Activities and Barriers of University Hospitals in the Drug Life Cycle: A Delphi study

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Samenvatting

Uitgaven aan receptgeneesmiddelen, toegepast in medisch-specialistische zorg, stijgen al jaren. Deze stijging vormt een bedreiging voor de betaalbaarheid en toegankelijkheid van geneesmiddelen en zet het huidig zorgstelstel onder druk. Meerdere stakeholders mengen zich in het maatschappelijk debat hierover, met name de farmaceutische industrie en de overheid. In het debat worden oorzaken van de stijgende uitgaven bij deze stakeholders gezocht en wordt voor mogelijke oplossingen maar beperkt gekeken andere betrokken stakeholders en de hele Drug Life Cycle (DLC). Zo zijn Universitair Medische Centra (UMC's) een essentiële stakeholder die betrokken zijn in bijna alle fasen van de DLC, maar nemen zij nauwelijks deel aan het maatschappelijk debat. Het doel van dit onderzoek is om te achterhalen hoe UMC's kunnen bijdragen aan betaalbare geneesmiddelen voor medisch-specialistische zorg en het beheersen van de totale uitgaven aan deze geneesmiddelen. Daartoe wordt onder verschillende Nederlandse stakeholders onderzocht welke activiteiten UMC's ondernemen en/of zouden moeten ondernemen in de DLC, en tegen welke barrières en dilemma's zij daarbij aanlopen. Hierbij wordt bepaald in hoeverre er overeenstemming is tussen de stakeholders.

In dit onderzoek is de Delphi techniek toegepast, waarbij er drie online vragenlijsten zijn verspreid onder panelleden. Voor het vormen van het panel zijn verschillende professionals werkzaam in UMC's, overheidsinstanties, zorgverzekeraars en de farmaceutische industrie uitgenodigd. In de eerste vragenlijst konden panelleden per fase van de DLC aangeven welke activiteiten UMC's (zouden moeten) ondernemen en tegen welke barrières en dilemma's zij daarbij aanlopen. In de tweede vragenlijst konden de panelleden aangeven in hoeverre zij het eens waren met de gegeven antwoorden op de eerste vragenlijst. In de derde vragenlijst konden panelleden hun mening heroverwegen en toelichten.

Volgens de meerderheid van het panel, zouden UMC's geneesmiddelen moeten (her)ontdekken, ontwikkelen, registreren, produceren en verkopen. Daarnaast zouden UMC's zich bezig moeten houden met de prijsstelling van geneesmiddelen. Ook zouden ze meer (onafhankelijk) onderzoek moeten doen naar veel verschillende onderwerpen. UMC's zouden naast standaard activiteiten, ook andere activiteiten m.b.t. het voorschrijven en vertrekken van geneesmiddelen moeten ondernemen. Tevens, zou er bij het opleiden en onderwijzen van medische professionals aandacht moeten worden geschonken aan farmacotherapie en geneesmiddelontwikkeling. Er was overeenstemming tussen de panelleden voor wat betreft de barrières en dilemma's die UMC's (kunnen) ondervinden, namelijk het gebrek aan resources, een gezamenlijke (data-)infrastructuur, expertise en kennis, en ondernemersgeest, visie, strategie en overzicht om geneesmiddelen op de markt te brengen. Daarnaast is wet- en regelgeving complex en beperkend en is de interactie met andere stakeholders belemmerend.

UMC's zouden kunnen bijdragen aan betaalbare geneesmiddelen voor medisch-specialistische zorg en het beheersen van de totale uitgaven aan deze geneesmiddelen door verscheidene activiteiten te ondernemen in de verschillende fasen van de DLC. Zo zijn er activiteiten die passen binnen de kerntaken van UMC's die eraan zouden kunnen bijdragen. Echter, als geneesmiddelenontwikkelaar en –producent zouden UMC's wellicht de grootste bijdrage kunnen leveren. Een aantal barrières en dilemma's bemoeilijken UMC's om deze activiteiten uit te voeren, maar ze zijn niet onoverkomelijk. UMC's moeten hun potentie benutten om bij te dragen aan betaalbare en toegankelijke geneesmiddelen. Hiervoor moeten ze assertief en moedig zijn om nieuwe taken en uitdagingen aan te gaan.

Introduction

Expenditures on healthcare are rising globally, due to multiple reasons. A substantial and growing part of these expenditures is spending on pharmaceuticals. The reason for increasing expenses on medication is twofold: a rise in costs of prescription drugs and an increase in consumption. (1-3) Over the past couple of decades there has been a marked trend of rising prices of innovative prescription medication. In the 1990s high prices of HIV/AIDS medication caused much controversy. (4) During the 2000s costly biologicals entered the market, including the TNF-alpha blockers. (5) More recently, medication for chronic hepatitis C and cystic fibrosis caused much debate due to their high prices. (6, 7) Currently, Zolgensma, a gene therapy for an orphan disease, holds the record for most expensive medicine in the world, costing almost 2 million euros per patient. (8) Prices of new pharmaceuticals have been rising at a high rate, considering 'high' drug prices went from thousands to millions of euros. (2) Besides, the trend of increasing prices is not only observed in innovative, patented prescription medication, but also even in some generic/off-patent prescription medication. (2, 9, 10)

Increasing spending on pharmaceuticals does not automatically pose a problem. Medicines offer health and economic benefits and prevent the utilization of expensive healthcare services. Nevertheless, rising expenditures on drugs challenge current healthcare systems given their budget constraints, to the extent that even high-income countries struggle with their finances. Additionally, the amount of expensive drugs and their prices are expected to grow further. This will have a major budget impact and serious implications for the affordability and accessibility of medicines. High-priced pharmaceuticals challenge the efficiency of healthcare spending, considered that they (may) displace other cost-effective healthcare services. Moreover, the high prices of medicines do not necessarily translate to proportional greater health benefits. (1, 2, 11, 12) These trends cause much public debate about (un)justifiable prices, (in)accessibility of medicines and (un)sustainability of healthcare systems.

Various reasons for the rising prices of pharmaceuticals have been described in grey and scientific literature. (2, 11) Although outlining those reasons is beyond the scope of this paper, it is important to consider the main identified causes when one tries to investigate how to turn the trend. According to literature, price increases are a result of: the malfunctioning of the pharmaceutical market, patent legislation, high R&D costs, high merger and acquisition activity and advancement in more personalized medicine. Moreover, interventions and policy of governments, such as orphan drug programs, also contributed to the trend of rising drug prices. (11, 13, 14) Essentially, developments in different phases of the drug life cycle (DLC) have altered the dynamics in the pharmaceutical market and the DLC, which caused growing costs of pharmaceuticals. (11)

Stakeholders

When causes of high drug prices are discussed in articles and debates, the focus tends to be on certain stakeholders, namely the suppliers (the pharmaceutical industry) and payers. The same holds true for when possible measures to encounter high-priced drugs are discussed. (11) However, many other stakeholders are involved in the pharmaceutical system, such as: health technology assessment (HTA) bodies, patients and civil society organizations, regulatory authorities, wholesalers and distributors, research institutions and healthcare providers. These stakeholders may also be part of the problem or may be able to offer solutions, but are not, or to a lesser extent, involved in the discussion. This is not in line with the Pharmaceutical Strategy for Europe, proposed by the European Commission, which states that all stakeholders should be involved to ensure affordability of medicines. (15) Moreover, current solutions do not consider the entire life cycle of medicines. Such a life cycle approach is recommended by the European Commission, as it offers a more comprehensive and integrated view to address the challenge of rising drug costs. (15)

Interestingly, a relevant stakeholder, university hospitals (UHs), seems not actively involved in the public debate of rising drug costs. This is remarkable because they deal with pharmaceuticals in many ways. Using the life cycle approach, we will elucidate their great involvement.

The Drug Life Cycle as a framework

A life cycle is the process a product, such as a drug, goes through from discovery through the withdrawal from the market. In current literature, the drug life cycle (DLC) is used to describe the market behavior of a drug and distinguishes different stages with respect to investments and revenues of pharmaceutical companies. In general, the following stages can be distinguished: development and introduction, growth, maturity and decline, as illustrated in figure 1. (11, 16)

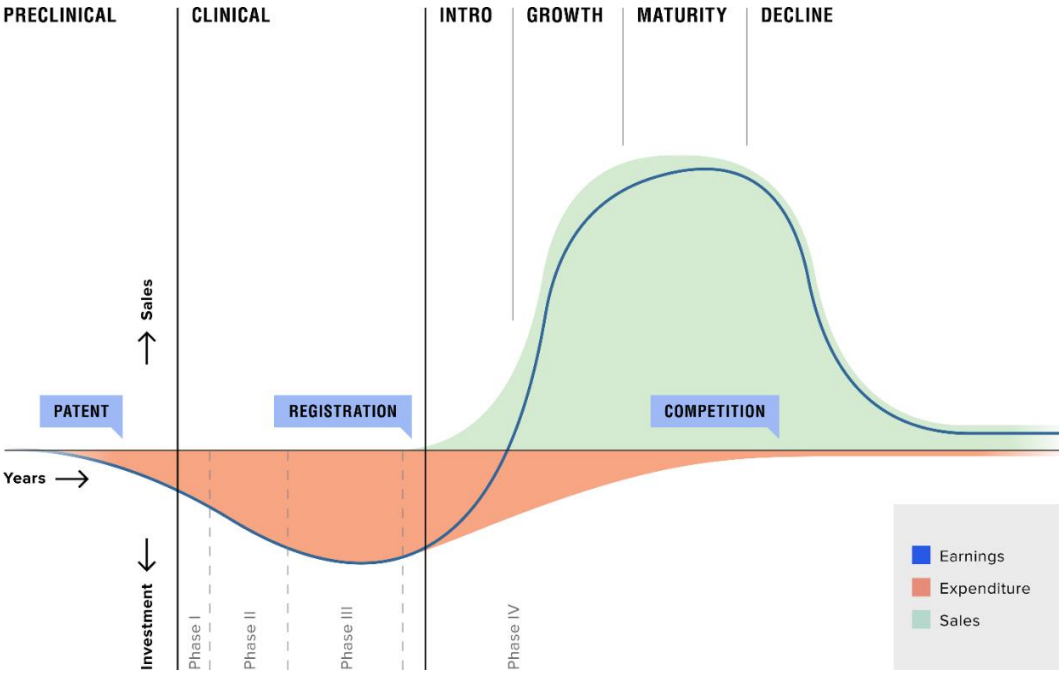

Figure 1: The DLC curve. Reprinted from: Gronde TV, Uyl-de Groot CA, Pieters T. 2017 (11)

Current literature describes the DLC from the perspective of the pharmaceutical industry. However, in the DLC multiple stakeholders are involved, which make this concept of limited use. We therefore propose an alternative concept of the DLC, which is more extensive and therefore may be of use by various stakeholders. Based on findings in literature, we were able to distinguish multiple phases in the DLC that relate to: R&D, market access, obtainment of medicines and the application in patient care. Brief descriptions of the phases are provided below.

There are three different, nevertheless interrelating phases in the DLC related to R&D, namely: *drug discovery, drug development* and the *post-marketing* phase. (17) Drug discovery is the process in which new potential drugs and new indications for existing drugs (repurposing) are identified. This phase consists of fundamental biomedical research, research on chemical compounds and preclinical research. This research produces knowledge, such as potential drug concepts, which is used or made available for social and/or economic purposes (valorization). If preclinical studies are successful, clinical studies (involving human subjects, including patients) are carried out, typically in three phases. These studies examine the pharmacokinetics and pharmacodynamics, optimal dose, efficacy and safety of the drug. This phase is well known as drug development. It is important to note that only drugs that are successful (proven to be safe and effective) move on to the next phase in drug development. (18) Data on effectiveness and safety is also collected when the drug is on the market (post-marketing), and is called real world data (RWD). This is used to generate real world evidence (RWE) on the benefits and risks of the medical product in clinical practice. Pharmacovigilance (detect, assess, understand and prevent adverse effects) and research on efficient use of medicinal products, are also subjects for research in the post-marketing phase. (19)

After successful clinical trials, medicines must be authorized before they can access the market and reach patients (outside trial setting). (20) To gain *market access*, the medicine developer submits a marketing authorization application to a competent authority. This application legally requires to include information on, amongst others, the efficacy and safety of the drug, as studied in the (pre)clinical trials. The authority carries out a scientific assessment of the application, in which they assess the benefit/risk profile of the drug. There are multiple procedures (centralized, decentralized and mutual recognition) available to gain market access, relating to the competent authority that assesses the marketing authorization application. Nowadays, most new innovative pharmaceuticals in Europe are evaluated though a centralized procedure by the European Medicines Agency (EMA). (21) Based on the authority's recommendations, the European Commission grants marketing authorization, which allows the medicine developer to market the medicine throughout the European Union. However, market access does not automatically translate to the availability of a medicine for a patient. A process is in place to determine whether, and possibly under what conditions, a medicine is reimbursed. This process, part of the *pricing and reimbursement* phase*,* is unique to every member state of the European Union, i.e. takes place on a national level. The marketing authorization holder files an application for reimbursement, which is assessed by HTA bodies, who advice or decide if a medicine should be reimbursed, and possibly at what price. (22)

Obtaining pharmaceuticals includes the *manufacturing* of medicines and the *procurement* thereof. Manufacturers produce pharmaceuticals according to a quality standard: Good Manufacturing Practice (GMP), which is legally required. In order to produce medicines manufacturers need to obtain a license, which state they are qualified to do so. (23) Nowadays, most medicinal products are produced on a large scale by the pharmaceutical industry. (24) However, medication is also produced on a smaller scale by pharmacies. Pharmacies are allowed to prepare medicines in bulk volumes or for an individual patient based on a prescription. Pharmaceutical compounding is applied when commercially available medicines do not meet the needs of the patient. Different laws apply to pharmaceutical compounding. (25) Subsequently, pharmaceuticals are procured. Pharmaceutical procurement take place on different levels (international, national, regional and local), involving different parties, such as governments and healthcare providers. Procurement often involves negotiating the price with the manufacturer or supplier (pharmaceutical companies and wholesalers). (26)

A patient gains access to a medicine through *prescribing* and *dispensing*. An authorized medical professional prescribes a medicine, based on medical and other considerations, for an individual patient. (27) Subsequently, the prescription is handled by the pharmacy, which checks the prescription. If deemed appropriate, the pharmacy dispenses medication. (28)

University hospitals

Overall, distinguishing these phases in the DLC offer a more systematic and accurate insight in the pharmaceutical system. Using this framework, the role of involved stakeholders in the DLC can be systematically assessed. Applying this concept of the DLC, it becomes apparent that UHs are a part of nearly every phase of the DLC. Table 1 gives a simplified and brief description of activities carried out by professionals in UHs in context of the DLC. These activities are performed as part of their core tasks, which are: providing (specialized) patient care, training medical professionals, performing and valorizing scientific research.

So, the great involvement of UHs throughout the DLC is apparent. Nevertheless, their visibility in the discussion of expensive medicines is scarce. This is even more striking considered that they are, beyond doubt, more frequently confronted with high-priced innovative medicines than other hospitals, due to the specialized medical care they, including the residing expertise centers, offer. (29) Only recently, UHs have started to get involved in this discussion, specifically on the subject of repurposing off-patent medicines. (30) Moreover, socially responsible licensing of (drug) inventions that originated in UHs also gained attention last year. (31)

Nonetheless, their involvement in the debate of rising drug costs is not proportional to their involvement in the DLC. This is remarkable, but may not be entirely incomprehensible. During the subsequent phases of the DLC UHs take on different roles, having different aims and responsibilities as part of their core tasks. This may result in barriers and dilemmas that UHs face when performing those roles. Having different roles, that come with barriers and dilemmas, may impede UHs to adopt a strong and explicit position in the debate.

However, their apparent nonappearance as a key stakeholder in the public debate about high cost drugs raises some questions, such as the awareness of UH professionals of their role in the DLC and their perception thereof. Their great involvement in the DLC also raises questions about their possible role in keeping medicines affordable. It is questioned if their role should be adapted and/or expanded adapted in order to contribute to keeping medicines affordable, and if they are capable and willing to do so.

To the best of our knowledge, these questions have not yet been coherently and systematically explored, according to the life cycle and interdisciplinary approach. Gaining insight in these issues will reveal current complications, the position and interrelations of UHs in the DLC and the possible role UHs could play in the DLC to turn the undesirable developments of high drug prices and increasing burden for healthcare systems. It will also give starting points to influence that, which may eventually result in more affordable and accessible medicines.

In this study, we aim to explore how UHs can contribute to affordable individual drugs and cost containment of total drug expenditures. To this end, we examine what roles UHs play and/or should play throughout the DLC and what barriers or dilemmas they face when doing so, according to various stakeholders and professionals. The primary objective is to determine consensus among various actors in the DLC on the role, and barriers and dilemmas of UHs in the DLC. The scope of this research extends to medicines applied in specialized medical care and the Dutch healthcare system.

Table 1: Activities of UHs during the phases of the DLC, involving different UH professionals (32)

DLC phase	Professionals	Activities
Drug discovery	Directors Researchers TTO	Perform fundamental (biomedical) research, fitting the set research lines of the UH, which gives leads for potential new medicines or repurposing existing ones. Perform translational research. Conduct preclinical studies in vitro and in vivo. Patent/license valuable knowledge and sell to/cooperate with other parties for further development.
Drug development	Directors Researchers Doctors/PI MREC	Review research protocols that involves research with human subjects. Carry out clinical trials that collect evidence on the efficacy and safety of the investigated drug.
Market access		Competent authorities engage UH professionals for their expertise.
Pricing and reimbursement		Reimbursement bodies may request (clinical) advice from UH professionals.
Manufacturing/ Pharmaceutical compounding	Pharmacists	Manufacture medicines, both during (early) drug discovery and development, and for patient use outside trial setting.
Procurement	Pharmacists	Procure medicines applying different strategies that affects (lowers) the purchase price.
Prescribing	Doctors	Prescribe medicines that are administered in-house or are used by patients in the domestic situation.
Drug dispensing	Pharmacists	Dispense medication. Prepare medication for administration.
Post-marketing	Doctors Pharmacists Researchers	Gather RWD/RDE. Practice post-marketing surveillance/pharmacovigilance. Do (observational) studies to determine effectiveness and safety in clinical practice. Investigate ways to increase (cost-)efficient application of medicines.

Method

As an essential stakeholder in the DLC, UHs may be in the position to contribute to affordable medicines for specialized medical care and to the containment of total expenditures on these medicines. The purpose of this study was to explore in what manner UHs can do that. Therefore, it was needed to question what activities they undertake or should undertake in the DLC, and what barriers and dilemmas they encounter when they do so. It was important that not only the perspective of UHs was taken into account, but also that of other stakeholders in the DLC. The government, health insurers and pharmaceutical companies are other relevant stakeholders involved in the DLC, who have immediate links with UHs and who may have different views.

Study design

It was decided that the best method for this study was the (classical) Delphi technique. The Delphi technique is a research method that is used to collect expert-based judgements to reach consensus on complex topics, which lack knowledge, or consensus. Concomitantly, areas of disagreement are identified. The method is also used to identify the opinion of experts on complicated issues, where knowledge is unsettled, and to develop various ideas and solutions for these issues. This method stimulates new ideas and widens knowledge. (33) This research method was therefore appropriate for our research purposes.

The technique applies a series of surveys – rounds – to gather information from a group of experts and – ideally- continues until consensus is reached. In each round, the results of the previous survey are presented to the experts, so they can revise their judgements. (34) The Delphi technique enabled us to combine the qualitative and quantitative aspects of our research: generate ideas and solutions and determine consensus on these among experts. Seen the exploratory nature of this study and the complexity of the issue at study, reaching consensus was not a goal in this study.

In the Delphi method a panel of experts is formed which participate in all rounds. The panel is composed of experts who have certain professional or scientific expertise, and who may offer different perspectives. In this type of study, a large number of experts with different disciplines can be included without geographical limitations. (35) Executing a Delphi study online offers the practical advantage when dealing with COVID- restrictions. During the surveys, the results are returned anonymously to the experts. The anonymity throughout the process avoids dominance or other biasing personality traits of individuals, associated with other research methods. (36) Moreover, experts may be more frank, especially on controversial subjects.

Expert panel

To assemble an expert panel for this study, various Dutch-speaking professionals representing different stakeholders in the DLC in the Netherlands were invited. Experts were approached by e-mail or LinkedIn. Besides, an open invitation was posted on LinkedIn©.

Professionals (directors, hospital pharmacists, doctors, TTO-experts, researchers and advisors/policy officers) from all seven Dutch UHs (Erasmus MC, Amsterdam UMC, Leids UMC, Maastricht UMC, Radboud UMC, UMC Groningen, UMC Utrecht) were invited. Moreover, the Dutch Federation of University Medical Centers (NFU) and the Dutch Association of Hospital Pharmacists (NVZA) were approached.

Professionals (directors, purchasing managers and advising pharmacists) employed at the four largest health insurers (Zilveren Kruis (Achmea), VGZ, CZ and Menzis) were solicited to participate. Additionally, the umbrella organization of health insurers (ZN) was requested to participate in the study.

Professionals with expertise in the field of pharmaceuticals employed at three governmental organizations were invited, namely the National Health Care Institute (ZIN), the Ministry of Health, Welfare and Sport (VWS) and the Dutch Healthcare Authority (NZa).

Medical directors of pharmaceutical companies were approached via the Association of Innovative Medicines (VIG) by an intermediary (senior policy advisor of the VIG).

Data collection

The Delphi process was conducted on the online survey platform Welphi©, which was licensed by the Erasmus MC. Three rounds of questionnaires were established for feasibility reasons and considering the exploratory nature of this study. Reaching consensus was not the objective of this study.

The first survey round was created to receive input from the participants on the research question by posing scaling and open questions. For each phase of the DLC, participants were asked to indicate: i) the current importance of the role of UHs, ii) the current activities of UHs, iii) the required activities of UHs, iv) barriers or dilemmas UHs (may) face when carrying out those activities. In the scaling question (i) participants were asked to give their opinion on a 5-point Likert scale (totally not important – not important – neutral – important – very important). Participants were not obliged to answer all questions, since not all professionals possess the expertise or experience in each phase of the DLC. Additionally, in order to describe the panel, participants were asked to confirm their gender, profession and the type of stakeholder they were affiliated. Moreover, panelists were asked to specify the amount of years they had work experience anywise related to medicines.

In the second round, the degree of consensus on the answers given in the previous round was measured. The answers were presented as statements that were developed as described under *Data analysis and processing*. Current and required activities (question i and ii in round 1) were clustered together, as well as barriers and dilemmas. Participants were asked to indicate the extent to which they (dis)agreed with the statements. The level of agreement was indicated on a 5-point Likert scale (completely disagree – disagree – neutral – agree – completely agree). An 'I don't know' option was also available to capture unfamiliarity and uncertainty.

In the third round, panelists were asked to reconsider the statements on which no consensus was found in the preceding round. The statements were presented with the results of the second round, shown as a percentage per given option. Panelists were asked to indicate the extent to which they (dis)agreed with the statements, but also to motivate their choice.
In all rounds, panelists were asked to provide feedback on the questionnaire.

Data management plan

A data management plan (DMP) was set up prior to the execution of the study. The DMP outlined the following issues: study details, agreements and intellectual property (IP), ethical and legal issues, informed consent, data description, standardization and documentation, data storage and backup, data archiving, data sharing and costs. Acquired data is under the responsibility of and owned by the Erasmus MC. Involved researchers are compliant with the following laws and regulations: Erasmus MC Research Code, Netherlands Code of Conduct for Research Integrity, General Data Protection Regulation (GDPR) and Code of Conduct for Health Research. An informed consent procedure was in place, which is elaborated in *Ethical considerations*. Multiple steps were taken to safeguard the anonymity and confidentiality of the participants. The data from the questionnaires was exported from the Welphi platform in a Microsoft Excel file, which was saved on a secured server that is only accessible for involved researchers. The data will be preserved for 15 years for compliancy and verification purposes.

Data analysis & processing

Uncompleted questionnaires were included and unanswered questions were coded as missing in the exported Excel file. Data was analyzed in Excel. In the first round, two types of questions (scale and open) were analyzed. The scaling questions were analyzed by calculating a median and an interquartile range (IQR). This was done by giving every option on the Likert scale a score: totally not important (1), not important (2), neutral (3), important (4), very important (5). Consensus was defined as an IQR ≤ 1.

The answers to the open-ended questions were analyzed individually by each researcher. Incomprehensible or unclear answers were disregarded. Both researchers independently clustered similar answers and formulated matching statements, based on participants' answers, for each cluster. Consequently, the clusters and statements set up by the two researchers were compared.

In the second and third round, data was analyzed by calculating the ratio, expressed as a percentage, of experts voting for a certain option on the Likert scale, to the total number of experts that voted. Voting for 'completely disagree' and 'disagree' was considered the same option, and the same applied for 'completely agree' and 'agree'. The 'I don't know' option was considered missing and thus experts who voted for the 'I don't know' option were excluded from the calculation. Consensus was defined as achieved when >50% of the experts voted for the same option.

Ethical considerations

The research protocol was reviewed by the Medical Research Ethics Committee (MREC) of the Erasmus Medical Center (UH located in Rotterdam, The Netherlands) on the submission to the Medical Research Involving Human Subjects Act (WMO). The research was declared not to be subjected to the Act by the MREC, as this research required legally capable, human subjects to fill out three online surveys (max. 3 hours in total) with no intrusive, burdensome or intimate questions.

An informed consent procedure was in place. Invitees had the right: to be informed, to object (refuse to participate), to erasure (withdraw consent) and to data portability (receive their data).
Invitees, who wished to participate in the study, were requested to sign an informed consent form (ICF) in order to be included in the study. The participants received a signed (by the researcher) ICF in return. The ICF (a PDF-file sent together with the invitation) contained information on: the background and purpose of the study, the procedures, inclusion criteria, potential benefits of participating in the study, the implications of participating, and contact details of the involved researchers.
Gaining insight in the position and role of UHs in the DLC and additional dilemmas, and contributing to a broader purpose (explore how UHs can contribute to affordable medicines and containing the total costs of medicines) were mentioned as, individual and collective, benefits of participating to the study. The implications of participating included: the anonymized collection, usage and storage of data for research purposes.

Results

Expert Panel

Between 21 September and 16 November 2021, 163 experts were invited by email and LinkedIn. Furthermore, a number of medical directors of pharmaceutical companies affiliated with the VIG was invited through an intermediary (senior policy advisor of the VIG). The majority of invited experts (N=92) did not respond to the invitation, in spite of sending a reminder. 37 experts stated not being able to participate for reasons of i) lack of time (N=16); ii) insufficient knowledge (N=3); iii) no or various reasons (N=11), and 7 experts referred to a colleague (included in the total number of invited experts). We received no response from any medical director.

Finally, 34 experts were included in the study, of which 19 (56%) were male. The majority (N=29) was affiliated with UHs (85%). Table 2 specifies the composition of the expert panel.

Table 2: Number of included experts, specified by stakeholder and profession

Stakeholder, profession	**Included N (%)**
Total	**34 (100)**
University hospital	**29 (85,3)**
Director	3
Hospital pharmacist	5
Doctor (prescriber, researcher, principal investigator)	11
TTO-expert	3
Researcher	4
Advisor/policy officer	2
NVZA: policy advisor	1
Health insurer	**3 (8,8)**
Purchasing manager pharmacy	1
Advising pharmacist	2
Government	**2 (5,9)**
ZIN: Secretary of the scientific advisory board	1
NZa: Policy maker	1

Rounds

In the first round, 31 experts replied to the questionnaire. The respondents had 20 years (median) work experience with pharmaceuticals in any manner. See Supplement 1 for data of round one.[1] Based on the answers to the open-ended questions in round one, the researchers generated 206 statements. These statements were submitted to the expert panel in round two and consensus was found on 174 statements among 29 experts. See Supplement 2 for data of round two.[2] In the third round, the 32 statements on which no consensus was found in the second round were presented to the participants. Consensus was found on 17 statements amongst 21 experts. See Supplement 3 for data of round three.[2] At the end of the Delphi process, 191 statements (92,7%) achieved consensus and no agreement was reached on 15 statements (7,3%). An overview of the Delphi process is provided in figure 2.

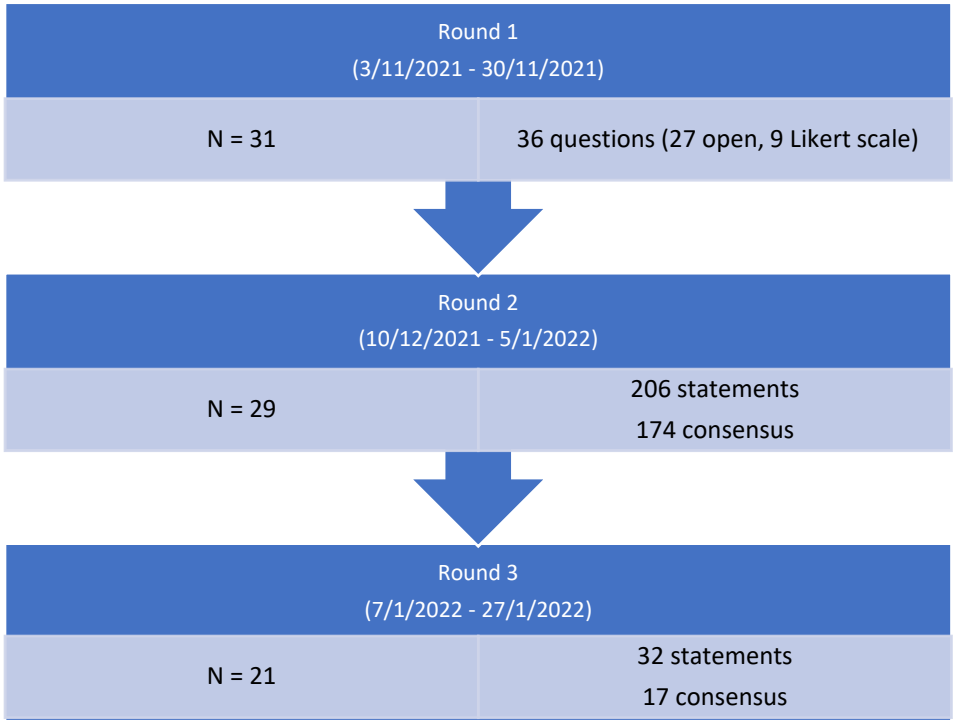

Figure 2: Diagram of the Delphi process. The period of time the survey was open for response is indicated. N: Number of experts that participated. The number of questions/statements per round is presented, as well as the number of statements that reached consensus.

[1] Please note that the original data (in Dutch) is presented.
[2] Please note that the original data (in Dutch) is presented. Consensus analysis is presented in English

Phases

This section provides an overview of the results per phase of the DLC. In figure 3, the results of the scaling question: *How important is the role of UHs in the DLC phase?* are presented.

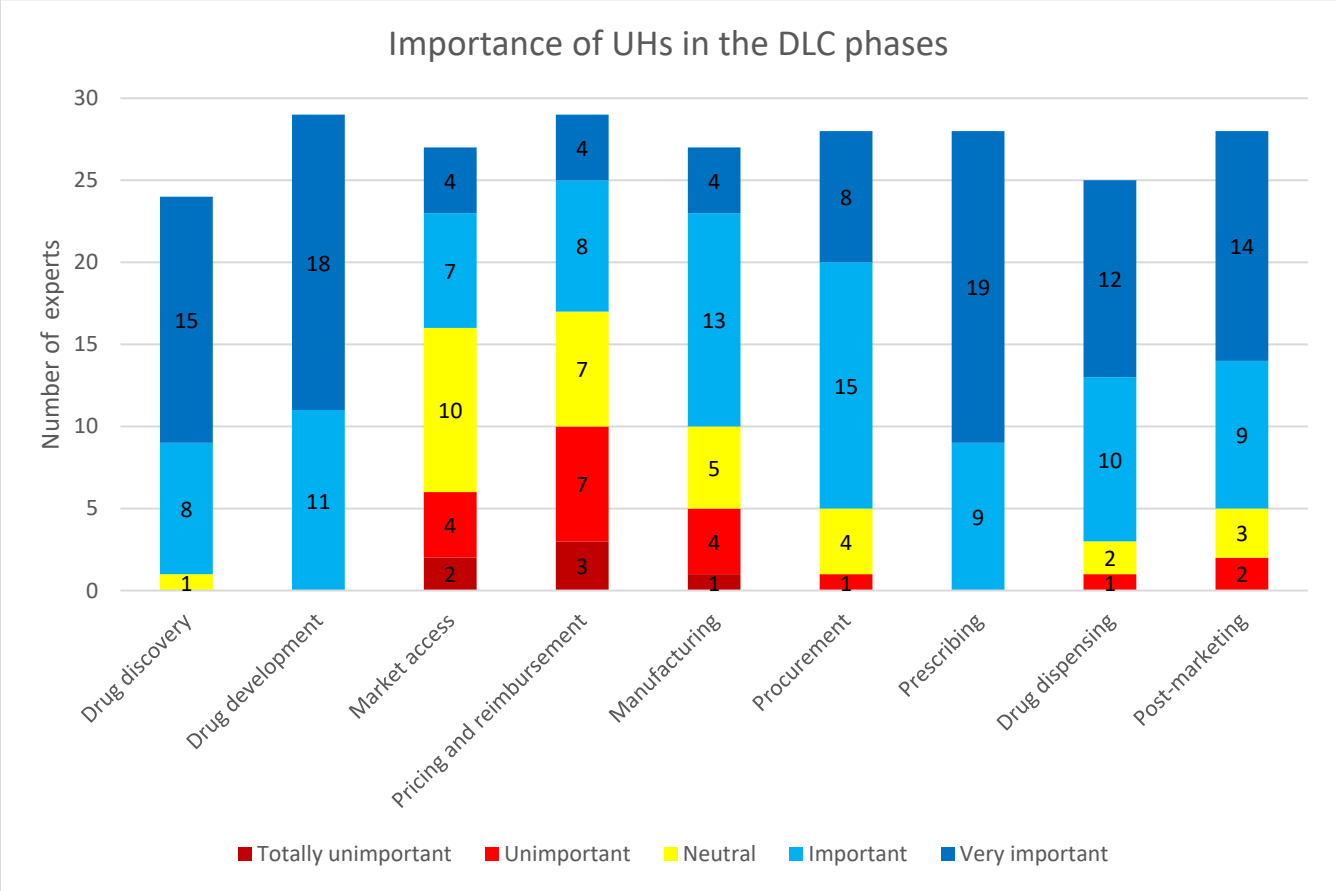

Figure 3: The importance of UHs in the DLC phases according to the panel. The Y-axis indicates the total number of experts that voted. The numbers in the colored columns indicate the number of experts voting for the corresponding colored option.

Drug discovery

The panel of experts considered the role of UHs in the drug discovery phase very important (median = 5; IQR =1). Participants agreed that UHs (should) carry out various research related activities, including: conduct fundamental and translational research, develop and provide models for preclinical research, update the pathophysiology of diseases, publish findings, apply for funding to conduct research and valorize inventions. In the opinion of the panel, training medical professionals is an activity performed by UHs.

According to the participants, UHs should be active at an earlier stage in drug discovery and play a greater role in this phase. The experts had different views on UHs holding on to discoveries longer, which resulted in consensus on a neutral position. Arguments in favor were offered by the experts, including: giving UHs a stronger position during valorization and with that more control on drug pricing. Others stated that is not about the amount of time that UHs hold on to a discovery, but it is about making good arrangements so public investments do not end up in the private sector.

The majority of participants acknowledged that in the academic setting, it is complicated to oversee the entire process. Moreover, the respondents agreed that there is a lack of vision on development. According to the panel, scientists are not entrepreneurs and are little aware of IP and valorization. In their view, UHs depend on commercial parties to advance scientific insights. The panelists did not assent with another on UHs not daring to go against the interests of a pharmaceutical company for fear of missing out on money or research. Some stated to have experienced it, while others do not recognize it. They did agree with the statement: the pharmaceutical industry insufficiently compensates UHs for the use of their data.

Furthermore, in the opinion of the panel, UHs should assess a reasonable price that can be asked for a drug, taking into account incurred costs, subsidies and co-ownership. In their view, the societal need for a potential new drug should be prioritized by UHs.

According to the experts, a budget should be reserved for the further development of medicines for rare hereditary diseases, to eventually apply them in the clinic. At the same time, they agreed that UHs lack financial resources for further development of medicines, but also workforce, time and support.

Drug development

The role of UHs in the drug development phase was considered very important (median = 5; IQR =1). Participants agreed on UHs performing multiple research activities, such as conducting investigator- and sponsor-initiated clinical studies and coordinating and executing phase II and III multicenter and/or multinational studies. In the opinion of the panel, UHs: fulfill the role of principal investigator (PI) and key opinion leader (KOL), have a pioneering role towards scientific associations and (should) provide education on drug development and training to medical students and professionals. The panel disagreed with the statement that doctors receive insufficient acknowledgement for their research, publications, and valorization.

The panel agreed that UHs should conduct more phase III studies, investigator-initiated research (independent of the pharmaceutical industry), studies that are linked to phase II trials, research on repurposing existing drugs and research aimed at better defining patient(groups). In their view, in case of less complex conditions 'routine' phase IIb and III studies can be performed by Cooperating Top Clinical Teaching Hospitals (STZ) or specialized Centers for Drug research. The respondents gave their assent to UHs setting up platforms for rare diseases and managing independent databases and biobanks in centers of expertise.

The panel disagreed on the Netherlands having too few centers with sufficient expertise and patients to participate in international phase II and III studies. The panel had a neutral position on finding suitable patients that meet inclusion criteria posing as a barrier. Experts commented that in some cases (certain disciplines or strict inclusion criteria), it is more difficult to find suitable patients, but also when patients are treated in peripheral hospitals. No consensus was found on UHs experiencing the dilemma of cooperating or competing with other UHs. In addition, no consensus was found on the speed of MRECs, being below the desired level. Some experienced it as slow, while others stated that it varies.

In the panel's view, UHs should offer more transparency through multiple activities. UHs should participate in clinical research under the condition that results will be made public and easily accessible to others (open source). In addition, UHs should (also) publish (more) outcomes that are negative. Furthermore, UHs should include their research in overviews, so both patients and professionals can conveniently find the studies that take place per indication. Besides, they should communicate more (clearly) about the chain from research to healthcare to other public stakeholders.

The experts agreed that UHs are financially and intellectually dependent on the pharmaceutical industry, and not willing to impose conditions that are not in the interests of the industry. Participating in seeding trials, under the name of clinical research, is still experienced as a dilemma. There was consensus on patents of manufacturers posing as a barrier. No consensus was reached on whether UHs establish the pipeline of the pharmaceutical industry, by repurposing drugs. It was commented that repurposing drugs is done separately by UHs and the pharmaceutical industry, but also in close cooperation.

According to the panel, to perform activities in this phase, UHs (will) lack: structural funding, workforce, time, expertise, infrastructure, support and knowledge about financing. The (increasingly more) complex laws and regulations, and obtaining hospital exemption when Advanced Therapy Medicinal Products

(ATMPs) are applied, are other barriers that UHs (will) encounter, according to the respondents. The panel agreed that UHs should build knowledge about drug development, regulatory affairs and a strategy for marketing authorization, so UHs will be in control of the process for longer and exert more influence on the price of medicines.

Market access

In the opinion of the expert panel, UHs are neither important nor unimportant in the market access phase (median = 3; IQR = 1). The panel agreed that UHs participate in clinical validation studies that are required for market access and in Horizon scan working groups. Besides, the expert panel agreed that UHs ensure that patients have access to new medicines as soon as possible.

Experts agreed on UHs lacking knowledge about the requirements and potential strategies for the development and marketing authorization of new drugs, and must build knowledge. The majority of experts thought that the possibilities to gain marketing authorization for a medicine are limited. Besides, it was agreed that legislation is complicated. Still, the panel disagreed on UHs not being able to market medicines themselves, or to independently conduct clinical trials.

The panel agreed that UHs should apply for marketing authorization for drugs that are developed in-house and sell medicines that they produce. A barrier that the majority of participants acknowledged was that marketing medicines is not a core activity of UHs, and is the responsibility of the pharmaceutical industry. The respondents agreed that setting up the required dossier is extremely labor intensive and not feasible as a non-commercial party. Moreover, it was also agreed that there is a shortage of resources and a lack of a good collaborative infrastructure between UHs.

However, the participants agreed that UHs must claim their social role within this domain and must not give it away to the pharmaceutical industry. The majority of experts think that UHs depend on (health insurers, the government and) the pharmaceutical industry, which leads to potential conflicts of interest, and sometimes lawsuits. The respondents agreed that being active in this phase of the DLC, UHs operate in the field between the pharmaceutical industry, the ministry and regulatory authorities, where the parties pit against one another. Participants agreed on UHs advising the competent authorities EMA and Medicines Evaluation Board (MEB), and KOLs are (un)noticed deployed in lobby towards the EMA/MEB. They agreed that UHs should be more proactive and provide more transparency towards public parties in the Dutch healthcare system. Besides, according to the panel, UHs should make all studies, including results, which they have participated in, public and offer these to the EMA/MEB to contribute to fair decision-making.

The majority of respondents thought that UHs should take a leadership role in shaping meaningful, cost-effective care. For example, they agreed that UHs should investigate appropriate use, assess (cost)effectiveness and pay attention to an optimal cost-effectiveness strategy for expensive drugs. Moreover, UHs should express themselves more emphatically about the usefulness and necessity of a new medicine in the pre-registration phase.

Furthermore, according to the panel, a balance ought to be found between the investments (with public money) and the gain in the availability of new therapies groups of patients. The respondents agreed that patients with rare diseases are often treated in a UH.

Pricing and reimbursement

The expert panel considered the role of UHs in the pricing and reimbursement phase neither important nor unimportant (median = 3), however, no consensus was found (IQR = 2). In addition, no consensus was found on the following statement: UHs are not about pricing and reimbursement and it should stay that way. A number of experts indicated that UHs should take their responsibility and should get involved in this process, while others referred to other stakeholders dealing with this. The panel agreed that UHs have insufficient knowledge in-house to play a role in pricing and reimbursement. Besides, according to the panel there is a culturally determined dilemma: the old-fashioned idea that doctors do not concern themselves with the costs of care and leave the problem for others to solve. The participants agreed that doctors are also afraid of limiting their treatment arsenal, due to costs. The panel held the opinion that the role of UHs is not clear, as they do draw up treatment guidelines, but are unaware of drug prices. However, respondents agreed that UHs should speak out about drug prices, also in relation to the effectiveness, exercise influence and set conditions on pricing and accessibility. The panel was neutral on UHs occasionally punching above their weight regarding pricing and wanting clauses on the price to be included in the licenses of their inventions. Some said UHs can and should influence the price, but it is hard to do so in reality. No consensus was found on UHs only being able to influence the drug price if the IP-rights belong to the UH.

Further, no consensus was found on UHs determining the price and discussing it with health insurers. Some experts pointed out that this is desirable, while others pointed out that other stakeholders should be dealing with this. The panel was of the opinion that UHs are less influential than health insurers on reimbursement issues. Besides, according to the panel, the pharmaceutical industry holds almost all cards in the pricing negotiations and offers no insight into the price structure. Moreover, the panel agreed that the industry has a strong lobby in the Hague and Brussels, more than UHs do. Other stakeholders in the DLC were also mentioned by the respondents. In the view of the panel, the government is unwilling to provide guidelines what costs for a new drug are (not) socially acceptable. The panel achieved consensus on the media being very responsive to patients who are denied new treatments, even if hardly any benefits are expected from the treatment.

Experts agreed that UHs already perform several activities in this phase, such as determining the clinical added value and positioning of the drug in guidelines, and advising the ZIN. Participants reached consensus on the information landscape not being in order due to the lack of correct and reliable records and the ability to access data necessary for assessing the added value of expensive medicines in daily practice. According to the panelists, UHs should generate data to achieve a responsible medico-economic impact of new medicines, which can serve as the basis for pricing regimes. They also agreed that UHs should develop new models for reasonable prices and engage in pharmaco-economic modelling. The panelists held the opinion that UHs need to clarify the price in relation to the necessary dosage that is required for the desired effect.

No consensus was found on health insurers applying their template for common diseases unchanged to rare diseases. The panel held the opinion that in case of rare diseases, experts, researchers and clinicians from UHs and patient representatives should be involved in this phase. The respondents agreed that UHs conduct a lot of research for the pharmaceutical industry or research that the industry

uses. They expressed consensus on UHs to retain much more control of the entire process and enforce publishing the results of research that has taken place in-house. Participants also agreed that UHs should be better protected against legal claims from manufacturers, because of the risk of to get sued.

Manufacturing

UHs have an important role in manufacturing pharmaceuticals, according to the expert panel (median = 4; IQR = 1). The panel agreed that UHs (should) produce medicines (in-house), through pharmaceutical compounding, also for research purposes. The expert panel expressed consensus on UHs drawing up protocols for pharmaceutical compounding, in order to produce medicines. The majority of experts held the opinion that UHs (should) conduct research on compounding and on the shelf life of medicines.

According to the panel, UHs produce medicines and should produce medicines that are not on the market and have an added value in healthcare. Furthermore, the panel was of the opinion that UHs should focus more on innovative, and less on standard pharmaceutical preparations, however, for this a good financing scheme must be in place. The respondents agreed that UHs should pay more attention and offer space for the (small-scale) production of new medicines, such as orphan drugs, ATMPs and radiopharmaceuticals. Participants agreed that UHs should also actively lobby politics with regard to the development of ATMPs and orphan drugs.

While the panel disagreed with UHs not having the knowledge to produce medicines, they did agree that UHs lack entrepreneurial spirit required to do so on a commercial scale. Besides, according to the panel, there is a lack of resources, which is needed for, amongst others, keeping GMP-production facilities up-to-date. Moreover, the majority of experts acknowledged that cooperation between UHs and a joint infrastructure is absent. The respondents agreed that current regulations do not match the need for pharmacy preparations. Besides, they agreed that resistance from the pharmaceutical industry poses as a barrier.

No consensus was found on whether UHs should produce pharmaceuticals under a separate entity, instead of under their own banner. Some indicated that UHs can produce drugs well under their own banner, but in some cases (rare diseases) or to prevent conflict of interests, it was deemed a good idea to separate it from the hospitals. No consensus was found on the presence of a risk not reaching all patients (outside the Netherlands), if UHs produce medicines. Experts acknowledged the risk, but provided ways to tackle it.

Procurement

UHs were considered important in the procurement phase by the expert panel (median = 4; IQR = 1). The majority of the panel affirmed that procurement is done by the hospital pharmacy department and UHs jointly procure drugs by means of the jointly purchase consortium of UHs (IZAAZ). According to the panel, discounts are negotiated with suppliers during this process. The experts assented with another that they should stick to national or regional procurement consortia. However, it was agreed that UHs have insufficient mandate and professional clout in the field of procurement. No consensus was found on UHs having too little purchase power. A few experts stated that the IZAAZ consortium has proven itself. Nevertheless, there is a lack of knowledge, overview and transparency about interests and outcomes; these preconditions are often not set, according to the panel. Moreover, there was no consensus with regard to whether UHs have an interest in overall low drug prices, considered that they can negotiate a margin on the purchase of drugs as a source of income. Some experts indicated that this is the reality, while others contradicted it.

It was agreed upon that the clinical and outpatient pharmacy must purchase medicines together. There was also consensus on the deployment of centers of expertise in the procurement of orphan drugs. In the view of the panel, UHs (should) obtain agreement with physicians on drug interchangeability. No consensus was reached regarding UHs refusing certain patients for budget reasons.

The panel assented with another on UHs jointly playing a role in the negotiations with pharmaceutical companies for the national procurement of a medicine. The experts agreed that UHs (should) form a reliable, professional and solid negotiating partner of the pharmaceutical industry.

Negotiating reimbursement rates with health insurers is also an activity of UHs in this phase, in the view of the respondents. In the opinion of the experts, health insurers must support procurement by UHs and give them more space to do so. According to the panel, national procurement of expensive medicines is better done by pharmacists than by health insurance companies or the government. They agreed that health insurers are increasingly taking on the role of hospitals with regard to the purchase of medicines. No consensus was found on individual health insurers waiving reimbursement despite a national reimbursement registration.

Likewise no agreement was found on whether annual substitution by a slightly cheaper generic should be avoided. Some experts stated that a substantial amount of money could be saved, due to the volume that is purchased. However, it was acknowledged that currently problems are associated with the annual substitution, and this should be balanced with the benefit of saving money.

Prescribing

The role of UHs in the prescribing phase of the DLC was considered very important (median = 5; IQR = 1). The group of experts agreed that UHs (should) prescribe medicines, as much as possible by substance name, via indication-oriented formularies. Medicines for rare indications are often prescribed off-label, according to the panel. The expert panel reached consensus on UHs (should be) drafting regional and/or national prescribing guidelines, adhering better to these guidelines and adjusting it when needed. The majority of respondents was of the opinion that the hospitals should deploy on better selection (prescribing the right medicines to patients) and prevent overtreatment.

According to the panel, UHs should continue research into more effective use of medication and seek for more connection with previous results of drug research. To this end (efficient use of medication), the panel agreed that UHs should work together with the Treatmeds foundation, which pursues to improve the efficiency and quality of healthcare when expensive drugs are used. (37) Besides, in their view, UHs should enhance coordination between scientific associations, provide education on rational pharmacotherapy and provide information about new medicines to medical specialists and general practitioners. The panel agreed that pharmacotherapy receives insufficient attention in medical education.

The expert group achieved consensus on UHs collecting real life data by tracking patients and recording the effectiveness of medicines in a structured manner. However, they were of the opinion that there are insufficient resources to set up and maintain good multi-purpose registers and that there is a fragmented data infrastructure with conflicting interests over data ownership.

Consensus on maintaining contact with drug manufacturers was reached in the third round. Cooperating with the pharmaceutical industry is useful, according to some experts. Others experts pointed out the possible conflict of interests. The experts agreed that there is an intertwining of prescribing and making choices in research, even though this is increasingly well separated. It was also recognized that phase III+ trials are often seeding trials, which have a more commercial value for the pharmaceutical company.

The experts agreed that health insurers decide what medicines are prescribed, as they reimburse medicines, in certain cases or centers. A national counter for individual applications for reimbursement of a drug, in combination with a database of all applications, should be provided according to the panel.

Drug dispensing

The group of experts considered the role of UHs in the drug delivery phase important (median = 4; IQR =1). According to the panel UHs perform various activities in this phase of the DLC, namely: processing received prescriptions, checking whether the prescribed medicine is suitable for the patient, medication monitoring, delivering the right medicine to the right patient, providing research medication and information on medication use. The majority of the participants held the opinion that during this process it should be checked whether the prescribed medicine is the most effective, in line with purchasing agreements with health insurers. The participants agreed that preparing medicines for administration and writing protocols for the preparation and administration of new drugs in clinical practice are activities UHs perform. UHs apply personalized medicine and should continue to develop it, according to the panel.

It was agreed upon that UHs should reduce and prevent medication wastage. However, experts expressed consensus on the restrictive legislation on redispensing medicines. According to them, UHs should be allowed to use pharmacy preparations provided by other UHs.

The majority of experts acknowledged that advising medical specialists is also an activity related to drug dispensing. They agreed that pharmacists are not always seen as a fellow-treating party by the prescriber, which poses as a barrier. The majority held the opinion that doctors and pharmacists (should) cooperate with regard to the pharmaceutical formulary and select which of the mutually replaceable medicines are kept in stock. In their view, UHs should deploy on therapeutic substitution, to stimulate competition.

The panel agreed that specialized treatments, including expensive drugs, are continued through the outpatient pharmacy and that UHs should better interweave the hospital and outpatient pharmacy, to enhance the continuity of care. The respondents agreed that restrictive laws and regulations make collaboration between pharmacies difficult. Besides, according to the panel, regulations and financing schemes are not in line with the increasingly more diffuse treatment location of the patient.

The majority of the panel held the opinion that during this phase, limited resources are available for the (desired) activities and that UHs must be alert to the pharmaceutical industry getting a grip on this part of healthcare. They also agreed that Early Access Programs or Named Patient Programs take a lot of time and effort to organize, while there is nothing in return for this.

Post-marketing

The role of UHs was considered (very) important in the post-marketing phase of the DLC (median = 4,5; IQR = 1). According to the expert panel, UHs (should) track patients, track and report side effects and should request and record more patient-reported outcome measures (PROMs). They agreed that UHs should conduct phase IV studies and study the mechanisms that lead to the found side effects. Furthermore, the majority of the panel was of the opinion that UHs should link fundamental research and efficiency research, and investigate the possibilities of applying a medicine in other diseases.

According to the experts, UHs should monitor the effect and method of use of medication for the purpose of optimizing treatments and adapting guidelines. Participants agreed that UHs should collect RWD and re-evaluate medicines based on RWE. They also agreed that medicines that already are on the market (for a long time) should be re-evaluated by UHs. The majority of the respondents held the opinion that the added value of a medicine should be determined by UHs by doing comparative research.

Besides, participants agreed that the hospitals should sustainably register the efficacy and effectiveness of medicines and set up disease-specific databases for rare diseases. However, the panel agreed that there are insufficient financial resources to set up good, independent registers. Furthermore, the respondents agreed that there are also limited resources, and these activities increase the registration burden. A barrier that was agreed upon was the restrictions due to GDPR and related privacy issues. Additionally, good data management, unambiguous data governance and correct recording and disclosure of data were also perceived as barriers by the panel.

Discussion

The aim of this study was to explore how UHs can contribute to affordable individual medicines applied in specialized medical care, and cost containment of total expenditures on these medicines. Therefore, we examined what activities UHs (should) perform throughout the DLC and what barriers and dilemmas they face when they (would) do so. For this, we questioned different stakeholders and professionals in the Dutch healthcare system, and determined consensus among them.

In general, professionals agreed that UHs should engage more in the social challenge of rising drug costs, not only by claiming their role in the DLC and taking a leadership role in shaping cost-effective healthcare, but also simply by speaking out about drug prices and the usefulness of a medicine. According to professionals, UHs could contribute to affordable medicines and cost containment of total expenditures on medicines in numerous ways. Therefore, they would have to play a bigger role throughout the DLC by performing activities that fall within, but also outside the scope of their current core tasks. However, there are a number of fundamental barriers and dilemmas that impede UHs from performing those activities.

The most striking result to emerge from this study is that UHs should market medicines in order to make a contribution to solve the social challenge. This means that UHs should develop medicines, apply for marketing authorization, manufacture medicines and trade them. Professionals agreed that UHs should engage in marketing medicines that are not provided by the market, but that are needed in healthcare. Besides, the focus should be on innovative and repurposed medicines that are produced on a small-scale, such as orphan drugs, ATMPs and radiopharmaceuticals. Another remarkable finding in this study is that UHs should concern themselves in the pricing of medicines. This involves clarifying the price in relation to the effectivity and developing models for reasonable pricing of a drug. These are notable findings because these activities are well beyond the scope of current core tasks of UHs.

We also found that UHs could contribute to sustainable financing of medicines by performing activities that fall within the scope of their core tasks. For instance, across all phases of the DLC carrying out research was mentioned as an activity. For this, a wide range of research topics was proposed that in some way could lead to sustainable financing of medicines. Furthermore, professionals agreed that standard prescribing and dispensing activities could contribute. Nevertheless, other nonstandard activities related to patient care, including revising the way it is delivered, were also proposed. Additionally, in multiple phases of the DLC training and providing education to medical professionals on certain topics were agreed upon as contributing activities of UHs.

Nonetheless, various barriers and dilemmas were found in this study that impede UHs from carrying out those activities. These barriers and dilemmas applied both to activities in and outside the scope of their core tasks. While specific barriers and dilemmas for each phase of the DLC were found, some seemed to be more common throughout the DLC. Frequently mentioned barriers were: the lack of resources, the absence of a collaborative (data)infrastructure, complicated and restrictive legislation and regulation, lack of expertise and knowledge, interplay between UHs and other stakeholders, and the lack of entrepreneurial attitude, vision, strategy and overview to market medicines.

UHs should market medicines & engage in pricing

As far as we know, this is the first study questioning multiple stakeholders and professionals, which found that UHs should market medicines with the intention to keep medicines affordable. While their involvement in drug discovery and drug development is widely recognized and described in literature, their engagement in the registration and commercialization of drugs is limitedly reported. However, in case of orphan drugs our findings confirm available literature. De Wilde et al. pled for the development, manufacturing (pharmaceutical compounding) and application for marketing authorization of orphan medicinal products by academia for the sake of affordability. (38) Their plea was a response to a steep price increase of an orphan drug, which first was produced through pharmaceutical compounding by hospital pharmacies, but now is licensed by a pharmaceutical company. Moreover, according to Van den Berg et al., repurposed orphan drugs often arise from academia, but academia fails to obtain marketing authorization, which regularly results in drugs with high prices set by the pharmaceutical industry. (39) Van den Berg et al, but also Davies et al. see a role for academia, as a non-profit organization, to engage in marketing authorization for orphan drugs. (30) In case of ATMPs, UHs currently use hospital exemptions, which allows them to produce highly specialized products without gaining marketing authorization via the centralized procedure. With the hospital exemption, UHs produce ATMPs on a small scale for national use in a non-profit manner. (40) Trias et al. indicated that the use of hospital exemptions reduces the costs incurred with the development and manufacturing of ATMPs. (41) Besides, ATMPs are often believed, and some cases even proved, not to be commercially viable, and hence are produced under hospital exemption. (42) Thus, regarding ATMPs our findings have similarities with previous literature. Concerning radiopharmaceuticals, our findings are not confirmed by previous research, due to a lack of available papers on the role of UHs in relation to price developments.

Our findings regarding UHs concerning themselves with the pricing of medicines are not supported by literature. Available literature describe other stakeholders, principally HTA bodies, dealing with drug pricing. Besides, various pricing models are present in literature; however, there is no specific call for the development of these models by UHs. However, collecting RWD and RWE, possibly in registries, for pricing and reimbursement purposes is supported by literature. For example, Hollak et al. described the necessity of healthcare professionals to generate RWD in independent registries for reimbursement decisions on orphan drugs. (43) Moreover, according to Facey et al. clinicians should collect data that is required for payer/HTA decisions. (44) It should be noted that UHs are not mentioned specifically for this activity.

Contributing activities within core tasks

The most conspicuous activities that fall within the core tasks were: integrating the hospital and outpatient pharmacy, and redispensing medication. The integration of the hospital and outpatient pharmacy is currently not described in literature. Our findings regarding reduction of medication waste and redispensing unused medication by (outpatient) pharmacies for economic reasons are consistent with previous results. Bekker et al. confirmed that redispensing expensive medicines by outpatient pharmacies is cost saving and indicated that pharmacists are in the position to lower medication waste. (45, 46)

Barriers and dilemmas of UHs

A number of barriers and dilemmas that were identified in this study are described in connection with certain activities in literature. For instance, Van der Gronde et al. indicated that academic institutions have inadequate financial resources, capacity and incentives to independently develop drugs. (11) Fitzgerald identified the lack of an infrastructure, capacity for production, human resources, interspersed knowledge and incentives as barriers in academic drug discovery and development. (47) Verbaanderd et al. identified several barriers for academia during drug development, namely: funding, required time and work intensity. (48) Verbaanderd et al. also recognized the lack of expertise and resources in academia to engage in regulatory procedures. (49) Starokozkhko et al. also confirmed the knowledge gap in regulatory affairs. (50) With regard to data infrastructure, the OECD confirmed that the fragmented health data infrastructure in the Netherlands restrain research and innovation in medicine. (51) Denton et al. described that the fragmented data infrastructure impair research efforts to develop drugs. (52) Concerning legislation and regulation, legal constraints regarding redispensing unused medication is confirmed by earlier research. (53)

Limitations

Even though some of our findings are confirmed by literature, we should sound a note of caution with regard to the interpretation of our findings as a number of limitations have influenced the results obtained. Firstly, the size and composition of the expert group are major limitations, with the consequence that the findings might not be generalizable nor robust. The size of the expert group was smaller than we anticipated, considering the number of invitations. Moreover, the response rate was rather low, especially in the last round. Besides, it is most likely that the composition of the panel influenced the results. As noted, the majority of participants were affiliated with UHs and were doctors. The government and health insurers were poorly represented by respectively two and three representatives and the perspective of the pharmaceutical industry was completely absent. We frequently reached out to the VIG, but did not get any response of the invited medical directors. We did not involve patients or other members of society, although they are another relevant stakeholder in the DLC. However, the setup of this research probably would most probably not tie in with their viewpoint. Furthermore, as already pointed out, the scope of this study reached out to the stakeholders in the Dutch healthcare system. Thus, findings might not be generalized to other countries or healthcare systems. Secondly, there are some remarks regarding the methodology. In the first round, we posed open questions in the most objective way, so correspondents were not influenced in any respect. However, based on the feedback, some correspondents considered the questions to be abstract and interpretable in multiple ways, which was reflected in their answers. We provided an introduction in the questionnaires explaining the setup, but perhaps this was not clear (enough). In the second round, we used the participants' statements from the first round, as researchers are required to interfere as little as possible with the Delphi process. However, based on the results and the feedback, the statements were not understandable for everyone. We frequently received feedback on the large extent of the questionnaire, which required a lot of time of the participants. This presumably influenced the response rate. Additionally, consensus was defined as 50%, which may be considered as a low cut-off value. This may have caused some contradictions in the findings, certainly considering the fluctuating response rate in the rounds. Nonetheless, most statements were (dis)agreed upon with rather high percentages.

Implications and recommendations

Despite these limitations, we believe that this study provides valuable ways to approach and tackle the growing challenge of keeping medicines affordable.
In this study, we applied a life cycle and interdisciplinary approach to systematically assess the potential role of UHs in tackling the challenge. Such a life cycle and interdisciplinary approach is stimulated by the European Commission, as described in their report *Pharmaceutical Strategy for Europe*. (15) We suggest that the same approach is applied in future research and policy. To this end, our framework of the DLC may serve as a tool. The framework may also serve as a tool for UHs, and other stakeholders, to grow awareness on their role in the DLC, and to critically review their role in light of current challenges.

The present findings suggest several courses of action in order for UHs to contribute to affordable individual medicines and cost containment of total expenditures on medicines. This work has demonstrated that there is a call for UHs to market medicines, and thus for UHs take on a role that currently is assigned to the pharmaceutical industry. Taking this in consideration, with the fact that UHs have no experience in this, it will take courage to make this bold move. Nonetheless, this study showed that professionals are convinced that UHs will be able to market medicines. However, this will require multiple actions. Firstly, UHs must build knowledge on the requirements of drug development and regulatory affairs. For this, we suggest UHs to establish contacts with regulatory agencies such as the EMA and MEB, which provide support to academia, and to get involved in the STARS project. (54) Secondly, UHs should develop a vision and strategy, which encompasses the entire DLC, from drug discovery to post-marketing. For this, it is important to involve professionals with appropriate expertise, experts with entrepreneurial insights and skills, and to interact with other stakeholders.

Our data suggest that UHs should engage in pricing of medicines, although limited to certain activities. Nonetheless, we advise to enter into dialogue with stakeholders that currently occupy themselves with pricing and reimbursement to see if and how UHs could provide input. In this way, (human) resources and expertise are efficiently deployed.

Within the core tasks of UHs multiple activities were proposed. As regards to research, this study offers many subjects of investigation that by some means could keep medicines affordable. It is recommended that these are considered when UHs set up and revise research lines. We are aware of the great demand of (independently executed) research and the feasibility thereof, considering the limited resources. Therefore, it should be considered to cooperate with other research institutes. For example, deploying STZ or specialized centers for drug research when ‘conventional’ clinical studies are performed in case of less complex conditions. Concerning patient care, we suggest that hospital and outpatient pharmacies explore interweaving for efficiency purposes, or at least cooperate in the procurement of medicines. Moreover, pharmacies must look for ways to redispense medication safely and efficiently to reduce wastage. Regarding training and educating medical professionals, we recommend to revise the medical curriculum regarding pharmacotherapy, so it receives adequate attention. This may lead to more rational prescribing, and more effective and efficient use of medication. Moreover, designers of the curriculum are advised to examine if, or/and how, education on drug development should be part of the curriculum.

Finally, we strongly advise that UHs cooperate and set up a collaborative (data)infrastructure to do so, for several reasons. Firstly, cooperation ensures that the limited resources are used more efficiently. Secondly, it may facilitate more efficient, and perhaps more productive, research. Collectively building knowledge on marketing medicines may also be more efficient than UHs separately doing so. Thirdly, collaboration enables a strong representation of UHs to the outside world and will help when engaging with other stakeholders, such as the pharmaceutical industry. More importantly, in order to remove legislative and regulatory barriers, lobbying politics as a strong unity is required. To set up collaborative infrastructures, existing partnerships, such as the NFU, may be used as a springboard.

Conclusion

This study shows that UHs could contribute to affordable individual medicines and cost containment of total expenditures on medicines by performing various activities throughout the DLC. While there is room within their core tasks to make a contribution, taking on a new role as a medicine developer and manufacturer may be the most promising. A number of barriers and dilemmas impede UHs to take on these new activities, however, they are not insurmountable. UHs have the potential to change the dynamics in the DLC and turn the trend of rising costs of medicines. To exploit this potential and really facilitate sustainable access to medicines, UHs must be daring and assertive to take on new tasks.

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List of abbreviations

ATMP	Advanced Therapy Medicinal Products
cieBOM	Committee for the Evaluation of Oncological Agents / Commissie ter Beoordeling van Oncologische Middelen
cieOOM	Commission Off-label Indication Oncological Drugs / Commissie Offlabel-indicatiestelling Oncologische Middelen
DLC	Drug Life Cycle
DRUP	Drug Rediscovery Protocol
EMA	European Medicines Agency
GDPR AVG	General Data Protection Regulation Algemene Verordening Gegevensbescherming
GMO	Genetically Modified Organisms
GMP	Good Manufacturing Practice
HTA	Health Technology Assessment
ICF	Informed consent form
IP	Intellectual Property
IQR	Interquartile range
IZAAZ	Purchase combination Hospital Pharmacies Academic Hospitals / Inkoopcombinatie Ziekenhuis Apotheken Academische Ziekenhuizen
KOL	Key Opinion Leader
MEB CBG	Medicines Evaluation Board College ter Beoordeling van Geneesmiddelen
MREC METC	Medical Research Ethics Committee Medisch Ethisch Toetsingscommissie
NFU	Dutch Federation of University Medical Centers / Nederlandse Federatie van Universitair Medische Centra
NVZA	Dutch Association of Hospital Pharmacists / Nederlandse Vereniging voor Ziekenhuisapothekers
NZa	Dutch Healthcare Authority / Nederlandse Zorgauthoriteit
PI	Principal Investigator
PROM	Patient Reported Outcome Measure
QALY	Quality Adjusted Life Year
R&D	Research & Development
RWD	Real World Data
RWE	Real Word Evidence
STZ	Cooperating Top Clinical Teaching Hospitals / Samenwerkende Topklinische opleidingsZiekenhuizen
TTO	Transfer Technology Office

UH UMC	University hospital University Medical Center
VIG	Association of Innovative Medicines / Vereniging Innovatieve Geneesmiddelen
VWS	Ministry of Health, Welfare and Sport / Ministerie van Volksgezondheid, Welzijn en Sport
WMO	Medical Research Involving Human Subjects Act / Wet Medisch-wetenschappelijk Onderzoek
ZIN	National Health care Institute / Zorginstituut Nederland
ZN	Umbrella organization of eleven health insurers / Zorgverzekeraars Nederland