January 2021 – December 2022
Contribution from ROR DGM	€100,000
Contractor	Erasmus MC
Person(s) involved	– Prof. P. (Pieter) Sonneveld (chair of registries) – Prof. J. (Jan) Hazelzet (co-chair of registries) – Dr. L. (Lidwine) Tick (Haematology Association of the Netherlands and WGZ-MM pilot) – H (Hans) Scheurer (Myleloma Patients Europe) – Dr. S.(Simone) Oerlemans (Comprehensive Cancer Centres, IKNL) – G. (Gert-Jan) van Boven (hospital data service, DHD) – Dr. C. (Christine) Bennink (Erasmus MC), project coordinator
Related projects	– **Pilot project for value-driven multiple myeloma care (WGZ-MM), (Erasmus MC**): started by an initiated from within the Erasmus MC, in consultation with the multiple myeloma working group of the Haemato-Oncological Foundation for Adults (HOVON) and the Haematology Association of the Netherlands (NVvH) – **Multiple myeloma working group (ZIN)**: drawing up frameworks and methods for assessment across the spectrum of indications for multiple myeloma – **H2O (Health Outcomes Observatory)** – **Possible new GGG project**: developing a new approach to insured package management for multiple myeloma (ZonMW, ZIN)
Context	Multiple myeloma (Kahler's disease) is a malignant condition of the bone marrow. Numerous new treatment combinations have appeared on the market for this in recent years. To quantify the outcomes – including the quality of life – of these various treatments, the Erasmus MC has set up a registry for the condition. They are doing this in collaboration with several pilot hospitals and the National Health Care Institute. Measuring and sharing clinical and patient-reported outcomes is done in the pilot project called Value-Driven Care for Multiple Myeloma (WGZ-MM) at five Dutch hospitals. This pilot, which started in 2018-2019, was initiated from the Erasmus MC in consultation with the multiple myeloma working group of the Haemato-Oncological Foundation for Adults in the Netherlands (Stichting Hemato-Oncologie voor Volwassen Nederland, HOVON) and later also with the Dutch Haematology Association (Nederlandse Vereniging voor Hematologie, NVvH). There are numerous initiatives that collect healthcare data for the clinical picture of multiple myeloma and there are numerous projects that need the data for multiple myeloma. However, there is currently no registry for the condition that has nationwide coverage and collects the requisite information associated with MM. This is because they are standalone initiatives that do not gather all the data items and that are neither interoperable nor connectable, both of which are needed if the required national-level data is to be obtained.

	There is no current question about inclusion in the care package that the National Health Care Institute can advise on. The added value for the National Health Care Institute is in the development of the data model for achieving not only quality improvement but also cost-effectiveness analysis (of new and existing medicines/cyclic health insurance package management), relying on population-based data from the disease-specific registry. That registry can consist of data from various data sources that are connected together.
Assignment (work plan)	A work plan has been drawn up jointly with the case study defining the following objectives: **General:** go through the process of starting up a registry for the disease MM as per the strategic plan, where it is important that the registry is as a minimum suitable for monitoring effectiveness and cost-effectiveness of expensive medicinal products for the purposes of cyclic insured package management and appropriateness. **Content:** use and test the procedure dataset (D4) to arrive at a specific dataset for the registry for the disease multiple myeloma that is as a minimum suitable for the purposes of cyclic insured package management and appropriateness. **Data/IT:** drawing up and implementing a system of agreements for the purposes of the MM registry about information standards and assumptions for IT systems, as well as defining the process for reaching this point, in order to promote reuse in other registries. **Governance and funding:** To define the context for the governance and funding structure of an MM registry and to obtain insights into the interaction between these frameworks and the nationwide governance and funding structure that is to be developed. This will in particular pay attention to the data exchange between the registry and the National Health Care Institute. This should yield agreements about the governance and funding of registries and a model for that.

Annex 5: Outcomes of the self-assessment case studies

The maturity model makes it possible not only to score the individual registers in terms of maturity and development but also to compare one register against another.

DHDS Maturity Model | Databeschikbaarheid voor primair en secundair gebruik

	Stakeholders	Governance	Financiering	Toepassing en toegang zorgdata	Dataset en dataverzameling	Data kwaliteit	Juridisch en privacy	IT-standaardisatie	IT-implementatie	Burgerparticipatie
Niveau 5 Mature	Stakeholders hebben gezamenlijke afspraken en handelen hier naar.	Besturing volgens domein specifieke governance in aansluiting op landelijke governance.	Structurele publieke financiering.	Uniforme data beschikbaar voor alle verschillende doelen via informatieloket: kwaliteit van zorg, doelmatige zorg, cyclisch pakketbeheer, onderzoek, PGO volledig in gebruik, keuze informatie/ samen-beslissen. Interactieve dashboards voor zorgprofessional. Burger heeft regie op eigen data.	Basisgegevensset zorg breed ingevoerd. EMA geaccrediteerd. Landelijke dataverzameling. Dataverzameling en ontsluiting uitsluitend bij de bron. Data uitwisseling op basis federatief model in werking.	Vertrouwen in datakwaliteit op basis van duidelijke afspraken. Data voldoet aan EMA criteria. Request tool volledig ingezet.	Geïntegreerde wet- en regelgeving. Grondslagen juridisch gewaarborgd. Koppeling data wettelijk toegestaan en uitgevoerd.	Afspraken over informatie-standaarden, codetabellen en FAIR principes zijn geïmplementeerd in primaire zorgsystemen en zijn bron voor zorgdata.	Gegevensuitwisseling via een landelijk dekkend netwerk van ICT-infrastructuren en –systemen.	**Vertrouwen** Burgers hebben vertrouwen in juist datagebruik. Gebruik zorgdata voor iedere toepassing geaccepteerd. Burger stelt eigen data beschikbaar.
Niveau 4 Corporate adoption	Stakeholders hebben (eigen) data behoefte in beeld op basis van legitieme recht/grondslag.	Solide organisatie: rollen, taken en verantwoor-delijkheden worden gedragen. Duidelijke rol overheid, onderzoek en industrie.	Structurele financiering.	Data is beperkt beschikbaar voor specifieke doelen. Via PGO is beperkte regie van burger op eigen data mogelijk. Beperkt aantal dashboards voor patiënt en zorgprofessionals.	Dataset verrijkt met data patiënt (PROMs, PGO). Grotendeels landelijke dataverzameling. Grotendeels geautomatiseerde aanlevering. Pilots met federatief model, bijv. Personal Health Train.	Alle items uit Request tool 1.0 zijn voldoende. Data voldoet aan FAIR principes.	Privacy is gewaarborgd. Duidelijke grondslagen. Privacy Preserving technologies toegepast. Systematiek voor unieke koppelsleutel, bijv. BSN.	Afspraken over informatie-standaarden, codetabellen en FAIR principes.	Bronsystemen zijn gekoppeld. Uitwisseling data tussen bronnen automatisch op basis van ZIB en OMOP.	**Acceptatie** Burger is het er mee eens dat bepaalde data nodig is voor specifieke vragen (maat-schappelijk of individueel) en dat hij/zij een bijdrage moet leveren. Burger heeft vertrouwen. Burger in ethische commissie.
Niveau 3 Skilled	Stakeholders weten hun rol, positie en belang. Via wetenschappelijke commissies / patiënten en andere stakeholders worden verbeteracties geformuleerd.	Aandoeningsgerichte besturing vanuit WV met patiëntvertegenwoordiging	Projectmatige financiering.	Duidelijk welke data nodig is voor verschillende doelen. Ontwikkeling dashboards om data toegankelijk te maken.	Met stakeholders afgestemde dataset. Regionale dataverzameling. Handmatige invoer.	Duidelijke eisen aan datakwaliteit en dataverzameling. Request tool 1.0 is toegepast, maar niet alle items voldoende. Data voldoet nog niet aan FAIR principes.	Privacy is gewaarborgd. Grondslagen in ontwikkeling. Structurele toetsing. Koppeling data niet mogelijk.	In data-dictionary zijn definities en betekenis van data beschreven.	Bronsystemen zijn bekend. Metadata is toegankelijk.	**Begrip** Burger snapt dat (gecombi-neerde) zorgdata antwoor-den kan geven op specifieke vraagstukken. Maatschappelijke discussie over privacy aspecten. Vertrouwen begint te groeien.
Niveau 2 Aware	Alle stakeholders geïdentificeerd. Beperkt aantal is betrokken.	Register met besturing en patiëntvertegenwoordiging	Incidentele financiering.	Data wordt als belangrijk gezien. Doelen om data te gebruiken geformuleerd. Beperkte toegang tot data.	Meer gestructureerde dataset Lokale dataverzameling. Handmatige invoer.	Afspraken over actualiteit, betrouwbaarheid en volledigheid van de gegevens.	Grondslagen in ontwikkeling. Incidentele toetsing. Koppeling data niet mogelijk.	Dataset sluit aan bij informatiestromen en informatie-objecten in het zorgproces.	Basis infrastructuur. Bronsystemen worden geïnventariseerd.	**Geïnformeerd** Burger weet wat zorgdata is en welke vraagstukken beantwoord moeten worden. Wantrouwen nog aanwezig.
Niveau 1 Unaware	Stakeholders niet allemaal in beeld.	Onduidelijke rol registers en partijen.	Geen structurele financiering.	Data niet gericht gebruikt; geen duidelijke doelen. Geen toegang tot data.	Willekeurige dataset, register specifiek. Lokale dataverzameling. Handmatige invoer.	Geen duidelijke afspraken over vastlegging data items.	Juridische barrières. Grondslagen en voorwaarden onduidelijk. Onbekend welke activiteiten er zijn rondom privacy. Koppeling data niet mogelijk	Dataset sluit niet aan bij informatiestromen en informatie-objecten in het zorgproces.	Data is versnipperd/ onvindbaar.	**Onwetend** Burger is onbekend met en niet betrokken bij gebruik zorgdata. Burger is wantrouwend.

Level 5 Mature	Stakeholders have made collective agreements to which they concur	Control is via domain-specific governance aligned to national-level governance	Structural public funding	Uniform availability of data for all the various purposes via an information desk: quality of care, targeted care, cyclic insured package management, research, individual healthcare environment fully in use, choice of information/joint decision-making Interactive dashboards for healthcare professionals. Members of the public have control over their own data	Basic dataset introduced throughout the care sector. EMA-accredited. Nationwide data collection. Data collection and access/use controlled exclusively at the source. Data exchange operational, based on a federative model	Confidence in data quality, based on clear agreements. Data complies with EMA criteria. Request Tool fully deployed	Legislation and regulation integrated. Principles given a legal basis. Links to the data are legally permitted and legally implemented	Agreements about information standards, code tables and FAIR principles have been implemented in the first-line healthcare systems and are a source of healthcare data	Data is exchanged through a network of IT infrastructural elements and systems with nationwide coverage	**Trust** The general public are confident that data is being used correctly. The use of healthcare data is accepted for each individual application. The general public make their own personal data available
Level 4 Corporate adoption	Stakeholders have a clear picture of their own data requirements, based on legitimate	A solid organisation: backing for the roles, tasks and responsibilitie	Structural funding	Availability of data is limited and for specific objectives. The IHE allows members of	Dataset enriched with patient data (PROMs, IHE). Mostly	All items from Request Tool 1.0 are sufficiently	Privacy is guaranteed. Clear principles. Privacy-preserving	Agreements about information standards, code tables	Source systems are connected. Data exchange between	**Acceptance** The public understand that certain data is needed for specific

	entitlement and principles	s. Clear role for central government, research and industry		the public a certain amount of control over their own data. A limited number of dashboards for patients and healthcare professionals	nationwide data collection. Largely provided automatically. Pilots for the federative model, e.g. Personal Health Train	available. Data complies with FAIR principles	technologies applied. Systematic in its use of a unique linking key, e.g. the social security number	and FAIR principles	sources is automatic, based on the ZIB building blocks and the OMOP model	questions (both social and individual) and that they have to make that contribution. The public have confidence in this. The general public are represented in the ethics committees.
Level 3 Skilled	Stakeholders understand their roles, positions and importance. Actions for making improvements are formulated through scientific committees/patients and other stakeholders.	Condition-oriented control from the scientific associations and patients' representation	Project-based funding	Clear what data is needed for various objectives. Development of dashboards to make data accessible	Dataset agreed with the stakeholders. Regional data collection. Manual input	Clear requirements for the data quality and data collection. Request Tool 1.0 applied, but not all items are yet sufficiently ready. DATA does not yet comply with FAIR principles	Privacy is guaranteed. Principles being developed. Structural testing. Links with the data components not possible	Definitions and meanings of data have been described in a data dictionary	The source systems are known. Metadata is accessible	**Understanding** The public understand the healthcare data (alone or combined) can provide answers to specific questions. Public debate about privacy aspects. Confidence beginning to grow

Level 2 Aware	All stakeholders identified. A limited number of them are involved.	Register of controllers and patient representation	Incidental funding	Data is seen to be important. Goals for data usage have been formulated. Limited access to data	A more structured dataset. Local data collection. Manual input.	Agreements about how up-to-date, reliable and complete the data must be	Principles being developed. Incidental testing. Links with the data components not possible	Dataset fits in with the information flows and information objects within the care process	Basic infrastructure. An inventory of source systems is made	**Informed** The public understand what healthcare data is and what questions need to be answered. Still some mistrust
Level 1 Unaware	Not all stakeholders in the picture	The roles of registers and the parties are unclear	No structural funding	Data use not targets; no clear objectives. No access to data	Random dataset, register-specific. Local data collection. Manual input	No clear agreements about recording the data items	Legal barriers. Principles and preconditions unclear. What activities there are relating to privacy is not known. Links with the data components not possible	Dataset does not fit in with the information flows and information objects within the care process	Data is fragmented or cannot be located	**Unaware** The public do not know about the use of healthcare data and are not involved. The public are suspicious.
	Stakeholders	**Governance**	**Funding**	**Applications of healthcare data and access to it**	**Dataset and data collection**	**Data quality**	**Legal and privacy**	**IT standardisation**	**IT implementation**	**Public participation**

The figure below gives a visual representation of the scores of the case studies after completion of that phase of ROR DGM.

Annex 6: Financial accountability

The overview below provides accountability for the budget and the realisation of the case study phase.

Financial reporting* (x 1,000)	2021 budget	Realisation in 2021	2022 budget	Realisation in 2022
Staff costs	500.4	514.1	622.9	635.7
External staff hired in	453.3	405.5	252.3	42.5
Office costs and miscellaneous	131	131	60	122.8
Cost committees	26.8	26.8	9	12.9
Total	**1,111.2**	**1,073.4**	**929.2**	**839.5**