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ReDIReCT

Repurposing of Drugs: Innovative Revision of Cancer Treatment

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Aan mijn liefste papa

Van wie we afscheid hebben moeten nemen tijdens dit onderzoeksproject

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LIST OF ABBREVIATIONS

ASCO	American Society of Clinical Oncology
ATRA	All-Trans-Retinoic Acid
BCG	Bacillus Calmette–Guérin
CCO	Cancer Care Ontario
CDCA	ChenoDeoxyCholic Acid
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CMS	Centers for Medicare & Medicaid Services
COREQ	Consolidated criteria for reporting qualitative research
COX	Cyclo-OXygenase
CTSA	Clinical and Translational Science Awards
CTTI	Clinical Trials Transformation Initiative
DNDi	Drugs for Neglected Diseases initiative
EAU	European Association of Urology
ECRIN	European Clinical Research Infrastructure Network
EDCTP	European and Developing Countries Clinical Trial Partnership
EEA	European Economic Area
EHRs	Electronic Health Records
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
EPAR	European Public Assessment Report
ER positive	Oestrogen Receptor positive
ERA-Net	European Research Area Network
ESMO	European Society of Medical Oncology
ESUOMs	Evidence Summaries: Unlicensed and Off-label Medicines
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GDPR	EU General Data Protection Regulation
HICs	High-Income Countries
HMA	Heads of Medicines Agencies
HTA	Health Technology Assessment
IMI	Innovative Medicines Initiative
IP	Intellectual Property
KCE	Belgian Healthcare Knowledge Center
LMICs	Low- and Middle Income Countries
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder
MMV	Medicines for Malaria Venture
MoA	Mechanisms of Action

MRC	Medical Research Council
NCA	National Competent Authorities
NCATS	National Center for Advancing Translational Sciences
NCCN	US National Comprehensive Cancer Network
NDA	New Drug Application
NICE	UK National Institute for Health and Care Excellence
NIH	UK National Institutes of Health
NIHR	National Institute for Health Research
NPC	NCATS Pharmaceutical Collection
NSAID	Non-Steroidal Anti-Inflammatory Drug
PIP	Paediatric Investigation Plan
PPP	Public-Private Partnership
PROs	Patient-Reported Outcomes
PSA	Prostate-Specific Antigen
PUMA	Paediatric Use Marketing Authorisation
QUAGOL	Qualitative Analysis Guide of Leuven
RCT	Randomized Controlled Trial
ReDO	Repurposing Drugs in Oncology
RepOG	Repurposing Observatory Group
ROI	Return On Investment
RWD	Real-World Data
RWE	Real-World Evidence
SA	Scientific Advice
SIB	Social Impact Bond
SPC	Supplementary Protection Certificate
SMEs	Small- and Medium sized Enterprises
sNDA	supplemental New Drug Application
STAMP	European Commission Expert Group on Safe and Timely Access to Medicines for Patients
US NIH	United States National Institutes of Health
YODA	Yale Open Data Access
WHO	World Health Organisation
WIPO	World Intellectual Property Organization

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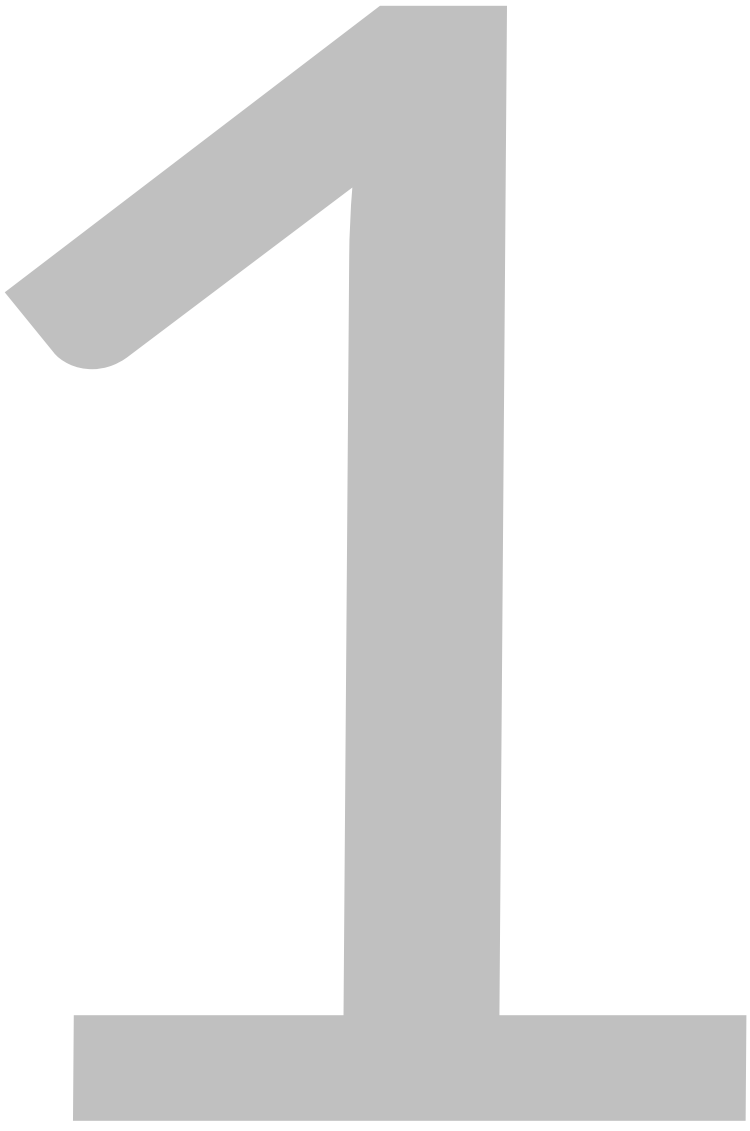
PART 1

GENERAL INTRODUCTION & OBJECTIVES



CHAPTER 1
General introduction

Parts of this chapter are adapted from

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NEED FOR SAFE, EFFECTIVE AND AFFORDABLE ANTICANCER THERAPIES

Cancer is a disease that affects many people's lives. In 2018, cancer was responsible for about 1.9 million deaths in Europe and about 9.6 million deaths worldwide (1,2). In the same year, the number of new cases of cancer was estimated at 3.9 million in Europe and 18.1 million globally. Cancer is responsible for about 1 in 6 deaths, making it the **second leading cause of death worldwide** and, in high-and upper-middle-income countries, it recently surpassed cardiovascular disease as the most common cause of death among adults (3–5). By 2030, the number of deaths due to cancer is expected to increase up to 13 million and the number of new cases of cancer a year is estimated to reach over 24 million cases globally (6,7). In addition, the individual lifetime risk of developing cancer is estimated at about 40% (8).

The scientific community has made **considerable progress** in understanding the disease mechanisms of cancer and in identifying new targets for treatment (9). This knowledge has led to the development of a variety of therapeutic options (*i.e.*, chemotherapy, radiotherapy, surgery, hormone therapy, stem cell transplants, targeted therapy and immunotherapy), which are often applied in combination to tackle the heterogeneous and complex nature of the disease (10,11). As a result of significant advances in cancer genomics, the concept of "precision oncology" has attracted a lot of attention in recent years (12,13). Precision oncology refers to diverse strategies in anticancer therapy ranging from the use of predictive biomarkers and diagnostic tests for identifying patient subgroups most likely to respond to a treatment, to using data from next-generation sequencing for selecting a therapy for an individual patient, independent of cancer type (14). However, despite these advances, **cancer remains an exceptionally complex disease to treat**, largely due to the high levels of tumour heterogeneity (15).

Furthermore, the research and development of new anticancer therapies is confronted with a **substantial risk of failure in clinical development, high development costs and long duration of clinical trials**, especially in comparison to other therapeutic areas (11,16,17). Still, the global pipeline of new anticancer medicines in late-stage development is expanding (from 711 in 2017 to 849 in 2018, 91% of which are targeted small molecule and biologic therapies) and the amount of anticancer medicines approved every year is increasing (11). To compensate for the high investment risks, pharmaceutical developers often set **high prices for new anticancer medicines**, which is enabled by a high willingness to pay by governments and patients alike (18–20). However, a number of recent studies raised questions about the clinical benefit and added therapeutic value of new anticancer medicines, as the majority of new oncology drugs that came onto the market in the past decade showed no clear evidence of benefit on overall survival or quality of life of patients (21–24). Additionally, studies showed that the increase in prices of novel anticancer medicines is not correlated to the magnitude of clinical benefit of these treatments (25,26).

Finally, the **economic burden of cancer** is high and affects both individual cancer patients and society as a whole (*i.e.*, increased healthcare spending and productivity losses from morbidity and premature mortality). In 2018, the total cost of cancer was about €199 billion in Europe (27). One of the key contributing factors to the increased global expenditure on cancer are the high prices of new anticancer medicines (28,29). In addition, the aging population, the earlier detection and treatment of cancer, and the increased need for combination regimens are putting substantial pressure on national healthcare budgets. **All of these factors may impede access to new treatment options for patients** (29–31).

UNTAPPED POTENTIAL OF DRUG REPURPOSING IN ONCOLOGY

Aforementioned challenges illustrate the urgent medical need for high-quality translational research to develop safe, effective and affordable treatments for cancer patients. **Repurposing existing medicines for new oncological indications** has been put forward as an innovative but largely untapped solution to address current medical needs**.** Drug repurposing is a treatment development strategy that seeks to use existing medicines for new medical indications rather than developing *de novo* molecules. This strategy has been **gaining momentum in many disease areas** that are poorly served by commercial drug development, particularly in the area of rare diseases (32). In oncology, the existing stock of medicinal products is increasingly being viewed as a reservoir of untapped agents that have the potential to make clinically important contributions. Yet, it is important to note that the aim of a repurposing strategy is not to replace existing or novel anticancer drugs but rather to complement *de novo* drug development.

DEFINITIONS AND TERMINOLOGY

The **concept of drug repurposing (also frequently referred to as drug repositioning) is not new**. In 2004, Ashburn and Thor described drug repositioning as "*the process of finding new uses outside the scope of the original medical indication for existing drugs*" (33). Since this first landmark article, the interest of the scientific community in drug repurposing has been steadily increasing, which is reflected by the rapidly growing number of PubMed search results each year (Figure 1). The terms "drug repurposing" and "drug repositioning" are most frequently used, but a **number of similar terms** have been introduced, such as "drug rediscovery", "drug reprofiling", "drug retasking", "drug redirecting", "drug rescue", "indication switching", "therapeutic switching", "indication expansion" and "candidate or compound repurposing" (34,35). While those terms are often used interchangeably, Langedijk et al. reported that they can have different meanings or can be interpreted in different ways (34). The **lack of a consistent terminology and homogenous definition for drug repurposing** often leads to confusion amongst involved stakeholders.

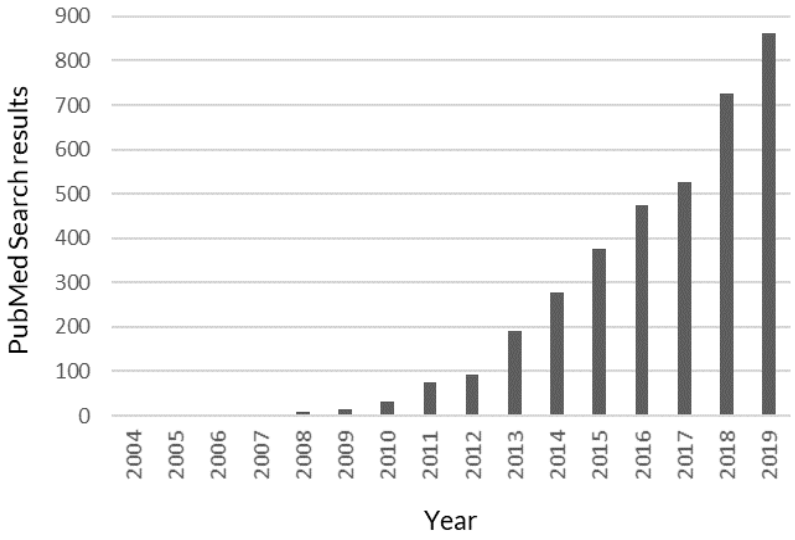


FIGURE 1. NUMBER OF NEW SCIENTIFIC ARTICLES CONCERNING DRUG REPURPOSING BY YEAR

Search term applied in PubMed database in June 2020: ("Drug Repositioning"[Mesh] OR "Repurposed drug*"[tiab] OR "Repositioned drug*"[tiab] OR "Drug repurposing"[tiab] OR "Drug repositioning"[tiab] OR "Drug reprofiling"[tiab] OR "Drug redirecting"[tiab] OR "Drug rediscovery"[tiab] OR "Drug retasking"[tiab])

In fact, the term drug repurposing covers a **number of scenarios**, depending on a combination of attributes of the repurposing candidates (Table 1). First, drug repurposing can refer to identifying new uses for **experimental or investigational assets** that went through several stages of clinical development (at least phase I safety trials), but were "shelved" due to a lack of efficacy or commercial interest, or **medicines that have been on the market but were withdrawn** for commercial or other reasons. Pharmaceutical developers are increasingly interested in such a repurposing strategy, also called "drug rescue", as this involves fewer risks compared to developing new chemical entities and may create opportunities for new or additional intellectual property (IP) claims (*i.e.*, patents for second and further medical uses) and regulatory exclusivities (36,37). Second, pharmaceutical developers often look for opportunities to identify new indications for **medicines that are already authorised** for one or more indication(s) and are still **under basic patent or regulatory protection**. Developing new uses for innovator products is often referred to as "life cycle management" of the drug, and may expand the patient population while delaying generic or biosimilar competition (38,39). Third, some repurposed medicines require **product changes** (*e.g.*, change in dose, pharmaceutical form, route of administration) or are **combined with other medicines or medical devices** in the new indication for the benefit of the patient. This can be a commercially interesting repurposing strategy as product changes may generate new IP and enable a pharmaceutical developer to rebrand a product for its new use (40–42). Finally, a fourth scenario covers the repurposing of **approved medicines that are out of basic patent or regulatory protection and used "as-is",** thus do not require any substantial product changes, which is sometimes termed "off-patent drug repurposing" (43).

Furthermore, a distinction can be made based on whether the repurposing involves a change in the **therapeutic area** of the drug. In oncology, the term "**soft repurposing**" has been introduced to refer to the identification of new oncological indications for approved anticancer treatments, while "**hard repurposing**" means finding new oncological indications for medicines that were originally developed outside of the oncology field (44,45). Researchers and pharmaceutical developers sometimes also distinguish between "**off-target and on-target repurposing**" based on whether the **underlying pharmacological mechanism** was newly discovered (or previously unexplored) or remained the same in the new indication compared to the original indication.

TABLE 1. ATTRIBUTES OF DRUG REPURPOSING CANDIDATES

REGULATORY APPROVAL	▪ Authorised medicines
	  ▪ No generic or biosimilar products available ("life cycle management")
	  ▪ Generic or biosimilar products available ("off-patent repurposing")
	▪ Withdrawn or discontinued medicines ("drug rescue")
	▪ Experimental, shelved or dormant assets ("drug rescue")

PRODUCT CHARACTERISTICS	▪ "Use as-is" (no product changes required) ▪ Reformulation (change in dose, pharmaceutical form, route of administration…) ▪ New combination with other medicines or medical devices
THERAPEUTIC AREA*	▪ Same therapeutic area ("soft repurposing") ▪ Different therapeutic area ("hard repurposing")
PHARMACOLOGICAL MECHANISM*	▪ Same pharmacological mechanism ("on-target repurposing") ▪ Different pharmacological mechanism ("off-target repurposing")

* Compared to the original indication

BENEFITS AND OPPORTUNITIES

The most famous **success story** of drug repurposing is the **case of sildenafil (Viagra)**, a drug that was originally in clinical development for the treatment of angina pectoris when it was found to induce penile erections and, subsequently, commercialized by Pfizer as a blockbuster drug for the treatment of erectile dysfunction. Later on, sildenafil was again repurposed for treating pulmonary arterial hypertension under the brand name Revatio. A number of other repurposing successes have been described in scientific literature (46,47) and drug repurposing research has **gained traction in many disease areas**, especially in oncology, neurology, cardiology, psychiatry and infectious diseases (48–51). A bibliometric review conducted by Baker et al. showed that over 60% of all drugs or drug candidates annotated in MEDLINE (approximately 35.000 chemicals) have been tested in at least one disease beyond the original use and 189 of these drugs were studied in more than 300 diseases each (52). Repurposing is considered particularly useful to provide timely and affordable treatment options for **rare and neglected diseases** with high medical needs, for which commercial interests to develop new chemical entities are lacking (53–57). Furthermore, it is apparent that researchers and pharmaceutical developers resort to repurposing strategies for a timely solution in **urgent medical situations**, as illustrated by the SARS-CoV-2 virus pandemic of 2020 (58).

The **advantages** of a repurposing strategy derive from the **existing body of knowledge** for each candidate drug (45,59). In contrast to newly developed molecules, repurposed medicines with a history of clinical use have an extensive body of knowledge and data associated with them. Such data can cover clinically relevant areas including safety, toxicity, dosing, drug interactions and patient-reported outcomes. Relevant non-clinical data typically include pharmacokinetics and pharmacodynamics, studies investigating putative mechanisms of action, molecular targets and possible interactions with cells, tissues or pathways relevant in the disease for which the drug is being investigated as a repurposing candidate. The availability of these data could allow a **shorter research and development time, less risk of failure in clinical trials and reduced development costs**.

Other important potential benefits include the **wide availability of existing medications**, particularly for approved drugs included on the World Health Organisation Essential Medicines List (WHO EML). Furthermore, many drugs with repurposing potential are off-patent and have been on the market for a long time, leading to a competitive commercial environment in which the existence of multiple manufacturers ensures that **drug pricing remains low**. This is an important consideration in many resource-constrained environments, not solely limited to health systems in low- and middle-income countries but also stressed public health systems in more developed economies.

REPURPOSING ACTIVITIES IN ONCOLOGY

In oncology, it is **standard practice** for pharmaceutical developers to seek **new oncological indications for approved oncology drugs** as long as these drugs are protected by IP rights or regulatory exclusivities (60). Typically, oncology drugs are repurposed for other cancer subtypes based on a **common target or disease mechanism** as the original indication. For example, sunitinib, a multi-targeted tyrosine kinase inhibitor with potent anti-angiogenic and anti-tumour activities, was first approved in 2006 for treating gastrointestinal stromal tumours and renal cell carcinoma and subsequently repurposed for treating

pancreatic neuroendocrine tumours in 2011 (61,62). A more recent example are the numerous new oncological indications that have been approved for the immune checkpoint inhibitors pembrolizumab and nivolumab, since their initial marketing authorisation for advanced melanoma in 2015. On the other hand, repurposing strategies often take advantage of the fact that most drugs have **multiple pharmacological mechanisms or targets** (sometimes referred to as polypharmacology or drug promiscuity) (45). For example, one of the first targeted therapies in oncology, imatinib, was found to address new targets in addition to the previously known BCR-ABL fusion protein, and therefore repurposed for multiple cancer types in addition to chronic myeloid leukaemia (35).

In addition, drug repurposing refers to identifying **new anticancer indications for approved drugs that were originally developed outside of the oncology field** (63–67). Only a few **success stories** of non-cancer medicines being repurposed for anticancer treatment exist. The most prominent example is thalidomide - a drug that was repurposed twice after being withdrawn from the market due to its disastrous teratogenic effects when used during pregnancy, first for treating erythema nodosum leprosum and again for treating multiple myeloma. Another example is all-trans-retinoic acid (ATRA), a vitamin A derivate used for the treatment of acne, that was repurposed for treating adult patients with newly diagnosed low-to-intermediate risk acute promyelocytic leukaemia in combination with Trisenox . A final example is the Bacillus Calmette–Guérin (BCG) vaccine against tuberculosis that was successfully repurposed as an intravesical immunotherapy for treating early-stage bladder cancer.

Although the number of successfully repurposed non-cancer medicines for anticancer treatment is limited, a lot of **preclinical and clinical research into these medicines is ongoing in oncology** (63–67). While aspirin and metformin are the most prominent examples, many other non-cancer drugs have demonstrated some level of evidence of anticancer activity. The **Repurposing Drugs in Oncology (ReDO) project**, a collaborative initiative between the Anticancer Fund (Belgium) and GlobalCures (US), collected encouraging evidence from literature regarding the anticancer effects of diclofenac, nitroglycerin, itraconazole, clarithromycin, cimetidine, mebendazole, propranolol, (hydroxy-) chloroquine and selective phosphodiesterase 5 inhibitors (45). Moreover, as part of the ReDO project, the **ReDO_DB** was developed, which is a database of approved non-cancer drugs with some evidence of anticancer activity from *in vitro*, *in vivo* or human research (68,69). In June 2020, this database listed **over 300 non-cancer drugs** based on data from peer-reviewed studies, medical case reports, observational studies and clinical trials (69).

In August 2018, we investigated the **clinical trial activity in oncology for each of the drugs in the ReDO_DB**, which included 268 drugs at that time, by searching three international clinical trial registries (ClinicalTrials.gov, WHO ICTRP and OpenTrials). In total, **190 active late-stage trials** (*i.e.*, phase II-III, phase III or phase III-IV trials) were identified, which involved **72 unique drugs** and which covered **all cancer types** (Table 2). In terms of trial sponsorship, only seven (3.7%) were sponsored by a pharmaceutical company, with the vast majority being sponsored directly by a university/hospital (n=127, 67%) or by a research institute, network or foundation (n=53, 28%). A small number of drugs were the subject of intense clinical trial activity, (*i.e.*, 10 or more active late-stage trials) and can be considered to be well advanced in terms of a 'repurposing drugs pipeline' in oncology. Figure 2 shows a map of the countries where the trials have been or are being conducted.

TABLE 2. CHARACTERISTICS OF THE 190 LATE STAGE TRIALS WITH DRUGS IN THE REDO_DB

CANCER TYPE*	N	%
Gastrointestinal	53	28
Breast	38	20
Haematological	23	12
Lung	14	7
Gynaecological	11	6
Brain & central nervous system	10	5
Other**	24	13
Paediatric	12	6
Not specified	23	12
SPONSOR	**N**	**%**
University and/or hospital	127	67
Research institute, organisation, foundation or network	53	28
Small-and medium-sized pharmaceutical companies	6	3
Government	3	2
Large pharmaceutical companies	1	1
DRUGS WITH MORE THAN 10 TRIALS	**N**	**%**
Acetylsalicylic acid	27	14
Celecoxib	12	6
Cholecalciferol	12	6
Metformin	17	9
Olanzapine	10	5
Zoledronic Acid	20	11

Adapted from Pantziarka P, Verbaanderd C et al. 2018, ecancermedicalscience
*Some trials include more than one cancer type and therefore the total is greater than the number of trials in the pipeline. ** < 10 trials per type: musculoskeletal, neuroendocrine, prostate, urinary, head & neck and skin cancer

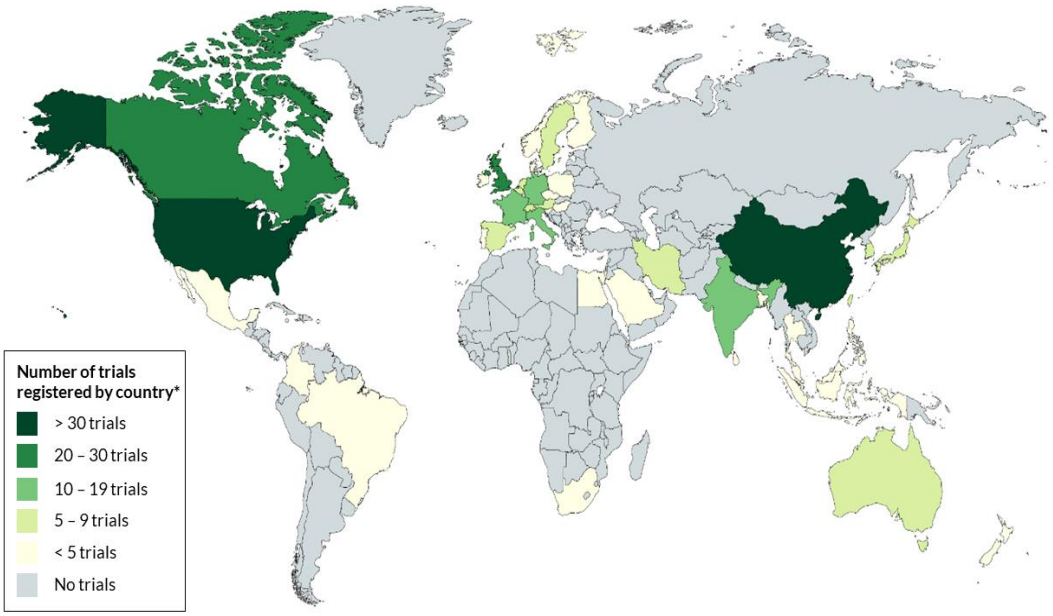


FIGURE 2. LATE STAGE TRIALS IN ONCOLOGY WITH DRUGS IN THE REDO_DB PER COUNTRY
*For international trials, only the country of the primary sponsor is indicated.
Adapted from Pantziarka P, Verbaanderd C et al. 2018, ecancermedicalscience

KEY CHALLENGES

Despite the potential benefits and the substantial increase in research activity, thus far, **only few repurposed medicines have successfully been translated into clinical practice in oncology**. In fact, the scientific and medical community is facing significant regulatory, legal and financial challenges with regard to the clinical research and implementation of repurposed medicines, in addition to challenges of scientific nature (70,71). Challenges are especially apparent for authorised medicines that are out of basic patent and regulatory protection, as illustrated by several examples in Table 3.

> *"Drug repurposing seems tantalizingly simple, faster and cheaper than new chemical entity development, with potential to address many unmet medical needs. So why have so few off-patent drugs been successfully repurposed?"*
>
> *Christopher P. Austin (Washington, December 2019)*
> *Director of the National Center for Advancing Translational Sciences at the NIH*

TABLE 3. ISSUES FACED BY A SAMPLE OF REPURPOSING CANDIDATES
Adapted from Pantziarka P, Verbaanderd C et al. 2020 (72)

DRUG	INDICATION(S) PURSUED IN TRIALS	SPECIFIC REPURPOSING ISSUES ENCOUNTERED
Nelfinavir	Rectal, cervical, lung, head and neck and pancreatic cancers, multiple myeloma, glioblastoma	Not frequently used for original indication (treatment of HIV) and therefore only one manufacturer in US/ Canada and no longer marketed in Europe, which complicates supply for clinical trials and may delay/hinder clinical adoption.
Aspirin	Chemoprevention in colorectal and gastric cancers. Adjuvant therapy colorectal, gastric, breast and other cancers	Over 20 ongoing late-stage clinical trials, included in various clinical guidelines for chemoprevention and often used off-label, but incentives are lacking to apply for regulatory approval.
Propranolol	Breast, prostate, colorectal, gastric, ovarian and pancreatic cancers, HCC, angiosarcoma, glioblastoma, melanoma, neuroblastoma	Reformulated and approved as Hemangiol (EU)/Hemangeol (US) for the treatment of children with proliferating infantile haemangioma (with additional patent protection and regulatory exclusivities for PUMA). However, there is a lack of incentives to apply for regulatory approval for indications where reformulation/rebranding is not required.
Auranofin	Glioblastoma, CLL, (N)SCLC, ovarian, primary peritoneal and fallopian tube cancer	Barely used for the original indication (rheumatoid arthritis), and therefore removed from most markets (except from *e.g.* Canada), which complicates supply for clinical trials and may delay/hinder clinical adoption.
Mebendazole	Colorectal, gastrointestinal and brain cancer	In Europe: available as a cheap, generic drug so there is a lack of incentives to apply for regulatory approval. In the US: taken of the market in 2011 and later reintroduced as a much more expensive version, which complicates supply for clinical trials.

Abbreviations: Human Immunodeficiency Virus (HIV), Hepatocellular carcinoma (HCC), Chronic lymphocytic leukaemia (CLL), (non-) small-cell lung carcinoma ((N)SCLC), Paediatric Use Marketing Authorisation (PUMA)

FINANCIAL INCENTIVES AND DISINCENTIVES FOR CLINICAL DEVELOPMENT

The repurposing of off-patent medications represents a particularly challenging set of financial obstacles due to the **high costs of conducting clinical research and a lack of economic incentives for some of the repurposing candidates**.

Pharmaceutical developers typically invest in clinical trials with a view to marketing the drug for a new medical indication as the only provider. In doing so, they may generate return on investment (ROI), thus justifying the investment in the trials. Developers can adopt **various strategies to secure ROI from repurposing projects**. First, developers can file a **patent for the new indication** (*i.e.*, patents for second and further medical uses in EU or method-of-use patents in the US) and **rebrand the repurposed medicinal product** to create legal and strategic protection from competitors (40–42,73,74). The new indication can potentially be combined with a reformulation, a new route of administration, a new dosage regime or a combination therapy depending on the patients' needs. Besides patent protection, **specific regulatory exclusivities** exist in Europe and the US to incentivize companies to invest in the development of new indications for marketed therapies, especially in areas with unmet needs such as for orphan and paediatric indications (elaborated on in Chapter 5 of this dissertation).

Because of the reduced development risk and the potential for ROI, **several companies specifically built their business model around finding and commercializing new uses for existing medicines** (*e.g.*, NovaLead, Hyloris, SOM biotech, SEEK, Rediscovery Life Sciences, Segue Therapeutics). In Europe, the Value Added Medicines Group, a sector group of Medicines for Europe, focuses on adding value to known molecules by "finding a new indication (drug repositioning), finding a better formulation or dosage (drug reformulation), or developing a combined drug regimen, adding a new device or providing a new service (drug combination)" (75). Additionally, several consulting firms are offering specific guidance to develop commercial drug repurposing strategies (*e.g.*, H.M. Pharma Consultancy, Avivia, Numedicus, Cycle Pharmaceuticals, Camargo Pharmaceutical Services). Second medical use patents and regulatory exclusivities have led to a number of commercial repurposing successes. For example, thalidomide was successfully repurposed for the treatment of multiple myeloma and obtained market exclusivity via the orphan medicinal product pathway (76). Another well-known example outside of the oncology field is Tecfidera, also called dimethyl fumerate or DMF (77). DMF was originally synthesized 50 years ago for the treatment of psoriasis and later developed by Biogen Idec for multiple sclerosis, protected by second medical use patents.

Nevertheless, **obtaining second medical use patents for new indications is difficult** because some experimental data should be included in the patent application to show that the repurposing candidate could be reasonably expected to treat the claimed indication (78). Yet, knowledge about the new medical use should not be available in published literature before patent application because, in that case, the inventiveness and novelty requirements in patent law are no longer met (79,80). Moreover, **enforcing second medical use patents against competitors may be challenging** due to the narrow scope of second medical use claims and due to the possibility of skinny labelling in most countries, meaning that a generic product can be approved and marketed with labelling that only includes unpatented or non-exclusive indications, so it is difficult to prevent doctors from prescribing a generic version for a patented use of a repurposed drug (38,81,82). In addition, regulatory exclusivities vary between Europe and the US and the

repurposing candidates typically have to meet a number of criteria for these incentives to apply, thus entailing a level of uncertainty. Moreover, previous research showed that **some of these regulatory exclusivities are underused and may not be sufficient to incentivize investments into drug repurposing** (83).

In short, developers of products that are off-patent and out of regulatory protection run the risk that successful clinical trials benefit competing developers. Consequently, the development of those products that do not require any product changes to differentiate them from competitors is often discontinued, even though promising evidence may exist to support a new use. This is a situation that has led to off-patent repurposing candidates being called "**financial orphans**" (84). As a result, new uses for off-patent medicines are mainly studied in **independent clinical trials** initiated and led by researchers from academia, research institutes or collaborative groups. (68). While many phase I and II proof-of-concept studies are performed, repurposing hypotheses are often not confirmed in phase III trials due to a **lack of public and philanthropic funds** (85). Box 1.1 describes several additional financial disincentives associated with conducting non-commercial trials.

BOX 1.1 | FINANCIAL DISINCENTIVES ASSOCIATED WITH NON-COMMERCIAL TRIALS

Adapted from Pantziarka P, Verbaanderd C et al. 2020 (72)

In the case of commercially-supported trials, all the drugs in the trial, including any placebos required for control arms, are normally paid for by the company. For an institution, this represents a saving in that the drugs, including standard of care agents, for all patients recruited to the trial do not come out of pharmacy budgets. In oncology, such a saving may be substantial. In contrast, without commercial support the costs of drug supply must be covered by the trial budget, including payment for the manufacture of placebos, which may be more expensive than the generic drug being tested. Furthermore, commercially-supported trials can be a source of institutional revenue. Commercial support may include payment per patient recruited, and payment of costs associated with additional medical procedures, including for patients on control arms of trials. For repurposing trials, many of which are academic or investigator-led, there may be no per patient payments and all costs must be borne by the institution or direct from the trial budget. In some cases, these per patient payments may act as incentives to steer patients into commercially-supported trials in contrast to competing repurposing trials. In some areas of oncology, where there are multiple commercial entities working in parallel on new treatments, the competition for patients may be such as to make non-commercial repurposing trials problematic (472). In such situations, the challenge is exacerbated when standard of care is in flux and therefore small repurposing trials with slow accrual may be rendered out of date before the trial has completed (473). Finally, there are other advantages that commercial sponsorship may bring to a trial. These include administrative support, protocol writing, statistical support, funding for meetings and conferences and so on. While it is difficult to assign a direct financial value to these services, they may have a significant bearing on institutional or investigator attitudes towards undertaking repurposing or other non-commercial trials.

BARRIERS FOR CLINICAL ADOPTION

Obtaining marketing authorisation of the new indication should be the standard approach for the clinical adoption of repurposed drugs and is a prerequisite for the reimbursement and the inclusion in clinical treatment guidelines and national formularies (Figure 3). However, in practice, there are **challenges that hinder that regulatory approval of repurposed medicines that are out of basic patent and regulatory protection**.

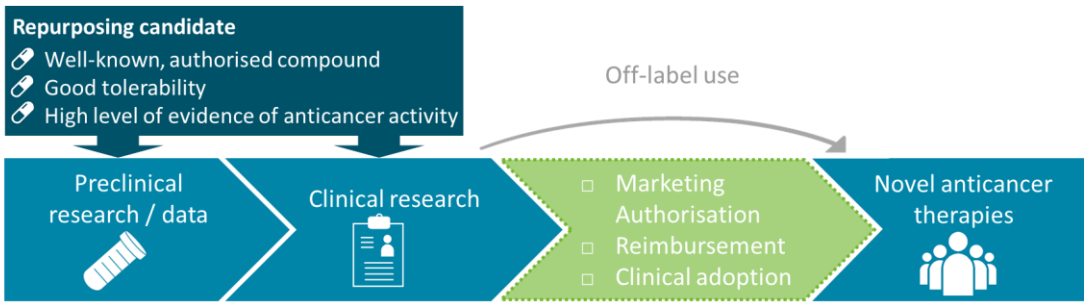


FIGURE 3. FROM REPURPOSING CANDIDATE TO ANTICANCER THERAPY
The overall aim of drug repurposing is to provide new treatment options to patients. To facilitate patient access to repurposed drugs, marketing authorisation, reimbursement and implementation in clinical guidelines should be pursued. Alternatively, drugs can be administered off-label but this has limitations.

Adapted from Verbaanderd C et al. 2017, Trends in Cancer

As long as the medicine is on patent and/or benefits from some kind of regulatory exclusivity, pharmaceutical companies are likely to seek marketing authorisation for new indications for two reasons. First, adding new therapeutic indications increases the patient population and thus the sales of the product. Second, strategically adding new uses, protected by second- and further medical use patents, may delay generic or biosimilar competitor products from entering the market. Once the medicine loses its patent and/or regulatory exclusivity, pharmaceutical companies are **no longer incentivised to invest in additional regulatory procedures** because generic or biosimilar competitor products will enter and adapt their labels based on the reference product. This is why the majority of label extensions for new medical indications occur during the period of exclusivity granted to the developers of new drugs, with one analysis of data from the European Medicines Agency (EMA) showing 92.5% of extensions for new indications were granted in this exclusivity period (38). An additional reason why pharmaceutical companies are not interested in engaging in regulatory procedures for repurposed drugs is the fact that most repurposing clinical trials are non-commercial and are being conducted independent from the company. If a company would use this external data to apply for a marketing authorisation procedure, they would need to **take responsibility for data that is not their own**.

Alternatively, in most countries, physicians are able to **prescribe drugs in an 'off-label' manner** - that is to prescribe approved drugs for new indications for which they are not approved. However, off-label prescribing, though widely used in some areas of medicine such as paediatrics, has significant downsides (*e.g.*, lack of reimbursement, legal liability for physicians, medical uncertainty, risk of supply issues) (86).

CHAPTER 2

Objectives & research design

SCOPE AND OBJECTIVES

For the purpose of this PhD project, we primarily focused on the **repurposing of authorised medicines that are out of basic patent and regulatory protection** (also referred to as "off-patent drug repurposing") as this specific category may offer opportunities in oncology but is also faced with a distinct set of scientific, regulatory, legal and financial challenges. Addressing these challenges is essential to enable efficient research in this field and to bridge the current gap between clinical research and practice.

The **overall aim of this PhD project** is to investigate the challenges that hinder the clinical research and implementation of drug repurposing and to explore possible solutions for unlocking the full potential of this strategy. This aim was translated in the following three objectives:

- **Objective 1:** To investigate data sharing initiatives, partnerships and new funding mechanisms that could facilitate the research and development of repurposed medicines.
- **Objective 2:** To portray the regulatory framework relevant for making repurposed medicines available to patients in Europe and to explore solutions that have been proposed to overcome regulatory and financial barriers for clinical adoption of repurposed medicines.
- **Objective 3:** To propose policy recommendations for addressing the current challenges in the clinical research and implementation of drug repurposing, while considering different stakeholder perspectives (*i.e.*, academia and non-profit sector, industry, regulators, health technology assessment (HTA) bodies and payers, healthcare professionals and patients).

RESEARCH DESIGN

To achieve the objectives outlined above, this project is divided into four parts. A schematic overview of the project is shown in Figure 4.

Part 1 comprises two chapters. **Chapter 1** provides a general introduction into the field of drug repurposing and clarifies the definitions, terminology, benefits, opportunities and current research activities in oncology. Moreover, several key challenges are introduced that were the starting point of the studies in this PhD project. **Chapter 2** describes the scope, objectives and research design of this project.

Part 2 addresses the **first objective**, which is focused on exploring ways to facilitate the research and development of repurposed medicines, and comprises two chapters. In **Chapter 3**, we performed semi-structured interviews and an in-depth literature review to explore how available data can be used during the research and development of repurposed medicines from candidate selection to clinical adoption. In addition, we investigated stakeholder views on data sharing and public-private partnerships. In **Chapter 4**, we searched scientific and grey literature to identify potential funding mechanisms for independent clinical research to repurpose medicines that are out of basic patent and regulatory protection. Moreover, we studied various perspectives on the application potential of the proposed funding mechanisms in Europe by conducting semi-structured interviews with European stakeholders.

Part 3 focuses on the **second objective** regarding the clinical implementation of repurposed medicines and comprises three chapters. **Chapter 5** portrays the regulatory framework relevant for bringing

repurposed medicines to cancer patients in Europe and is based on an analysis of the European and national legislation and guidelines, consultations with experts and a review of scientific and grey literature in this field. In this chapter, we also explored specific policy recommendations that were proposed by various stakeholders to address the current regulatory and financial barriers for clinical adoption of new indications for marketed, off-patent medicines. In **Chapter 6,** we identified and analysed promising repurposing candidates in oncology for a pilot to test the repurposing framework proposed by the European Commission expert group on Safe and Timely Access to Medicines for Patients (STAMP)**.** In **Chapter 7**, we conducted semi-structured interviews with Belgian cancer patients and health care professionals, primarily specialized in oncology, to explore their perspectives on the clinical implementation of repurposed medicines for anticancer treatment. Furthermore, we organised focus group discussions with the same stakeholder groups to explore proposals that could facilitate drug repurposing in oncology research and practice.

Part 4 concerns the **third objective**. In **Chapter 8,** we integrated the knowledge obtained from all previous studies to propose pragmatic policy recommendations for addressing the current challenges in the clinical research and implementation of drug repurposing, taking into account different stakeholder perspectives. These recommendations aim to capitalize on the economic and societal benefits of drug repurposing, as this treatment development strategy holds the promise of contributing to more sustainable health care systems in the long term.

During this project, the concept of drug repurposing was studied with a primary focus on the **application in oncology**. Nonetheless, the studies in Part 2 are not limited to oncology and the findings in Part 3 and recommendations in Part 4 may be extrapolated to other medical fields as well.

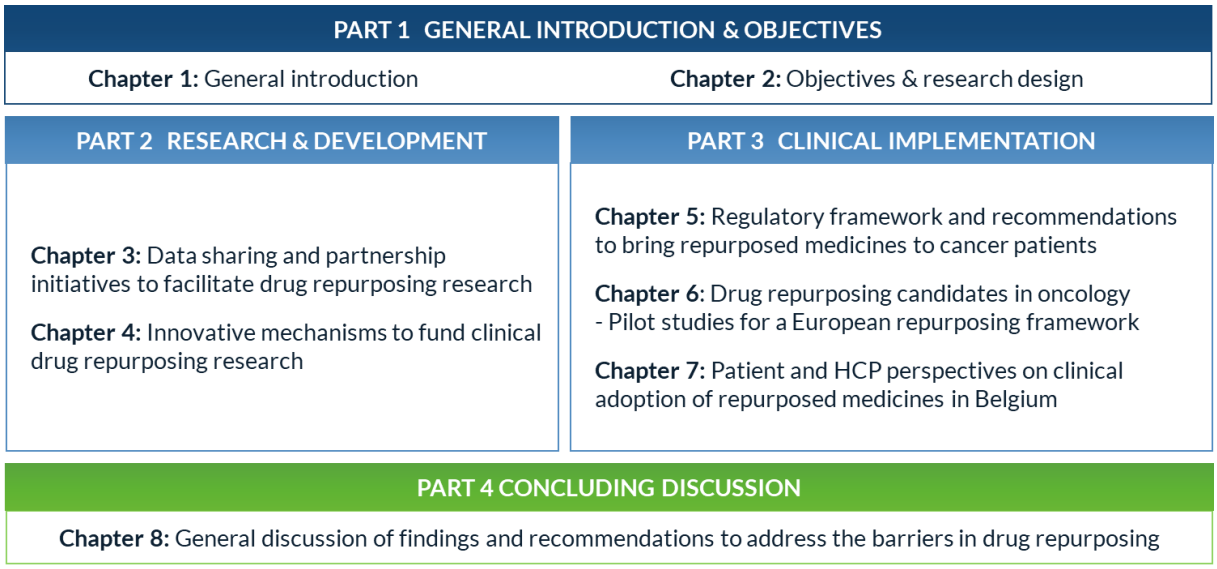
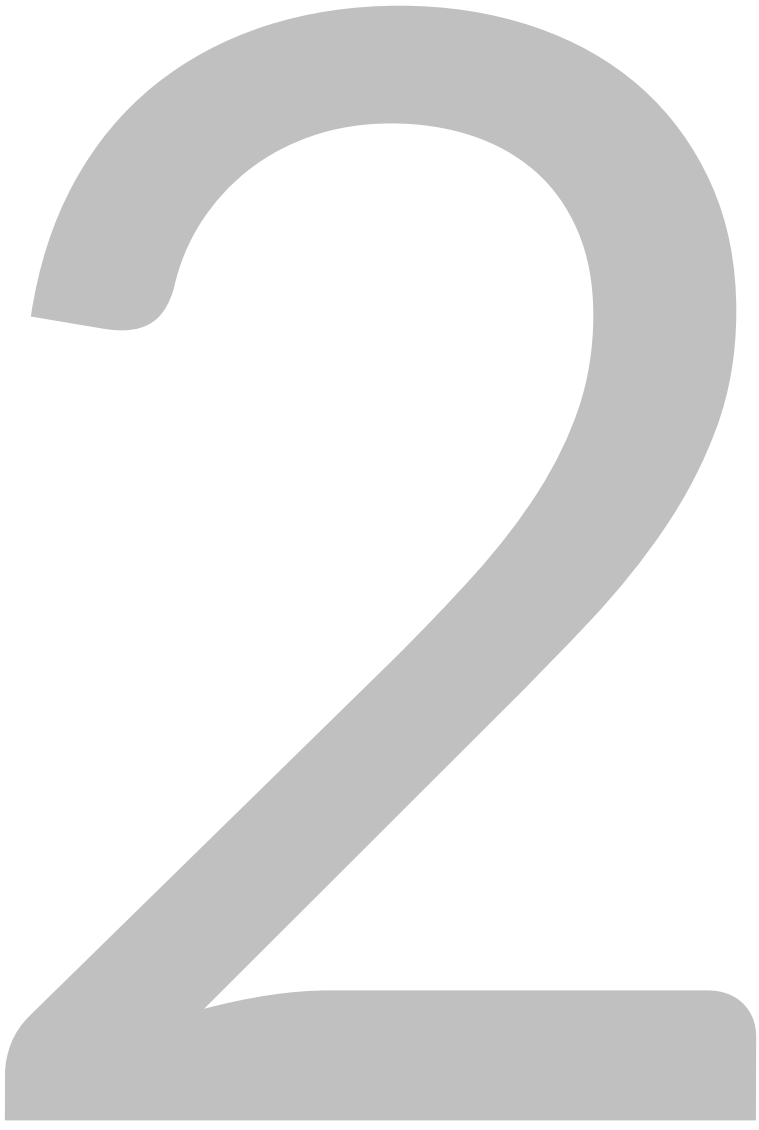


FIGURE 4. RESEARCH DESIGN OF THE PROJECT

PART 2

RESEARCH AND DEVELOPMENT OF REPURPOSED MEDICINES



CHAPTER 3

Data sharing and partnership initiatives to facilitate drug repurposing research

Manuscript in Preparation

Verbaanderd C, Rooman I, Huys I.
Data-driven drug repurposing: Tapping into the potential of data sharing and partnership initiatives.

ABSTRACT

A key strategic advantage of drug repurposing compared to *de novo* drug development is the substantial amount of available data and knowledge regarding existing medicines, allowing a shorter research and development time, less risk of failure in clinical trials, and reduced development costs. The aim of this study was to explore how available data can be used during the research and development of repurposed medicines from candidate selection to clinical adoption. In addition, we aimed to explore stakeholder views on data sharing in databases and public-private partnerships. Fourteen semi-structured interviews with representatives of the life science industry, academia and non-profit organisations from Europe and the US were performed and complemented with information from scientific literature. According to interviewees, a combination of different methods and technologies is usually applied to systematically collect and analyse the extensive amount of existing data from various sources for the identification, prioritisation and validation of repurposing candidates. Furthermore, available human data on tolerability, bioavailability, pharmacokinetics and toxicity may obviate the need to repeat preclinical and phase I clinical trials, unless the product underwent substantial changes for its use in the new indication. Data to support the proof-of-principle and to demonstrate safety and clinical benefit of repurposed medicines still need to be generated through phase II and III clinical trials. Yet, interviewees pointed out that regulators are increasingly open to the use of real-world evidence to complement randomized controlled trials. While interviewees recognized the importance and advantages of sharing both non-clinical and clinical data to facilitate research and development of repurposed medicines, they emphasized that data sharing is a sensitive topic, especially when it comes to the sharing of clinical trial and patient-level data. Overall, stakeholders might be more willing to share data if there is a formal agreement between involved parties and a clear objective for sharing the data. In view of that, interviewees were positive about multi-stakeholder public-private partnerships that could provide a structured framework to align priorities, efficiently share data and resources, and protect stakeholder's interests. Finally, we summarized the key stages of drug repurposing in a streamlined process to guide the future research and development of repurposed medicines.

INTRODUCTION

Drug repurposing, also known as drug repositioning, is **gaining momentum in all disease areas**. Many research activities are ongoing in oncology, neurology, cardiology, psychiatry and infectious diseases (48–51). Repurposing is especially attractive to find timely and affordable treatment options for rare and neglected diseases with high medical needs, for which commercial interests to develop new chemical entities are lacking (53–57). Furthermore, drug repurposing could play an essential role in rapidly treating patients and preventing the global spread of highly infectious diseases, as demonstrated by the recent Ebola virus disease, Zika virus, and Corona virus outbreaks (87–92). As of June 2020, the Covid19_DB reported more than 800 ongoing clinical trials that investigated the role of a wide variety of repurposed drugs for the treatment and prevention of the SARS-CoV-2 virus (93–96). Due to the lack of a consistent definition for drug repurposing, the meaning is often interpreted differently by different stakeholders. For the purpose of this study, drug repurposing refers to **finding and developing new uses for approved medicines or for investigational compounds that successfully completed phase I clinical trials.**

A **key strategic advantage** of repurposing existing compounds compared to *de novo* development of new molecules is the **substantial amount of available data and knowledge** regarding those medicines, allowing a shorter research and development time, less risk of failure in clinical trials due to well-established safety, and reduced development costs (59,72,97,98). More specifically, available data relevant to drug repurposing include information from *in silico*, *in vitro* and *in vivo* animal studies about pharmacokinetics, pharmacodynamics, dosing, toxicity, safety, putative mechanisms of action, interactions with disease pathways and molecular targets of the candidate compound. In addition, human clinical trials with the medicine in the original medical indication provided data concerning the pharmacokinetics, safety, tolerability, adverse events and recommended dosing of the compound. Following regulatory approval, the authorisation details, product information and assessment history of a medicine are summarized in reports published by regulatory agencies. After market entry, information about adverse events, cost-effectiveness and off-label use of the medicine accumulates and is captured by electronic health records (EHRs), observational studies, post-marketing surveillance trials, HTAs, insurance & payer databases, patient registries and e-health apps (Figure 5).

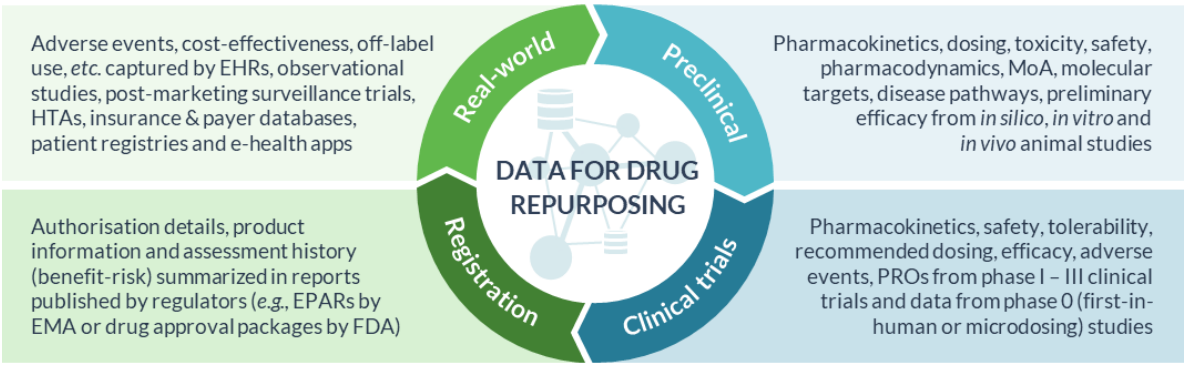


FIGURE 5. OVERVIEW OF DATA GENERATION DURING A DRUG'S LIFE CYCLE

A drug repurposing strategy can typically make use of a large amount of data generated during the different stages of a drug's life cycle. Abbreviations: Mechanisms of Action (MoA), Patient Reported Outcomes (PROs), Electronic Health Records (EHRs), Health Technology Assessments (HTAs), European Public Assessment Reports (EPARs)

With over 3000 approved medicines and many more shelved and investigational compounds in pharmaceutical compound libraries worldwide, innovative approaches are needed to **efficiently identify, prioritise and validate the most promising candidate compounds for repurposing** in a given indication (99,100). Once a viable repurposing candidate is selected, it needs to **be investigated in clinical research and, if effective, adopted in clinical practice** for use in the new indication.

The **aim of the present study** was to explore how the large amount of available data can be used to enable the research and development of repurposed medicines. More specifically, we aimed to identify available data and data sources that can be applied for the identification, prioritization, validation and selection of candidate compounds for repurposing, and for the clinical adoption of repurposed medicines. In addition, based on the hypothesis that increased data availability may facilitate the repurposing process, we aimed to explore stakeholder views on **data sharing via open access databases and public-private partnerships**.

METHODS

Representatives from pharmaceutical companies, academic institutions and not-for-profit research foundations with knowledge about drug repurposing were invited to participate in a **semi-structured interview** to explore their perspectives on the role of available data and data sharing in drug repurposing. Study participants were identified through conference proceedings, author lists of scientific publications and the network of the research group through purposive sampling (101). Participants were contacted via e-mail and received an information sheet describing the objectives and design of the study. An interview guide was developed based on background information from scientific literature with questions relating to the following topics: i) Identification, prioritization and selection of candidate compounds for repurposing, ii) Level of evidence needed for marketing authorisation of new therapeutic indications, iii) Advantages and disadvantages of data sharing through databases and partnerships (Appendix A).

The interviews took place between October 2017 and January 2018 and were performed by four researchers with a background in pharmaceutical and biomedical sciences. Before the start of this study, three pilot interviews were performed to optimize the interview guide. The first interview was conducted in the presence of all four interviewers to standardize the interview approach. The subsequent interviews were conducted in pairs or individually, either face-to-face or via phone or video call. The interviews were carried out in English or Dutch, and lasted about 30 to 45 minutes each. All interviews were audio-recorded with written informed consent from the study participants, transcribed *ad verbatim* and pseudonymized to protect participants' personal information. The interview transcripts were analysed based on the **framework analysis method** using the NVivo qualitative data analysis software (102,103).

To substantiate the various concepts mentioned by interviewees, **recent scientific literature** about data, data sources and data sharing initiatives in the context of drug repurposing was searched in MEDLINE (via PubMed) and Embase databases using search queries consisting of MeSH terms and key words in title and abstract (Appendix B). Articles published between January 2015 and January 2020, in English, of which the full-text publication was available were included. Grey literature, relevant publications from reference lists of the identified literature, and reports or presentations from scientific conferences with a primary focus on drug repurposing were included as well. The **results of the literature review and the stakeholder interviews are collectively summarized** in the results section below.

RESULTS

Fourteen interviews were performed involving stakeholders that represented the life sciences industry (N=9), researchers from academic institutions (N=2), and representatives from not-for-profit research foundations (N=3) (Table 4).

TABLE 4. CHARACTERISTICS OF INTERVIEW PARTICIPANTS

INTERVIEW	STAKEHOLDER GROUP	COUNTRY
A	Not-for-profit research foundation	The United States
B	Large pharmaceutical company (originator)	Belgium
C	Academic institution	The United States
D	Specialized pharmaceutical development SME	The Netherlands
E	Large pharmaceutical company (generic)	Belgium
F	Not-for-profit research foundation	The United Kingdom
G	Clinical research organisation	The United States
H	Not-for-profit research foundation	The United States
I	*In vivo* pharmacology clinical research organisation	The United States
J	Bioinformatics and systems biology service provider	Spain
K	Specialized life sciences consultancy	Austria
L	Pharmaceutical industry association	Belgium
M	Academic institution	The United States
N	Large corporate research organisation	The United States

Abbreviations: Small- and Medium sized enterprises (SMEs)

IDENTIFICATION AND PRIORITISATION OF CANDIDATES FOR DRUG REPURPOSING

Historically, new therapeutic uses for approved medicines or investigational products were identified through serendipitous clinical observations (*e.g.*, sildenafil for erectile dysfunction) but in view of the rapidly increasing amount of available data, researchers are now applying more rational and systematic approaches to repurpose existing compounds (32,33). Based on their own practical experience, interviewees emphasized that there is **not one standardized approach** to identify and prioritise repurposing candidates. In fact, researchers increasingly use a **combination of different methods and technologies** to systematically collect and analyse existing data, and/or to generate new data. Several interviewees also mentioned that **different starting points** might be applied for drug repurposing. For example, pharmaceutical companies typically start from their own approved or investigational products and try to identify additional indications, whereas researchers from academia or other research institutes usually start with a specific target or disease mechanism for which they try to find new treatments.

Via an in-depth analysis of the scientific literature and with input from the interviews, we identified three main strategies for the identification and prioritization of candidate drugs. The first strategy covers **data-driven approaches** that involve a systematic analysis of drug- and disease-related big data (*e.g.*, omics data, adverse events profiles, disease biology, *in silico*, *in vitro and in vivo* screening data, drug characteristics, molecular targets and real-world data). In this strategy, researchers are using and combining data from

various open access or commercial data resources. For example, several interviewees in this study used DrugBank, DrugCentral, Drug Repurposing Hub, PubChem, Gene Expression Omnibus, ChEMBL, Kyoto Encyclopedia of Genes and Genomes, Reactome and SciFinder in their drug repurposing research. Moreover, researchers could request access to **coded or anonymized data from payer and insurance databases, medical records and patient registries** to generate repurposing hypotheses via retrospective analyses of clinical effects of medicines that are on the market and prescribed for their original indication(s) or used off-label (100,104–114). Data-driven approaches are highly diverse, so previous studies have categorized them further into signature-based, structure-based, target-based, targeted mechanism-based, knowledge-based and pathway- or network-based methods (32,98,115,116).

Second, several interviewees had experience with **experimental approaches** to identify new drug repurposing opportunities**,** such as binding assays for demonstrating specific target interactions with candidate compounds or phenotypic screening assays for exploring disease-relevant effects in cellular or animal disease models (32,98). Gaining access to compound libraries to conduct experimental assays may be challenging, especially when it comes to companies' shelved experimental assets, but several **open science initiatives** have been set up to address this challenge. A recent example of such an experimental approach is the high-throughput screening of about 15,000 approved and investigational compounds included in the ReFRAME drug collection to find an effective antiviral drug against SARS-CoV-2 at the University of Leuven (Belgium) (117). The National Center for Advancing Translational Sciences (NCATS) Pharmaceutical Collection (NPC) is another example of a comprehensive collection of currently approved and marketed small molecule medicines that can be used for high-throughput screening purposes (56).

Third, interviewees specified that many repurposing hypotheses come from systematically screening the scientific and grey literature or from observations in the clinic, which is also known as **literature-based or knowledge-based drug repurposing.** Additionally, one interviewee said that intellectual property (IP) documents, including granted patents and published applications, are a highly relevant but often overlooked data source for identifying repurposing candidates. Although not peer-reviewed, patent documents could provide a comprehensive perspective of drug repositioning activities in industry and academia that are not (yet) published elsewhere (118–120). However, searching and analysing IP documents requires some expertise, which may be a barrier for biomedical researchers.

To integrate and process all of this data, powerful **computational tools** such as bio- and cheminformatics, network and systems biology, algorithmic data and text mining, machine learning and artificial intelligence are becoming indispensable. In fact, computational drug repurposing research is a rapidly expanding field, as illustrated by the vast amount of scientific literature published on this specific topic in recent years (10,105,108–114,116,121–150). In addition, **specialized companies** have emerged with a primary focus on systematically identifying candidates for drug repurposing (*e.g.*, Melior Discovery, Healx, NuMedii, SeaChange Pharmaceuticals, NovaLead, Biovista, SEEK, ReDiscovery LifeSciences, Segue Therapeutics, SOM Biotech) (10,36,42,46,151,152). Their activities range from developing innovative computational tools for drug repurposing to providing high-throughput screening platform services. Some companies even initiated their own drug repurposing pipelines. Moreover, several consulting firms are offering specific guidance to develop drug repurposing strategies (*e.g.*, H.M. Pharma Consultancy, Avivia, Numedicus, Cycle Pharmaceuticals, Camargo Pharmaceutical Services).

Innovative computational tools could also greatly facilitate the use of **drug repurposing in precision medicine**, which is an emerging concept in various disease domains, especially in oncology (Box 3.1).

BOX 3.1 | DRUG REPURPOSING FOR PRECISION MEDICINE

Precision medicine can be defined as an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment and lifestyle for each person (188). The emergence of relatively low-cost, high-precision molecular profiling techniques and computational tools that systematically integrate multiple layers of information could greatly facilitate precision medicine and tailor therapeutic recommendations to an individual patient's characteristics (44,148,474). Interestingly, computer-aided drug repurposing approaches could lead to personalised, evidence-based and timely treatments for patients by predicting responders to existing medicines originally developed for the same or an entirely different disease (474–478). For example, researchers from the BC Cancer Personalized Oncogenomics initiative reported an interesting case of a patient with metastatic colorectal cancer resistant to standard chemotherapy and radiation (479). Immunohistochemical analysis, whole-genome sequencing and whole transcriptome sequencing was performed, and the integrative molecular analysis indicated genetic and transcriptional overexpression of the JUN and FOS genes that encode the activating protein-1 (AP-1) complex. Based on these findings, it was hypothesized that blocking the renin–angiotensin system, which is an upstream activator of the AP-1 complex, could be a valid treatment option. The antihypertensive angiotensin II receptor antagonist, irbesartan, was administered as an anticancer therapy, resulting in a substantial and durable response.

Most of the recent successes of personalised drug repurposing come from oncology but other therapeutic areas are expected to follow, with some examples from psychiatry and neurology in basic research (474). Personalised drug repurposing could be particularly rewarding for rare diseases that lack standard treatments and are difficult to study in clinical trials due to their low prevalence, or for diseases that have specific target mutations (435,480,481).

VALIDATION AND SELECTION OF CANDIDATES FOR DRUG REPURPOSING

Aforementioned computational tools and experimental approaches are valuable to reduce the number of possible repurposing candidates but they usually predict multiple interesting hits. To narrow down and select viable candidates, an **in-depth analysis of all available data should be performed** before testing a repurposing hypothesis in prospective preclinical and clinical studies (39,99,116,148,153). Even though such an analysis may seem evident, one of the interviewees described several failures in drug repurposing for rare diseases that could have been prevented if the researchers had reviewed all available data before progressing to clinical trials. Additionally, interviewees considered **preclinical validation** in *in vitro* and animal models an essential step to confirm the desired effect of a candidate compound in a certain indication or against a disease-specific target. Yet, under certain circumstances, it may be justified to initiate small human proof-of-concept clinical studies without conducting preclinical efficacy studies first (*e.g.*, in case robust data is already available or in an emergency situation with urgent medical needs) (154).

To facilitate the prioritisation and selection process of repurposing candidates to be tested in clinical trials, we adapted the **candidate drug characteristics** proposed by the Repurposing Drugs in Oncology (ReDO) project to cover all disease domains (45).

1. Robust scientific evidence for use in the new therapeutic indication (level of evidence: human trial data > observational data and case reports > *in vivo* data > *in vitro* data > *in silico* data) (147);
2. Good tolerability profile with low or manageable toxicity (based on *in vivo* and human data);
3. Relevant putative mechanism of action in the new therapeutic indication;
4. Evidence of efficacy at dosing known not to be associated with unacceptable toxicity.

As part of the validation process, several industry representatives mentioned that pharmaceutical developers usually seek support from multiple **scientific experts or key-opinion-leaders** in the field and check the **commercial viability of a repurposing candidate** (Box 3.2). If commercial incentives to support the development of a repurposing candidate are lacking (*e.g.*, off-patent medicines that do not require any product changes), the research is typically discontinued. In contrast, researchers from academia or research institutes who have no financial objective may still want to perform this research.

BOX 3.2 | COMMERCIAL VIABILITY OF A REPURPOSING CANDIDATE

Pharmaceutical developers typically start by conducting an in-depth market analysis and assess the pricing and reimbursement opportunities for the repurposing candidate (33). Subsequently, the existing intellectual property (IP) landscape is portrayed to ensure freedom-to-operate (*i.e.*, patent applications, granted patents and supplementary protection certificates) (79). Even if a patent is still in force, preclinical and clinical research with the repurposing candidate can often be performed because most countries have exemptions for using patented products for research purposes that would otherwise qualify as patent infringement (482). However, a repurposed medicine cannot be commercialized until the relevant patents have expired, unless a license is obtained from the IP holder to manufacture and market the product for a new indication (33,79).

Opportunities for generating new IP and obtaining regulatory exclusivities (*e.g.*, for orphan or paediatric uses) will also be explored at this time (483,484). When filing a patent for a new use (*i.e.*, patents for second and further medical uses in EU or method-of-use patents in the US), some experimental data should be included in the application to show that the repurposing candidate could be reasonably expected to treat the claimed indication (78). However, knowledge about the new medical use should not be made public before patent application because, in that case, the inventiveness and novelty requirements are no longer met (79,80). The enforceability of patents for new indications for existing medicines may be limited due to the narrow scope of such claims, and due to the possibility of off-label prescribing and skinny labelling (*i.e.*, a generic applicant is permitted to “carve-out” from the SmPC any indications or dosage forms that are protected by patents) in most countries (38,81). To generate stronger IP protection, commercial developers will likely try to differentiate the repurposed product from potential competitors by creating a new formulation, dosage form, route of administration, or (fixed) combination, depending on the patients’ needs (73).

TRANSLATION TO CLINICAL RESEARCH

Available human data on tolerability, bioavailability, pharmacokinetics and toxicity may obviate the need to repeat **phase I clinical trials** for the use of existing small molecules in a new indication (45). Nonetheless, interviewees noted that phase I trials may still be required in case the product underwent substantial changes for its new use, such as a higher dose or a different route of administration, that may significantly affect any of the aforementioned properties or when it is used in new combinations with other medicines (risk of cumulative toxicity or drug-drug interactions). Phase I trials may also need to be repeated in case the data package from initial clinical trials no longer meets current regulatory requirements for marketing authorisation (71). According to the interviewees, **phase II and III clinical trials** to show proof-of-principle and to demonstrate safety and clinical benefit of repurposed medicines are still required and comparable to clinical trials with new chemical entities.

In addition, the scientific community is increasingly looking into the value of **real-world data (RWD) and real world evidence (RWE) studies** as a complement to randomized controlled trials (RCTs) in the research and development of marketed repurposing candidates (106,155). RWD is broadly defined as data relating to the patient health status and/or the delivery of health care obtained in the real world setting rather than conventional, structured data from RCTs (156). RWD encompasses patient demographics, diagnoses, procedures and treatment regimens, cost of treatment, patient history, disease characteristics and progression, biomarker results, molecular and genetic data and imaging data. Potential sources of RWD include paper and electronic health records, observational studies, disease or product-based patient registries, health insurance and reimbursement claims in payers' databases, patient-generated data (*e.g.*, e-health apps, patient-reported outcomes and wearables) and social media (39,156,157).

RWE derives from the analysis and /or synthesis of RWD (158). RWE studies present a unique and largely untapped opportunity for obtaining valuable information about the safety and efficacy of a repurposing candidate in a large heterogeneous population over a long period of time, instead of in a restricted RCT population with short-term follow-up (39,159,160). Today, RWE is assessed by the European Medicines Agency (EMA) and the Food and Drug Administration (FDA) to support regulatory decision-making on an *ad hoc* basis (158,161,162). However, a lack of control over the quality of the data, the large, non-standardized datasets, the restricted access to such data, and privacy-related concerns are critical barriers in RWE studies (159). Rigorous statistical modelling, machine learning and artificial intelligence may help to reduce bias inherent to RWE studies and to integrate big data from various sources.

Furthermore, **innovative hybrid study designs and pragmatic trials are emerging to combine the strengths from RCTs and RWE studies** (159,163). Pragmatic trials are run in a real-world setting, with broad eligibility criteria, and are designed to be straightforward and externally valid by using practical clinical procedures and outcomes that are important to patients (164). Other examples of trial designs relevant to drug repurposing include registry-based RCTs, aggregated N-of-1 trials and open-label, non-randomized single-arm real-world studies (165–167). Further research on research methodology is needed to investigate whether such trial designs can be used to generate robust data for regulatory and clinical decision-making.

CLINICAL ADOPTION OF REPURPOSED MEDICINES

The standard route to clinical adoption of new therapeutic indications is via **regulatory approval**, followed by procedures relating to reimbursement of the repurposed medicine (168). All interviewees stated that, evidently, **robust clinical evidence** is required to demonstrate efficacy and safety of the drug in the new indication. Most interviewees indicated that the data package to apply for a marketing authorisation of a repurposed medicine should meet the **same evidentiary standards** as for new medicinal products (*i.e.*, data from one or more phase III pivotal RCTs in compliance with Good Clinical Practice (GCP) guidelines). However, some interviewees stressed the importance of regulatory flexibility in case of unmet needs and were of the opinion that it should be possible to apply for **conditional approval** of a new indication for an existing medicine based on phase II studies, followed by one or more confirmatory studies and real-world monitoring. Interviewees mentioned that regulators are also increasingly open to the use of **RWE to support marketing authorisation applications**. In Europe and the US, various pathways are available to obtain marketing authorisation for repurposed medicines (Box 3.3).

BOX 3.3 | OVERVIEW OF REGULATORY PATHWAYS RELEVANT TO DRUG REPURPOSING

In Europe, various legal bases can be applied to get new therapeutic indications approved (49). First, the applicant can apply for a full-mixed marketing authorisation that allows bibliographical references to support or replace some of the (non-) clinical data in the regulatory dossier (Art 8(3) Directive 2001/83/EC). Second, a well-established use or "literature-only" application can be submitted for a well-known active substance if safety and efficacy can be demonstrated by extensive and continued use in the specific indication in the EU over a period of at least 10 years (Art 10(a) Directive 2001/83/EC). Third, the hybrid application route has been suggested in the context of drug repurposing (Art 10(3) Directive 2001/83/EC). Yet, in practice, this route is typically used for applications of generic medicines where there are only "minor" differences with the reference medicinal product (*e.g.*, minor changes in therapeutic indications within the same therapeutic field). Finally, only the marketing authorisation holder of an already authorised medicinal product can apply for a type II variation or extension of indication to add a new therapeutic indication to the product label (Commission Regulation (EC) No 1234/2008).

In the US, Section 505(b)(2) of the Federal Food, Drug and Cosmetic Act, also called the hybrid application route, is specifically recommended for New Drug Applications (NDAs) for new dosage forms, strengths, administration routes, dosing regimens or indications. This route allows cross-referencing to safety and efficacy evaluations of the FDA for an already approved product and to published literature. Consequently, the applicant should not conduct studies on what is already known (*e.g.*, basic toxicology) but is expected to establish a bridge to justify reliance on non-proprietary or bibliographic data (*e.g.*, same active ingredient). The applicant should also include sufficient data to support any differences between the product they are proposing and the previously approved drug, for example studies of safety and efficacy for the new use. Similar to the EU, the license (or marketing authorisation) holder can add a new indication to the existing label, which is called a supplemental NDA (sNDA).

Depending on the regulatory pathway, the data package submitted to regulatory authorities in the EU or the US may consist of the **applicant's own data from non-clinical and clinical studies, complemented with data from published literature** (Box 3.3). Additionally, the 505(b)(2) procedure in the US allows applicants to rely on the Food & Drug Administration (FDA)'s prior findings of safety and efficacy for previously approved drugs to the extent that the proposed product shares characteristics with that drug. However, both in the EU and the US, **third parties do not have direct access to non-clinical and clinical data** submitted as part of previous dossiers or included in the US Drug Master Files. Consequently, in case an application for a new indication is introduced by someone else than the original marketing authorisation holder, they need to reach an agreement with the original developer to get access to the existing data or potentially seek the information via a freedom of information request to the regulatory authorities.

An important challenge in the clinical adoption of repurposed medicines is the fact that **many repurposing activities are initiated and led by researchers from academia or collaborative groups**, especially when it comes to repurposing low-cost authorised medicines that are readily available for testing in clinical trials (68). Academic researchers typically do not have the expertise, resources or intention to be involved in regulatory procedures and therefore would need to collaborate with a marketing authorisation holder. However, according to an industry representative in this study, pharmaceutical companies are reluctant to rely on external data from investigator-initiated studies because even though these trials may apply scientific rigor and generate high quality data, they rarely meet the strict requirements set by regulatory authorities for marketing authorisation. Besides, pharmaceutical companies often decide not to pursue new indications for marketed, off-patent medicines as it is typically not possible to obtain premium pricing for these repurposed medicines and it is particularly challenging to recoup the costs that come with a marketing authorisation application, especially in case competitor products can be prescribed as well.

Some interviewees were of the opinion that, for marketed medicines, **off-label prescribing** is a viable alternative solution for translating a new use into clinical practice when sufficient evidence of clinical efficacy is available but incentives or resources to apply for regulatory approval are absent. In Europe, the use of medicinal products in medical practice is not regulated by EU legislation so management of off-label use is at the discretion of the Member States. Some Member States have established legal and regulatory frameworks regarding off-label prescribing and reimbursement, which are summarized elsewhere (49,169). Likewise, off-label use is considered legal in the US but is not regulated by the FDA, so physicians are free to prescribe approved drugs as they see fit, as long as they have exhausted standard-of-care approaches and have robust evidence to support safety and clinical benefit of the drug in the new use (170). According to federal law, the Centers for Medicare & Medicaid Services (CMS) must provide coverage for an off-label drug if it is referenced in one or more federally designated third-party drug compendia (171). In some states, private payers also need to consider recommendations from specific compendia for coverage decisions. Similar to the requirements for regulatory approval, **well-designed RCTs** are needed to change clinical practice and convince physicians that a particular treatment is effective in an off-label indication. Since companies are not allowed to promote off-label use or to add it to the product label, other means of communication are needed for distributing clinical safety and efficacy data with regard to off-label use of repurposed medicines. Relevant resources to guide clinical decision-making include consensus-based or evidence-based treatment guidelines, drug compendia, presentations at scientific conferences and peer-reviewed scientific publications (49,72).

DATA SHARING AND CROWDSOURCING IN DRUG REPURPOSING RESEARCH

Over 30 open access web-based databases and platforms were identified from scientific literature that could accelerate the identification, prioritisation, validation and/or evidence generation in drug repurposing (104,172)(Table 5). Most databases and platforms comprise drug-, disease- or target-related data, and some offer advanced computational functions to predict drug-disease-target relationships. Moreover, they frequently encompass comprehensive annotations for investigational or approved drugs, (*e.g.*, chemical structures, clinical trial information, side effects, therapeutic indications, authorisation details, mechanisms of action, physicochemical properties, drug–drug interactions and vendors). Some platforms enable crowdsourcing, which is a collaborative approach to obtain information or input into a task or project from a large number of people with a variety of expertise, typically via the Internet. In drug repurposing, crowdsourcing could help to generate new insights based on the available data, improve consensus on repurposing hypotheses and facilitate data curation and annotation processes (107,173).

All interviewees recognized the **importance and advantages of sharing both non-clinical and clinical data** to facilitate drug repurposing research**.** Interviewees were of the opinion that increased sharing of data and study results could stimulate new ideas and save time and money by avoiding duplication and fragmentation of research. Several interviewees considered it unethical that many investigator-initiated and industry-led clinical trials with repurposed medicines, which are registered and can be found in publicly available clinical trials registries (*e.g.*, ClinicalTrials.gov, EU Clinical Trials Register, WHO International Clinical Trials Registry Platform), have no published trial results after study completion. Moreover, they indicated that increased data sharing could improve the research quality due to feedback from peers and it could increase the likelihood and speed of clinical adoption of repurposed medicines, for example by sharing clinical evidence to reduce uncertainty and to support off-label use of a medicine.

> *"When it comes to aggregated data about the study and even detailed aggregated data, our philosophy is: it's better to show it to everybody. Because if the crowd, in other words the global supply of brainpower out there, is able to critique and make suggestions about the data. You might find out something about the data that could be very useful." (Interview G)*

Despite these clear advantages, interviewees emphasized that **data sharing is a sensitive topic.** While all interviewees were of the opinion that both positive and negative results from publicly funded research should be shared in the public domain (via scientific publications, conferences or open access databases), some pointed out that this could compromise the possibility of obtaining patent protection for a repurposing candidate, which would complicate future partnerships with industry to develop the drug. Interviewees were also concerned that increased sharing of data could create disincentives for other researchers to produce new data. Moreover, several interviewees considered the sharing of clinical trial and real-world patient data particularly difficult due to requirements for anonymization and data management, in accordance with the data protection and privacy-related legislative frameworks (*e.g.*, the EU General Data Protection Regulation (GDPR) 2016/679).

> *"Part of the reason that we have trouble getting people to participate in our data sharing is because they are afraid that somebody is going to steal their data or they are afraid that they won't be able to file a patent afterwards, if they wanted to." (Interview M)*

TABLE 5. WEB-BASED DATABASES AND PLATFORMS TO FACILITATE DRUG REPURPOSING

NAME	URL	DRUG REPURPOSING APPLICATION	REF
MOAD	http://bindingmoad.org/	Compute pairwise ligand and binding-site similarities to identify potential polypharmacology pairs.	(485)
CANDO (BINDNET)	http://protinfo.compbio.buffalo.edu/cando/servers/bindnet/	Predict the most likely binding partners for an input ligand within a structural proteome of interest.	(486)
CDEK	http://cdek.wustl.edu/	Search aggregated metadata surrounding drugs such as clinical trial information, clinical indications, organizations responsible for development, mechanism of action, *etc.*	(487)
Chemotext	http://chemotext.mml.unc.edu/	Mine the published literature in PubMed annotated by Medline Subject Heading terms to identify all known drug-target-disease relationships and infer missing links.	(488)
Depmap	https://depmap.org/repurposing/	Retrieve data on growth-inhibitory activity of 4,518 drugs tested across 578 human cancer cell lines.	(459)
Drug Repurposing Hub	https://clue.io/repurposing	Search comprehensive annotations for a total of 6,125 compounds, including clinical status, drug indication, disease areas, mechanism of action, drug target, purity, and/or vendor.	(489)
Drug Target Commons	https://drugtargetcommons.fimm.fi/	Improve consensus and use of drug-target interactions via crowdsourcing.	(173)
Drug Voyager	http://databio.gachon.ac.kr/tools/	Understand unintended drug actions by constructing drug-signalling pathways based on pharmacologic, pharmacogenomic, transcriptomic, and phenotypic data related to drug response.	(490)
Drugbank 5.0	https://www.drugbank.ca/releases/5-0-1	Browse data on hundreds of investigational drug clinical trials and various drug repurposing trials along with thousands of up-to-date drug images of approved drugs.	(491)
Drug-Path	http://www.cuilab.cn/drugpath	Search drug-induced pathway data predicted from drug-induced gene expression data based on the Connectivity Map.	(492)
DrugPredict	http://www.drugpredict.com/default/main	Browse the database of FDA-approved small-molecule drugs to find new, hidden therapeutic applications, in a disease or drug-centric way.	(493)
DrugR+	http://drugr.ir/	Search key information on data structures for drug repurposing via an SQL query capability for professional users and an appropriate method with different options for unprofessional users.	(494)
Drug Repurposing Online	https://drugrepurposing.info/	Find information about repurposing opportunities for 9040 investigational or approved compounds, covering 469 indications, with 997 mechanisms.	(99)
DrugSig	http://biotechlab.fudan.edu.cn/database/drugsig/	Query and retrieve information on drug signatures based on data from literate and public databases.	(495)
DRUGSURV	http://www.bioprofiling.de/GEO/DRUGSURV/index.html	Explore the potential of ±1700 FDA approved drugs and ±5000 experimental drugs to target genes that are significantly associated with survival in clinical cancer expression datasets.	(496)
DTome	https://bioinfo.uth.edu/DTome/	Construct drug-target networks by integrating the drug-drug interactions, drug-target interactions, drug-gene associations and target/gene-protein interactions.	(497)

NAME	URL	DRUG REPURPOSING APPLICATION	REF
DT-Web	https://alpha.dmi.unict.it/dtweb/index.php	Browse all predictions inferred by the DT-Hybrid algorithm, upload custom data for predictions, and find drugs that can act simultaneously on multiple targets in a multi-pathway environment.	(498)
e-Drug3D	https://chemoinfo.ipmc.cnrs.fr/MOLDB/index.php	Explore structures and experimental properties of FDA approved drugs and active metabolites (*i.e.*, 1930 molecular structures approved between 1939 and 2019).	(499)
eRepo-ORP	https://osf.io/qdjup/	Search a drug repurposing dataset containing results of a large-scale pocket matching between target sites for known drugs and binding pockets identified in proteins linked to rare diseases.	(500)
EK-DRD	http://www.idruglab.com/drd/index.php	Search the structure, function, pathway, disease, network and related experimentally validated drug repositioning annotation for 1861 FDA-approved and 102 withdrawn small molecule drugs.	(501)
eTOXsys	http://etoxsys.com/	Obtain improved early drug candidate safety assessments through intuitive access to proprietary toxicology data and predictive models.	(502)
geneXpharma	http://genexpharma.org/	Explore statistically evaluated gene expressions and their drug interactions for 48 diseases under seven different disease categories.	(503)
MeSHDD	http://apps.chiragjpgroup.org/MeSHDD/	Explore a database of similarity-based drug clusters of FDA approved drugs via an interactive application in a drug or disease-centric way.	(504)
Open Targets	https://www.opentargets.org/	Mine integrated public domain data to enable target identification and prioritisation.	(505)
Open PHACTS	http://www.openphacts.org/2/sci/index.html	Mine integrated and interoperable pharmacological data from multiple publicly available databases.	(506)
PathFX	https://www.pathfxweb.net/	Predict repurposing opportunities based on interaction paths that associate a marketed drug to a new disease.	(507)
Project Rephetio	https://het.io/repurpose/	Browse predictions of new uses for existing drugs based on predicting treatment edges in Hetionet v1.0.	(508)
PROMISCUOUS	http://bioinformatics.charite.de/promiscuous/	Explore a uniform data set for drug repositioning comprising three different types of entities: drugs, proteins and side effects, and associated relationships.	(509)
ReDO_DB	http://www.redo-project.org/db/	Search a curated listing of non-cancer drugs that have shown some evidence of anticancer activity.	(68)
ReFRAME	https://reframedb.org/	Explore pharmaceutical and biological properties of 12,000 molecules, and associated screening data.	(510)
repoDB	http://apps.chiragjpgroup.org/repoDB/	Search a standard set of drug repositioning successes and failures to benchmark computational repositioning methods.	(511)
RepurposeDB	http://repurposedb.dudleylab.org/index	Search a collection of repurposed drugs, drug targets and diseases, which was assembled, indexed and annotated from public data.	(512)
SuperDRUG2	http://cheminfo.charite.de/superdrug2/	Search 4,600 approved drugs, annotated with regulatory details, chemical structures, drug targets, physicochemical properties, side effects, pharmacokinetics and drug–drug interactions.	(513)

Furthermore, interviewees emphasized that **for-profit organisations**, especially large pharmaceutical companies, are much **more reluctant** to share proprietary data and knowledge about discontinued or approved products, presumably because this could limit their chances of obtaining return on investment.

> *"There are lots of times more incentives not to share than to share." (Interview J)*

> *"Big companies are much more hesitant […] to share information of any kind, even though the benefits are really obvious to us." (Interview G)*

In view of that, interviewees noted that the willingness of pharmaceutical developers to share data and information via open or controlled access databases or platforms might **depend on the commercial viability of a product**. In addition, one interviewee suspected that pharmaceutical companies might also be less willing to share certain data about approved medicines because they want to **limit exposure to possible liabilities**, which could entail the risk of losing the marketing authorisation.

> *"I think the concern from the pharmaceutical company's points of view is that they may be exposing themselves somehow or another to liabilities." (Interview I)*

In **research domains where the commercial interests and competitive pressure is low**, for example in neglected tropical diseases, data sharing might be more common and better organised than in domains where there is a lot of competition to develop innovative products (*e.g.*, oncology).

> *"In our field, in neglected tropical disease, it's really important because resources are so limited that […] duplicating effort is really a very bad idea. So, that's why we do as much data sharing as we do." (Interview M)*

To protect and keep control over their data, several industry representatives stated that pharmaceutical developers prefer to publish data and knowledge through patent literature or controlled access models instead of providing data in open access databases. As a rule, interviewees mentioned that they would be more willing to share data if there is a **formal agreement between involved parties and a clear objective for sharing the data**. For example, most large pharmaceutical companies do not share their data in open access databases but they often have an online research portal where external researchers can submit a request for specific non-clinical or clinical data relevant to their research objectives, which is reviewed by a specific committee on a case-by-case basis.

> *"Opening up everything […] doesn't take you very far unless you do it with a very particular purpose." (Interview K)*

Overall, researchers from industry and non-industry organisations appear to be willing to publish and share an analysis of their results but the complete set of raw data is rarely shared. Several industry representatives also referred to **public assessment reports for approved medicines** as an important source of information. These assessment reports are generated by regulatory authorities upon marketing authorisation of a product and are usually available via their website (*e.g.*, European Public Assessment Reports by the EMA (174,175) or Drug Approval Packages by the FDA (176)). The format and contents of these reports vary between countries but they generally contain summaries of non-clinical and clinical study reports, authorisation details, product information, the scientific rationale for approval and the assessment history (including any variations or extensions of the product label).

STRATEGIC PARTNERSHIPS IN DRUG REPURPOSING RESEARCH AND DEVELOPMENT

Collaborative models such as **multi-stakeholder public-private partnerships (PPPs)** are emerging in all disease areas and across all disciplines of drug development, and could significantly facilitate data sharing throughout the development of a repurposed medicine (37,39,47,172,177,178). All interviewees viewed PPPs as **win-win collaborations** that may promote sharing of knowledge, expertise and resources between different stakeholders, which enables complementarity and increases the scale, speed and quality of the research. While researchers in academia, university hospitals, not-for-profit research organisations or small biotech companies can share their profound expertise in disease biology or provide access to their specialised research facilities, large pharmaceutical companies can engage by opening up their internal compound libraries and sharing unpublished clinical and non-clinical data for repurposing candidates. Large companies can also offer expertise and resources to facilitate clinical translation, market access and commercialisation of repurposed medicines, whereas academia or small biotech companies typically lack these capabilities.

> *"In the end, both parties profit because everybody does what he does best: innovation and development. Big pharma is best in doing clinical trials, marketing, etc.: everything that costs wagonloads of money and needs a lot of organisation. Small companies and universities are better in innovation that comes out of unrestricted thinking, creativity." (Interview K)*

For a PPP to be successful, it is imperative to establish a clear memorandum of understanding, common objectives, a comprehensive data management plan and adequate legal agreements that **align priorities and protect the interests from all involved stakeholders**. Interviewees recommended various models for sharing and pooling IP rights including patent pools, in- and out-licensing agreements in exchange for royalties and open innovation models. Interviewees highlighted that **private partners are less likely to engage in PPPs if there is no business case** to be made, except maybe with the intention of promoting social corporate responsibility or when public funding is involved. In addition, an industry representative was of the opinion that the bureaucracy in the public sector is an important hurdle in setting up PPPs.

Several **government-sponsored PPPs** have already been established to identify new uses for discontinued or shelved compounds (37,179–182). The UK Medical Research Council (MRC) Mechanisms for Human Diseases Initiative was launched in 2011 to provide academic researchers access to discontinued AstraZeneca compounds. In 2012, the US NIH launched the NCATS Discovering New Therapeutic Uses for Existing Molecules initiative to crowdsource repurposing hypotheses across a broad range of human diseases for a selection of discontinued compounds from eight pharmaceutical companies (*i.e.*, Abbott, Bristol-Myers Squibb, GlaxoSmithKline, Johnson & Johnson, Sanofi, AstraZeneca, Eli Lilly and Pfizer). In both partnership programs, the MRC and NCATS functioned as intermediaries to facilitate the collaboration between academic researchers and pharmaceutical companies, for example by providing template agreements (183,184). Frail and colleagues describe the progress and learnings from both pilot programs in greater detail (37). In Europe, the Innovative Medicines Initiative (IMI) pilot programme on a clinical compound bank for repurposing was established to investigate the therapeutic potential of nine shelved clinical compounds from AstraZeneca and Servier in new clinical indications in specific areas of high unmet need.

Moreover, the US Clinical and Translational Science Awards (CTSA) Pharmaceutical Assets Portal created the infrastructure and mechanisms to facilitate industry-academic collaborations for identifying new uses for shelved compounds (180,185). The US-based Learning Collaborative combines resources and expertise from the US NIH Chemical Genomics Center and its Therapeutics for Rare and Neglected Diseases program, The Leukemia & Lymphoma Society, and University of Kansas Cancer Center to efficiently identify and develop new therapies for blood cancers, for example, by repurposing approved or shelved compounds (186). The REPO-TRIAL, a European collaborative research project funded by the Horizon 2020 programme, aims to improve the efficacy and precision of predicting new purposes for approved drugs through *in silico* drug repurposing tools (187). Finally, **several well-established global PPPs with a primary focus on neglected diseases** have shown interest in drug repurposing as well (*e.g.*, the World Intellectual Property Organization (WIPO) Re:Search consortium, the Drugs for Neglected Diseases initiative (DNDi) and the Medicines for Malaria Venture (MMV)) (177,188–190).

DISCUSSION

Because of the continuous research and development efforts of the entire medical community, the number of approved and investigational compounds that could be repurposed for new indications is growing rapidly, as is the data and knowledge associated with these compounds. To guide and facilitate future research and development of repurposed medicines, we **summarized and depicted the key stages of drug repurposing in a streamlined process** (Figure 6), emphasizing the importance of cross-disciplinary and translational research. The process consists of four consecutive stages: (i) the identification and prioritisation of candidates, (ii) the validation and selection of the best candidate(s), (iii) the translation of the repurposing hypothesis into clinical research and (iv) the clinical adoption of a successfully repurposed medicine. Under certain circumstances, it may be appropriate or justified to deviate from the stages in this process (*e.g.*, in case data is already available or in an urgent situation).

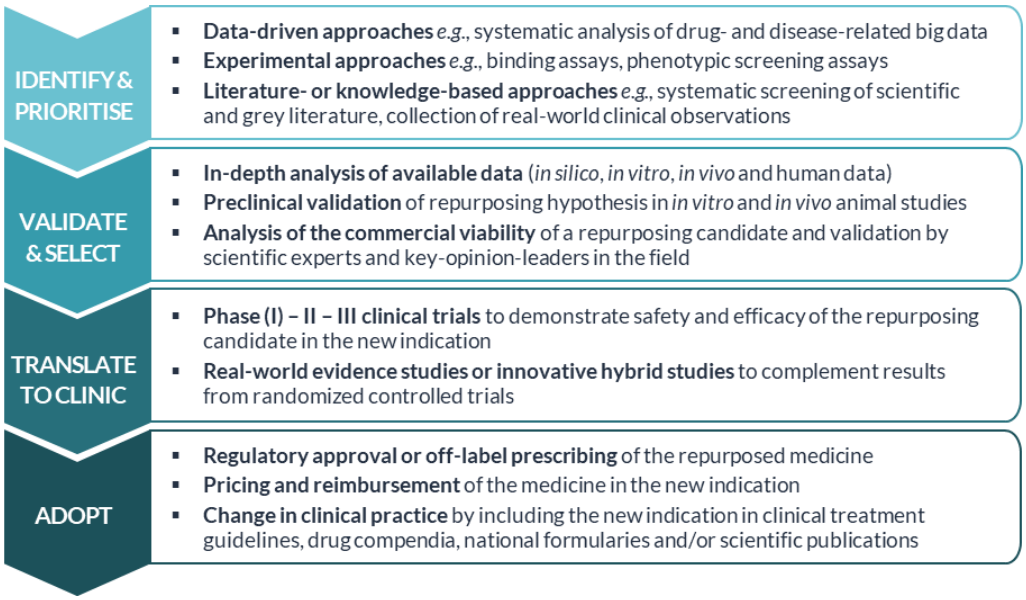


FIGURE 6. KEY STAGES IN DRUG REPURPOSING RESEARCH AND DEVELOPMENT
The research and development of repurposed medicines comprises four important stages: (i) identification and prioritisation of repurposing candidates, (ii) validation and selection of viable candidate(s), (iii) translation of the repurposing hypothesis into clinical research, and (iv) clinical adoption of a successfully repurposed medicine.

Several other key findings can be derived from this study. First, **data relevant to the repurposing of existing medicines are dispersed among many different sources, in non-standardized formats** (104,124,191,192). Innovative computational tools could be used to integrate and analyse these data. However, the accuracy of computational predictions and models is contingent upon the availability, the accessibility and the quality of the underlying data. Therefore, researchers have highlighted the **need for reliable platforms** that collect, integrate and carefully annotate data from various sources and convert it to standardized, searchable formats (32,193). This need is not specific to drug repurposing but is in fact gaining attention in all research settings, as illustrated by the development of the FAIR Data Principles (*i.e.*, Findability, Accessibility, Interoperability, and Reusability) (194). To address the need for integration and interoperability of myriad biomedical data sources, the US National Institutes of Health (NIH) NCATS launched the Biomedical Data Translator program in October 2016 (195).

Second, **RWE derived from RWD** plays an increasingly important role in the various research and development stages of repurposed medicines. Retrospective analyses of patient data from insurance or payer databases, medical records or patient registries could be used for generating and validating drug repurposing hypotheses (106). Additionally, RWD could potentially be used as (historical) controls for single arm trials and regulatory authorities are increasingly looking into the value of RWE to support regulatory decision-making. However, several challenges with regard to the quality and the heterogeneity of the data, the interpretation and valuation of real-world endpoints and privacy-related concerns remain to be addressed (158,159,161,162,196). Of note, the FDA and the NIH recently launched a web-based tool, called CURE ID, that enables clinicians to report real-world experience with regard to novel uses of existing drugs for infectious diseases (197). The CURE ID press release stated the following: "*the systematic collection of real-world experience in the app will help identify drug candidates for additional study, encourage further drug development, and may serve as a resource for practitioners making individual patient treatment decisions in the absence of established safe and effective options.*"

Third, it is notable that the **commercial viability of a repurposing candidate often runs counter to its "developability"**. On the one hand, product changes such as a different route of administration, a different dose or new (fixed) combinations for the benefit of patients can create an exclusivity position by making off-patent repurposing candidates less substitutable. However, product changes also come with more requirements to generate preclinical and phase I clinical data before these repurposing candidates can be moved into clinical proof-of-concept trials. On the other hand, investigational compounds, which never entered the market before, can be more easily protected from competition through regulatory exclusivities and additional IP rights (33,46,198). Yet, the available data for such investigational compounds are usually limited to preclinical and early (phase I - II) clinical studies, whereas marketed medicines have a large body of preclinical, clinical and RWD that can be used for the development of new indications.

Fourth, even though interviewees acknowledged that **data sharing** could improve the quality and reduce duplication of drug repurposing research, they emphasized that it is a **delicate topic**, especially when it comes to the sharing of clinical trial and patient-level data. Nonetheless, numerous initiatives have been introduced in recent years to increase data transparency, which could benefit drug repurposing strategies. For example, both non-commercial and commercial sponsors are increasingly expanding access to data

from clinical trials, including participant-level data, either via their own research portals or via independent initiatives such as the Yale Open Data Access (YODA) initiative or the Project Data Sphere platform in cancer (199–203). Furthermore, regulatory agencies such as the EMA and the FDA are also taking significant steps to improve transparency with regard to clinical trial data underpinning regulatory approval (204–206).

Fifth, the substantial amount of available data and knowledge is an important benefit of drug repurposing but at the same time, adds a layer of complexity. To effectively make use of the available data, a multidisciplinary team of researchers is needed. **Multi-stakeholder PPPs** create opportunities to bring together a wide variety of stakeholders with a common interest in repurposing existing medicines (*e.g.*, the pharmaceutical industry, researchers from academia and research institutes, bioinformatics experts, health care professionals, patients and patient advocacy groups, regulatory and payer agencies). PPPs could provide a structured framework to **align priorities, efficiently share data and resources, and safeguard different stakeholder interests** (32,188). Several PPPs have already been initiated to facilitate the research and development of repurposed compounds, especially in the precompetitive setting with a focus on experimental or shelved assets (37,179–182). It is important to note though that it has proven particularly difficult to involve pharmaceutical companies in a PPP if there is no business case for the repurposing candidate(s), unless in disease domains where the competitive pressure to develop new treatments is low or when there is sufficient public funding available.

The current study provides some interesting new insights into different aspects of the research and development of repurposed medicines but it was exploratory in nature and therefore has **three main limitations**. First, due to the variety of targeted stakeholder groups and the international scope, the interviews were not conducted until data saturation was reached. Nonetheless, the multi-stakeholder and international approach allowed us to capture a wide range of insights about the research and development of repurposed medicines from various perspectives. Second, this study applied qualitative research methods (*i.e.*, semi-structured interviews). Therefore, our results do not allow us to quantify the participants' perspectives and we cannot draw any definite conclusions about potential links between stakeholder group and the willingness to share data. A follow-up quantitative study, through surveys for example, could be useful to investigate this in more detail. Third, the scope of this study was rather broad, thus making it difficult to achieve an in-depth understanding of the many topics that were discussed. However, literature was searched extensively to substantiate and clarify the various concepts mentioned by the interviewees.

CONCLUSION

The present study highlighted that **data availability is essential to unlock the potential of drug repurposing**. While innovative technological and computational advances could significantly accelerate the evidence-based prioritisation and selection of repurposing candidates, data need to be available, accessible and of sufficient quality to make optimal use of these technologies. Numerous web-based databases and platforms to share data already exist, most of which even offer advanced computational functions to predict repurposing opportunities (Table 5). However, given the wide array of platforms, which offer diverse functionalities and comprise different datasets, researchers may find it difficult to select the right platform to achieve their research objectives. A transformative improvement in drug repurposing research would therefore be to create **an international, standardized, all-encompassing platform** that integrates the diverse capabilities and datasets from existing platforms. Furthermore, study participants emphasized the importance of RWD for generating repurposing hypotheses and for supporting regulatory approval with repurposed medicines. Yet, challenges with regard to the quality and the accessibility of RWD remain to be addressed.

CHAPTER 4

Innovative mechanisms to fund clinical drug repurposing research

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New mechanisms to fund independent clinical trials for repurposing off-patent or generic medicines.

ABSTRACT

Finding new therapeutic uses for approved, off-patent or generic medicines could lead to safe, affordable and timely new treatment options for patients with high medical needs. However, due to a lack of economic incentives, pharmaceutical developers are rarely interested to invest in this type of research. Consequently, potential new uses for off-patent or generic medicines are mainly studied in independent proof-of-concept clinical trials initiated and led by researchers from academia, research institutes or collaborative groups. Yet, these researchers need additional financial support to conduct expensive phase III clinical trials to confirm the results from exploratory research. In this study, scientific and grey literature was searched to identify and evaluate new mechanisms for funding clinical trials with repurposed medicines. Semi-structured interviews were conducted with 16 European stakeholders with expertise in clinical research, funding mechanisms and/or drug repurposing between November 2018 and February 2019 to consider the future perspectives of applying new funding mechanisms. Traditional grant funding awarded by government and philanthropic organisations or companies is well known and widely implemented in all research fields. In contrast, the application potential of newer mechanisms to fund independent clinical research, such as social impact bonds or crowdfunding, is not yet known. Interviewees stated that there is a substantial need for additional financial support in health research, especially in disease domains where there is limited commercial interest. However, the implementation of new funding mechanisms is facing several practical and financial challenges, such as a lack of expertise and guidelines, high transaction costs and difficulties to measure health outcomes. Furthermore, increased collaboration and centralisation at a European and international level is recommended to make clinical research more efficient and reduce the need for additional funding. New funding mechanisms to support clinical research may become more important in the future, but the unresolved issues warrant further exploration.

INTRODUCTION

Drug repurposing means finding new therapeutic indications for existing medicines and covers at least **four different scenarios** (33,34). First, drug repurposing can refer to identifying new uses for **unapproved, shelved compounds** that initially failed in clinical trials for another indication, usually due to a lack of efficacy, or that are discontinued for commercial reasons. Pharmaceutical developers are increasingly interested in this type of drug repurposing, also called drug rescue, because the clinical development is partly de-risked and the medicine can often be protected through new or additional intellectual property (IP) claims (*i.e.*, patents for second and further medical uses) and regulatory exclusivities (36,37). Second, pharmaceutical developers continuously monitor and investigate potential new uses for **approved medicines that are still under patent or regulatory protection**. Developing new uses for innovator products may expand the patient population while delaying generic or biosimilar competition, and falls within a company's drug life cycle management programs (38,39). Third, sometimes a **new dosage form, route of administration, strength, fixed combination or formulation of the existing medicine** is needed for use in a new therapeutic indication. Such changes may generate new IP and can enable a pharmaceutical developer to rebrand a product for its new use, making it a commercially interesting repurposing opportunity (40–42). A fourth scenario covers the repurposing of **approved medicines that are out of basic patent or regulatory protection and that do not require any significant product changes**, which is sometimes referred to as "off-patent drug repurposing" (43). A major benefit is that the pharmacokinetics, pharmacodynamics and toxicity profiles of approved medicines are well-known, so the new use can more easily be translated into Phase II/III clinical trials (32,59,207,208). Off-patent small molecule medicines are widely available and relatively cheap owing to generic competition, which facilitates clinical research and enables timely and affordable access for patients by prescribing the medicines off-label (49,209,210). However, return on investment (ROI) is expected to be low or absent in this last scenario due to a lack of economic incentives (38,39). Pharmaceutical developers and their shareholders are therefore rarely interested to invest in repurposing opportunities for off-patent or generic medicines, essentially making these medicines 'financial orphans' (70,84).

Due to this lack of commercial interest, **new uses for off-patent and generic medicines are mainly studied in independent clinical trials** initiated and led by researchers from academia, research institutes or collaborative groups (68). These trials are typically supported by public and philanthropic funds and aim to answer clinical questions that have an important impact on public health and patient needs but that are not addressed by industry-led trials (211,212). Synonyms include academic, non-commercial, physician-led, investigator-driven, investigator-initiated, investigator-sponsored or publicly funded clinical trials (213). So far, researchers have been running numerous small proof-of-concept trials (*i.e.*, phase I or II) to test the activity and safety of approved medicines in new therapeutic indications. The next step should be to confirm the results from exploratory trials in large confirmatory randomized controlled trials (RCTs) to avoid unproven off-label use of medicines based on low levels of clinical evidence (85). However, confirmatory RCTs are expensive, time-consuming and labour-intensive, and a lack of funding remains one of the most important barriers for initiating and completing these studies (214–216). The average cost of a phase III clinical trial is difficult to establish as it depends on many factors and varies across therapeutic areas. In a study on pharmaceutical trials in the USA between 2004–2012, the cost of phase III trials ranged from US$11.5 million (dermatology) to US$52.9 million (pain and anaesthesia) (216,217). Even if

we assume that an investigator-driven trial with approved medicines is less expensive than an industry-led trial with new medicines, for which the median cost was estimated at US$19 million (218), investments would still need to be substantial (189). Therefore, additional financial support is needed to conduct robust, phase III clinical trials that address the translational gap in off-patent drug repurposing (18,207).

The **aim of this study** was to search scientific and grey literature to identify and examine potential new mechanisms to fund clinical off-patent drug repurposing research. Moreover, we considered various perspectives on the application potential of the proposed funding mechanisms in Europe by conducting semi-structured interviews with European stakeholders.

METHODS

Literature was searched to identify and explore innovative models for organising and funding clinical drug repurposing research. Scientific literature was searched in MEDLINE (via PubMed) and Embase databases using search queries consisting of MeSH terms and key words in title and abstract (Appendix C). Only articles published between January 2010 and November 2019, in English, of which the full-text publication was available were selected. Moreover, additional literature was hand searched to clarify the structure, involved stakeholders, advantages, disadvantages and previous applications of the identified funding mechanisms for independent clinical research. Grey literature and publications from reference lists of the identified literature were also included.

Stakeholders with knowledge about clinical research, research funding mechanisms and/or drug repurposing were invited to participate in a **semi-structured interview** to identify new funding models and explore their application potential in Europe. Study participants were identified from author lists of scientific publications or grey literature and via the network of the research group and were selected via purposive sampling (101). Twenty-six people were contacted via e-mail and received an information sheet describing the objectives and design of the study. An interview guide was developed based on background information from scientific literature (Appendix D). Questions related to the following topics: i) the need for new finance models to support independent clinical research, ii) interviewees' experience with new finance models (i.e., public-private partnerships, social impact bonds, crowdfunding, other), iii) stakeholders' role in selected models, iv) advantages, disadvantages and risks of selected models, and v) the future role of new funding models for independent clinical research.

The interviews took place between November 2018 and February 2019. First, two pilot interviews were performed in the presence of the three interviewers with a background in pharmaceutical and biomedical sciences to optimize the interview guide and to standardize the interview approach. The subsequent interviews were conducted in pairs or individually by the same interviewers, either face-to-face in the workplace of the participant or via phone or video call. The interviews were carried out in English or Dutch, and lasted about 30 to 45 minutes each. All interviews were audio-recorded with informed consent from the study participants and transcribed *ad verbatim* and pseudonymized to protect participants' personal information and ensure confidentiality. The interview transcripts, together with field notes, were analysed based on the **framework analysis method** using the NVivo qualitative data analysis software (102,103).

RESULTS

Based on the literature review, **four potential mechanisms for funding independent clinical research with off-patent or generic repurposed medicines** were identified and are summarized in Figure 7. Next, fourteen interviews were conducted with sixteen participants (two interviews involved two study participants simultaneously) to learn more about the application potential of such models in Europe. Interviewees represent various stakeholder groups, including not-for-profit or governmental organisations (N = 6), university hospitals and academia (N = 5), pharmaceutical industry (N = 2), a private bank (N = 1), a consultancy company (N = 1) and a health technology assessment body (N = 1) (Table 6).

TABLE 6. CHARACTERISTICS OF INTERVIEW PARTICIPANTS

INTERVIEW	STAKEHOLDER GROUP	COUNTRY
A	Academia	Ireland
B	University hospital	Belgium
C	Not-for-profit research organisation	The Netherlands
D	Consultancy & private bank (2 participants)	Belgium
E	Not-for-profit organisation	The United Kingdom
F	Not-for-profit organisation	Belgium
G	Health technology assessment body	Belgium
H	Not-for-profit research organisation	Belgium
I	University hospital	Belgium
J	Governmental funding organisation	The Netherlands
K	Academia	Belgium
L	Not-for-profit research organisation	Belgium
M	Academia	Belgium
N	Pharmaceutical industry (2 participants)	Belgium

GRANT OR DONATION-BASED FUNDING MECHANISMS

TRADITIONAL GRANT FUNDING

The best-known mechanism to fund independent clinical trials is through **grant funding programs**, which typically involve a funding body and numerous applicants (*i.e.*, academia and research institutes). Funding can come from different sources, such as government agencies, not-for-profit and philanthropic organisations, universities, research foundations and pharmaceutical companies. In most cases, the research project should meet specific criteria to be eligible for the grant, and a project proposal has to be submitted for review by a committee of scientific experts and, sometimes, patients.

Even though grant funding is well established in all types of research, it has **several limitations**. Most importantly, grant funding programs are highly competitive and the available funds are limited (219). Funding applications for clinical trials with off-patent or generic medicines in new therapeutic indications are often at a disadvantage because drug repurposing is not considered sufficiently innovative. *"Innovation in science and medicine is often measured by creation of something new, not by repurposing something old and available"* (9). However, Dr Richard Thompson from Findacure defended the innovative nature of drug

repurposing in his paper for Medical News (220): *"Innovation is also equally about innovative ideas – finding new ways to deliver a service or improved ways to use current resources. Drug repurposing is an excellent example of this form of innovation: using a scientific approach to identify new uses for existing drugs"*.

Not-for-profit organisations, government agencies and pharmaceutical companies are increasingly awarding **grants specifically focused on clinical drug repurposing research** in all disease areas (Table 7) (47,53,73,79,221). For example, the Anticancer Fund, a Belgian-based not-for-profit organisation scientifically and financially supports independent clinical trials with off-patent or generic repurposed medicines in cancer patients, and recently launched a call for research proposals together with the Swiss Rising Tide Foundation for Clinical Cancer Research (222). CuresWithinReach and the Michael J. Fox Foundation, two US-based not-for-profit organisations, have also awarded multiple grants for investigating new therapeutic uses of existing medicines in various disease areas (223,224). Moreover, several government organisations, such as the Belgian Healthcare Knowledge Center (KCE), the Dutch ZonMw and the UK National Institute for Health Research (NIHR), have included drug repurposing as a focus area in their calls for funding of independent clinical research (225–227). Some pharmaceutical companies also provide grants to support investigator-initiated clinical research with their approved medicines (228–232). Bayer even ran a specific 'Grants4Indications' program that provided grants and further financial support to explore new therapeutic indications for their own compounds (233).

Interviewees highlighted the need for **additional government funding to support independent research in all areas where there is market failure** due to a lack of incentives and ROI. Besides for the repurposing of off-patent or generic medicines, funding is needed for the research into new treatment options for rare, paediatric and neglected diseases, psychotherapy research, research on surgical techniques, clinical trials with diet and life-style interventions, development of new antibiotics, and post-marketing trials to optimize existing treatments.

> *"The trick is of course to think of areas where things are not going well. […] Only if there were a real market failure, you would have to look for other ways to finance this, through government funding in my case." (Interview J)*

Several interviewees also mentioned the **increased need for a top-down or demand-oriented approach** in which governments identify the most important unmet needs in healthcare, and allocate research funding accordingly. A more active role of patient organisations in raising and allocating funds for independent research into treatment options addressing the highest patients' needs was also mentioned several times during the interviews. However, interviewees argued that not every patient organisation is equally well organised, and that not every disease is well represented, which is especially a problem for (ultra-)rare diseases.

Finally, some interviewees were concerned that a clinical research project that was funded with public money, once de-risked, may be taken over by a pharmaceutical company and end up in for-profit development.

> *"Traditional grant funding can work. […] You have to rebuild a strong case based on the science for that and that can also deliver, but tends to end up reeling down to pharmaceutical pathway ultimately, so ends up generating the pharma profits." (Interview E)*

TABLE 7. FUNDING OPPORTUNITIES FOR INDEPENDENT CLINICAL REPURPOSING RESEARCH

Funding source	Organisation	Name of funding opportunity*	Available funds	Duration of research	Geographic area	Disease area
Government organisations	Belgian Healthcare knowledge center (KCE) (BE)	KCE investigator-led trials	€10,000,000 per year, no defined max. amount per project	Results preferably within 5 years	International study possible under certain conditions	All
	ZonMw (NL)	Goed Gebruik Geneesmiddelen – Drug Rediscovery	Max. €1,000,000 per call	Not specified	International study possible if chief investigator and lead institution are NL-based	All
	National Institute for Health Research (NIHR) and Medical Research Council (MRC) (UK)	19/136 Call for Evaluating interventions for the diagnosis and treatment of autoimmune diseases	Case by case negotiations	Not specified	International study possible if chief investigator and lead institution are UK-based	Autoimmune diseases
Companies	Bayer	Grants4Indications	Case by case negotiations	Max. 2 years	International	All
	CuresWithinReach	ReGRoW Pilot	US$ 25,000 - 50,000 per project	12 – 36 months	Low and lower-middle income countries (LMICs)	Any unsolved disease in LMICs
Not-for-profit organisations	Michael J. Fox Foundation	Therapeutic Pipeline Program	US$2,000,000 per project	2 - 3 years	International	Parkinson's disease
	The Anticancer Fund (ACF) and Rising Tide Foundation for Clinical Cancer Research (RTFCCR)	The RTFCCR/ACF Multi-arm Clinical Trial Award	US$ 3,000,000 in total	Not specified	International	Cancer

* Non-exhaustive list of research calls with a focus on drug repurposing between January 2017 and January 2020

CROWDFUNDING

An alternative model to fund independent clinical research is by raising small donations from a large number of people via online platforms or portals, which is called crowdfunding (Box 4.1, Figure 7). One of the major **benefits of crowdfunding** for clinical research is the opportunity to raise funds for innovative projects with a potentially high societal or patient impact but low commercial return, as is the case for repurposing off-patent or generic medicines. The NeoART study, a phase II RCT investigating the efficacy of the anti-malarial agent artesunate in colorectal cancer, is an example of a drug repurposing project that collected funds (£54,247) through a crowdfunding campaign on FutSci.com (234). Additionally, crowdfunding enables patient and public engagement in prioritizing clinical research goals and increases public awareness of research needs (235,236). Crowdfunding can be particularly interesting for early-career investigators, who usually have a lower chance of success in competitive grant programs (237,238).

BOX 4.1 | CROWDFUNDING: BASIC PRINCIPLES

Crowdfunding can be either reward-based, equity-based or donation-based depending on the return that is offered to the funders (243). Donation-based crowdfunding is most relevant to fund independent clinical research where financial ROI and other rewards are lacking. A donation-based crowdfunding model typically involves three types of stakeholders: the project initiator (in this case a research organisation seeking funding to conduct a clinical trial), the donors, and the online platform provider. Campaigns to fund clinical research can either be hosted on general-purpose (*e.g.*, Indiegogo.com, Kickstarter.com) or research-focused crowdfunding platforms (*e.g.*, Experiment.com, Consano.org). Each campaign features a description of the research project in lay language, a monetary goal, and an indication of how close the campaign is to meeting this goal. Most campaigns specify a limited period to accept contributions. Some campaigns adhere to an "all-or-nothing" or "fixed-funding" model, meaning that donations are kept only if the monetary goal is met or exceeded.

However, some **practical limitations and ethical concerns** regarding crowdfunding for clinical research have been raised. First, setting up a successful crowdfunding campaign can be time-consuming and challenging as it requires a lot of strategic planning and a multidisciplinary support team (237). High overhead and administrative costs, including transaction costs of platforms, can make crowdfunding efforts less efficient (239). One interviewee, having had experience with setting up crowdfunding campaigns, confirmed this challenge.

> *"We've run a few crowdfunding campaigns ourselves […] they are lots of hard work for limited success." (Interview E)*

The **success of a crowdfunding campaign is not guaranteed.** For example, in 2015, Sharma *et al.* identified twenty campaigns for clinical research, of which seven were still ongoing. Of the thirteen completed campaigns, only eight (62%) reached their financial goal. The funds raised in these campaigns ranged from US$3600 to about US$3 million, with an average of US$540,000, and a median of US$167,000 (240,241). An inconclusive or negative trial outcome could also erode public trust (242).

Previous research suggests that crowdfunding could be a **viable model to support small proof-of-concept trials**, but would not be sufficient to fund larger RCTs (238,243). All interviewees agreed that large clinical trials are too expensive to fund via a crowdfunding approach. Still, it could be used to de-risk early-stage projects and thus increase their chance of success in obtaining traditional research grants (240,241,243).

> *"Clinical trials are expensive, so getting that amount in a crowdfunding effort is close to impossible." (Interview H)*

Furthermore, research that receives the most funds via crowdfunding may **not always address the highest unmet medical needs**. A US-based survey showed that researchers working on therapies for rare and/or age-related diseases will have more difficulty to reach their financial goal in crowdfunding campaigns than others (244). Two interviewees pointed out that research into rare diseases is at a disadvantage in crowdfunding campaigns because fewer people have an emotional connection to such diseases.

> *"Because conditions are rare, there isn't a huge public understanding of many of the conditions and probably not a huge public understanding of what is needed to deliver research either, so I think that makes it a challenging route and certainly not sustainable route." (Interview E)*

Additional ethical concerns of crowdfunded research, which were not mentioned by the interviewees, include a lack of control over the quality, scientific integrity and feasibility of crowdfunded research (235,237,239,242).

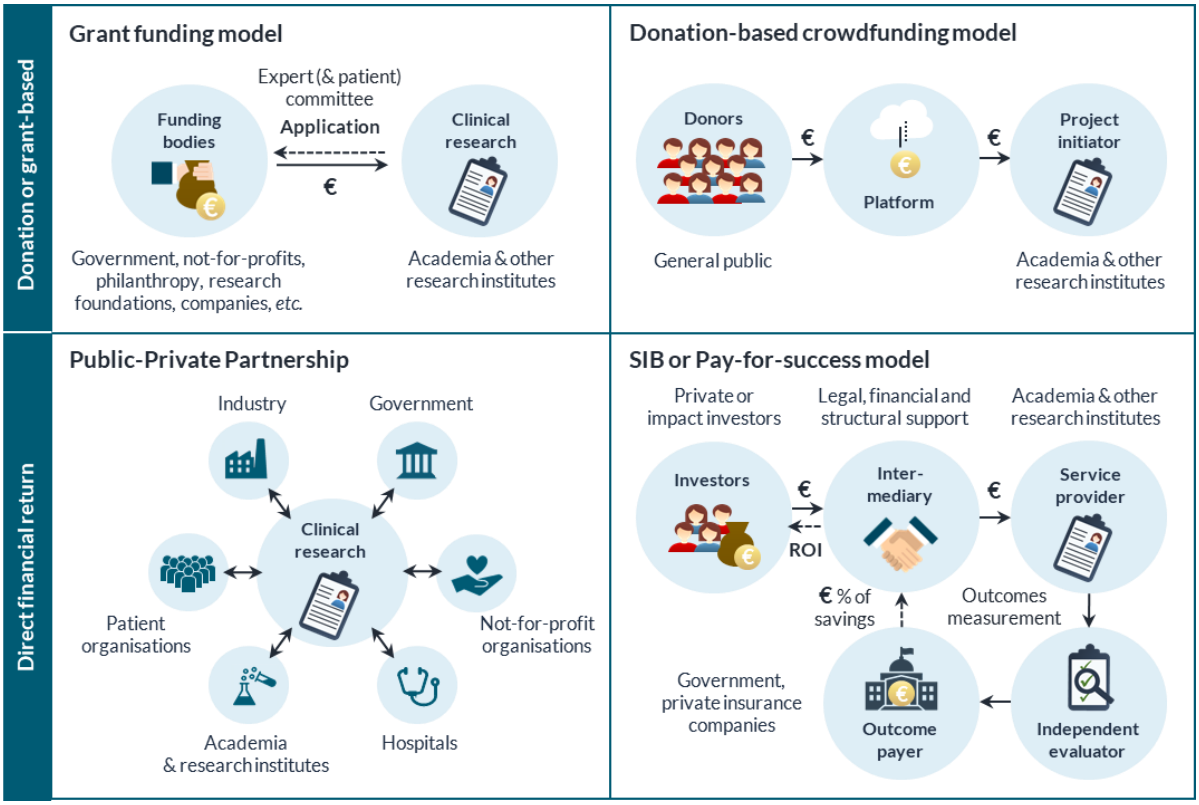

FIGURE 7. OVERVIEW OF MECHANISMS TO FUND CLINICAL DRUG REPURPOSING RESEARCH
Abbreviations: Social Impact Bond (SIB); Return On Investment (ROI)

MECHANISMS WITH A DIRECT FINANCIAL RETURN

PUBLIC-PRIVATE PARTNERSHIPS

A public-private partnership (PPP) is a collaboration between at least one public partner and one private partner with a common goal, for example improving health outcomes. **PPPs** are no longer a new concept in the healthcare sector and have been established to **serve many different purposes** (245,246). Some PPPs tackle specific precompetitive issues, while others focus more on development or access to medicines. The structure of each PPP may vary depending on the involved stakeholders, such as the pharmaceutical industry, academia, government, not-for-profit organisations, hospitals, research and patient organisations (Figure 7). Multi-stakeholder PPPs allow synergies and sharing of knowledge, expertise and resources between all partners. A PPP can be seen as a win-win model that aims to reduce development costs, to increase the scale and scope of the research, and to share the financial risks of drug development between all partners (189). Consequently, PPPs have been proposed as a potential model to facilitate and fund drug repurposing research (186,247).

Indeed, various **PPPs have been established between academic researchers, public funders and the pharmaceutical industry to support drug repurposing research**, but most are situated in the precompetitive space and focus on the repurposing of shelved compounds. Examples include the UK Medical Research Council (MRC) Mechanisms for Human Diseases Initiative, the US National Center for Advancing Translational Sciences (NCATS) Discovering New Therapeutic Uses for Existing Molecules initiative, the US Clinical and Translational Science Awards (CTSA) Pharmaceutical assets Portal and the EU Innovative Medicines Initiative (IMI) pilot programme on a clinical compound bank for repurposing (37,180). In the product development area, there is one US-based PPP between the Therapeutics for Rare and Neglected Diseases program of the US National Institutes of Health (US NIH) Chemical Genomics Center, The Leukemia & Lymphoma Society, and University of Kansas Cancer Center, which is called The Learning Collaborative. This partnership repurposed auranofin, an off-patent medicine initially approved to treat rheumatoid arthritis in the mid-1980s, for the treatment for relapsed chronic lymphocytic leukaemia (186). Moreover, the UK-based aPODD foundation is open to supporting partnerships in drug repurposing projects for paediatric oncology indications (248) and the Dutch Fair Medicine foundation proposes a coalition model between patient associations, hospitals, researchers, health insurers, large and small investors and pharmaceutical developers to develop sustainable and affordable medicines, including repurposed medicines (79).

Despite the many potential benefits of PPPs, interviewees argued that they **do not offer a sustainable solution for off-patent drug repurposing due to the lack of incentives for the private partners**. Social corporate responsibility was mentioned as a potential reason for companies to participate in such a PPP but this was not deemed as sufficiently motivating, unless in areas where the competitive pressure is low, for example for finding new treatment options for neglected diseases in low- and middle income countries (LMICs) (59). The Drugs for Neglected Diseases initiative (DNDi) and the Medicines for Malaria Venture (MMV), both well-established global PPPs, already included several rescued and repurposed medicines in their research portfolios (188–190).

SOCIAL IMPACT BONDS OR PAY-FOR-SUCCESS MODELS

A social impact bond (SIB) is an **innovative model that leverages private investments to develop public health services or interventions**. A SIB, also referred to as pay-for-success financing, is a formal agreement between an outcome payer (typically a government, payer or private insurance company) and a service provider (in this case a not-for-profit or research organisation seeking funding to conduct one or more clinical trial), where the outcome payer specifies a desired outcome and guarantees to pay back the investors their upfront investments plus a return if this outcome is reached (Box 4.2, Figure 7). So far, SIBs have predominantly been applied to fund preventive health measures that could result in significant long-term health care savings (249,250). The UK-based organisation Findacure started exploring a **SIB model to incentivize investment into drug repurposing clinical trials** in rare diseases, in collaboration with various organisations including CuresWithinReach, Mission:Cure, Numbers4Good and Costello Medical (79,221,250–252). More specifically, the goal of this Rare Disease Drug Repurposing SIB is to create a portfolio of up to ten phase II efficacy clinical trials that, if successful, could lead to off-label prescription of affordable repurposed medicines for patients with rare diseases who currently have no treatment. The improved outcomes and reduced care needs of those patients would then result in significant savings for healthcare systems and a proportion of these savings would subsequently be paid back by the outcome payer (in this example, the UK National Health Service) to the investors as a success payment (210). Recently, the US-based think tank Helena and its partners proposed a similar financial model to fund generic drug repurposing for Alzheimer's disease (253).

A SIB concept is a **win-win-win model** that, if successful, improves health outcomes, reduces healthcare spending and realizes economic return (254). Additionally, SIBs enable a shift in financial risk from governments to investors compared to the grant funding model, attract new sources of capital to scale up health programs and research, and stimulate not-for-profit organisations and researchers to focus on productivity and outcomes (249). SIBs could also be scaled-up to an international level to share the risks among more investors and distribute the pay-outs between outcome payers (251). SIBs are a relatively new way to fund health programs, so evidence with regard to their efficacy to support clinical research with off-patent and generic medicines is limited. Accordingly, only few interviewees had experience with SIBs, although everyone was open to the idea and recognized their potential value for off-patent drug repurposing.

Still, **several difficulties and potential drawbacks** of SIBs have been reported in literature (255), some of which were confirmed by interviewees in this study. First, not every not-for-profit program is fit for a SIB. SIBs need easily quantifiable outcomes that can be achieved in a limited time period and lead to clear government savings (255). Interviewees voiced some concerns about the identification of robust clinical outcome measures to demonstrate social impact and cost savings of a new treatment, and about the long duration and low success rates of most clinical trials.

> *"There is actually a big risk to those organisations [service providers] in getting involved if they haven't set up the measure of success well or they've been over ambitious in what they're saying they can achieve and don't deliver. They won't receive the returns they need to pay their costs." (Interview E)*

BOX 4.2 | IMPACT INVESTING: BASIC PRINCIPLES

Currently, about 441 million dollars have been raised for 138 Social Impact Bonds (SIBs) worldwide (514). The use of the term "bond", which refers to a fixed income instrument in finance circles, is somewhat misleading because the investors' return in a SIB is dependent on the success of achieving predefined outcomes (515). In fact, a SIB is more similar to a public-private partnership between private or impact investors, a service provider and an outcome payer (Figure 7) (516). Most SIBs include an intermediary to convene all stakeholders and provide legal, financial and structural support. An independent evaluator typically measures the outcomes, which are key to determine the cost savings, success payments and social impact of a project. For a SIB to be successful, outcomes should be quantifiable and should lead to clear societal and government savings.

The SIB model should not be confused with another upcoming finance model, which is called "venture philanthropy". The venture philanthropy model is based on a partnership between a charity and a drug company and provides a mechanism for not-for-profit organisations to help finance the development of a treatment in return for a share in profits, which can later be reinvested in other new treatments (79). For example, the Cystic Fibrosis Foundation invested US$150 million in Vertex Pharmaceuticals for the development of ivacaftor, and had a return of US$3.3 billion in exchange for its royalty interests (517). Even though this model may lead to promising new treatments, ethical questions have been raised about the sustainability of a model that maximizes profits using philanthropic funds (518).

Besides, establishing a SIB requires a long-term vision and the political will of governments, payers and/or insurance companies to guarantee success payments for projects that will only pay off in a couple of years (210,256). Interviewees who had experience with SIBs confirmed the **difficulty of securing commitment and resources from governments**, especially in multi-level governance and multi-payer systems.

> *"It will not be a problem to find private investments. […] I think the bottleneck is in the public funds." (Interview D)*

Finally, **statistical, legal and contracting expertise is required** for establishing a SIB, and the transaction costs and organisational burden are high. Therefore, sufficient start-up funding is needed. One interviewee was of the opinion that governments should provide administrative, legal and financial support for setting up SIBs that aim to achieve better social and health outcomes. If SIBs were to become more common, transaction costs would automatically decrease as a result of the standardization of legal forms and contracts.

> *"I think given that charities and third sector organisations are generally those organisations that are going to deliver these interventions, they don't have a huge amount of disposable income to put all of that work and infrastructure in place." (Interview E)*

Overall, interviewees believed that the potential benefits of SIBs outweigh their costs and risks, and that their **application potential at a national and international level warrants further exploration**.

IMPROVING EFFICIENCY OF INDEPENDENT CLINICAL RESEARCH

Interviewees highlighted that, in addition to exploring new funding mechanisms, **independent clinical research should become more efficient**. Even though parallelism in research may increase productivity to some extent, there is a lot of fragmentation and duplication of research efforts. Moreover, independent clinical trials are often not sufficiently powered to show evidence of clinical efficacy, probably also due to the limited funds and less organisational support compared to industry-sponsored trials.

> *"I am not saying that it's always the case, but it is a personal opinion that there is probably too much fragmentation to be very efficient." (Interview N)*

Increased national and international cooperation and consortium-building between research groups and foundations could be key to address this problem (73,172). Furthermore, interviewees mentioned that funding efforts to support clinical research, such as grant-funding programs and SIBs, should be organised at a European or international level to become more feasible and efficient.

> *"You have to organise [research funding] on an international level to reach critical mass, that is just a given." (Interview K)*

Yet, harmonisation and centralisation of independent clinical research on a European level would require the **establishment of one or more coordinating centres** or, as suggested by one of the interviewees, a multi-stakeholder review board or steering committee overviewing independent clinical trials in Europe. The European Organisation for Research and Treatment of Cancer (EORTC) was put forward several times as an ideal candidate to fulfil such a role within cancer research.

> *"We see a third partner to guide the process and to make sure that it is useful, that it is done in a correct way and that you can also make connections with European funds or with other research institutes in other countries." (Interview N)*

RCTs are still the golden standard for determining the efficacy of a medicine in a new therapeutic indication but they entail high costs, a long duration and a substantial administrative burden (160). Interviewees mentioned the potential of **optimizing clinical trial designs and methodology for drug repurposing research**. Various cost-effective and robust study designs have been proposed in scientific literature to replace or at least complement traditional RCTs, such as pragmatic and low-interventional trials (164), registry-based RCTs (257,258), N-of-1 trials for rare diseases (167), multi-arm/multi-stage or platform trials (259–261), and real-world patient data studies (157,209). Yet, further research focused on clinical research methodology is needed to explore the application potential of such study designs to drug repurposing.

> *"What is important to us to consider first, is an optimization of the methodology of the trial to be able to use other designs, other methodology, other technology that can limit the need for financing or the costs, if I may say, for the trial." (Interview N)*

DISCUSSION

This explorative study aimed to **address a key financial challenge of repurposing approved off-patent or generic medicines**, which is to find sufficient funding to conduct robust, phase III clinical trials. Even though the costs of repurposing an existing medicine are said to be lower than for developing a *de novo* compound, they are still relatively high and the development carries a lot of risk (32,151). Yet, revenues for off-patent and generic medicines are not expected to increase substantially after adding a new therapeutic indication since payers are unlikely to agree to pay a higher price for an existing medicine, which is often already prescribed off-label for the new indication. Moreover, new uses for off-patent or generic medicines are particularly difficult to protect from generic competition (49). As a result, pharmaceutical companies rarely pursue new indications after expiry of basic patent and/or regulatory protection, especially for inexpensive small-molecule medicines (38).

Researchers from academia, government and other research institutes conduct many small proof-of-concept studies to test repurposing hypotheses, but **often lack the funding to confirm their results in large (and expensive) confirmatory trials** (85). Involved stakeholders have proposed various funding mechanisms to support independent clinical research with repurposed medicines, ranging from traditional grant funding programs to highly innovative SIB models. In addition to outlining the theoretical aspects, we considered various perspectives on the potential value of such funding mechanisms in Europe through semi-structured interviews with experts in this field. **Several key learnings** about the future perspectives of the proposed funding mechanisms can be derived from this study.

First, **traditional grant funding** by government and philanthropic organisations is still the **main driver to support independent clinical trials** (53). With investments of more than US$40 billion a year, the US NIH is the largest public funder of biomedical research in the world (262). In Europe, the European Commission is supporting multinational research through its Horizon Research and Innovation programs, the last framework program 'Horizon 2020' provided about €80 billion of funding over 7 years (2014-2020) (263). Moreover, numerous national funders are investing in independent clinical research, for example the UK NIHR and MRC, the Belgian KCE and the Research Foundation Flanders (*e.g.*, via their Applied Biomedical Research with a Primary Social finality program (264)), the Dutch ZonMw, the German Research Foundation, the French Institut national de la santé et de la recherche médicale (INSERM), the Innovation Fund Denmark, and many more. However, all these programs are extremely competitive and have relatively low acceptance rates (215). Interviewees were of the opinion that governments should invest more in independent clinical research in all areas where there is market failure, not only in repurposing off-patent or generic medicines. Nonetheless, they acknowledged that the available funds are limited. One way to address this problem is for governments to prioritize research areas that aim to address the highest unmet needs in healthcare and distribute funding accordingly, possibly in consultation with patient organisations and society at large, for example via citizens workshops and questionnaires measuring societal preferences.

Second, **crowdfunding** could be an innovative way to **raise funds for early-phase clinical studies**, but it is **not sustainable to support large and expensive RCTs** (238,243). It was also argued that research funding should be based on a project's scientific merit rather than its potential to attract emotional donations

(235,239,242,265). It is therefore recommended to have all crowdfunding campaigns for clinical research reviewed by an independent ethics committee and a scientific advisory board (237,265).

Third, **multi-stakeholder PPPs** have proven to be extremely valuable in facilitating drug development over the years (245,246), but interviewees in this study cautioned that they should not be considered as the "*holy grail for solving all problems*". While several large PPPs were established to identify repurposing opportunities for shelved compounds (37,180), this model would **not be sustainable for repurposing off-patent or generic medicines due to the lack of financial incentives for private partners**. Still, lessons can be learned from successful international product development partnerships like DNDi and MMV that leverage companies' social corporate responsibility objectives to achieve their goal and typically operate in areas with low competitive pressure, like neglected diseases in LMICs (189,266).

Fourth, **SIBs** could be a **scalable source of funding for independent clinical research** and may stimulate non-profit actors to focus on relevant outcomes and address unmet needs (250). Moreover, governments, payers, private insurance companies and social security organisations could actually save money in the long term by supporting clinical research. However, these models are still relatively new and their value needs yet to be confirmed. One critical unresolved issue that needs to be addressed is the difficulty to measure the social impact and predict the cost savings that could be delivered by using repurposed medicines in clinical practice. Experience in measuring these outcomes may be gained from pay-for-performance or outcome-based managed entry agreements that are increasingly being used for market access of high-cost innovative medicines in Europe (267,268). Additionally, all new funding mechanisms entail relatively high transaction and implementation costs compared to traditional grant funding, and are typically associated with some risks. While those challenges should definitely be taken into account, interviewees were of the opinion that it should not prevent new funding mechanisms from being tested, for example in one or more pilot projects.

In addition to identifying new funding mechanisms, interviewees expressed the **need to enhance collaboration and centralisation at a European level to make clinical research more efficient and maximize the value of limited resources**. This finding is in line with emerging recommendations from the scientific community to increase international clinical trial collaboration in multiple disease areas, particularly also the collaboration between high-income countries (HICs) and LMICs (269–272). Despite the clear benefits for increased cross-border collaboration in clinical research, only about 3% of academic trials are multinational, compared to 30% of industry-led trials (273). Inadequate funding mechanisms, like national grants with geographic restrictions, and mismatches in international clinical regulations and guidelines may stifle multinational independent research (214,215). Several multinational grant funding programs have been set up to overcome this challenge. One example is the European and Developing Countries Clinical Trial Partnership (EDCTP), which is focused on finding solutions for HIV/AIDS, tuberculosis and malaria as well as other poverty-related infectious diseases in sub-Saharan Africa. The EDCTP combines investments from the European Commission, national member countries and other international partners (274). Another example is the Nordic Trial Alliance that aims to enhance Nordic cooperation on clinical multi-centre trials and is funded by the Nordic Council of Ministers and NordForsk (275). Moreover, European countries could join forces in transnational research and innovation projects via a European Research Area Network (ERA-Net) co-fund scheme (215,276). Other

collaborative initiatives such as the US Clinical Trials Transformation Initiative (CTTI), the European Clinical Research Infrastructure Network (ECRIN) or multinational disease-specific research organisations (*e.g.*, EORTC) could potentially function as coordinating centres and facilitate patient-centred approaches for increasing the quality and efficiency of international clinical trials. Furthermore, advancements in research methodology and technology could lead to more innovative trial designs, such as multi-arm/multi-stage or registry-based trials, for accelerating drug repurposing research (259–261).

Finally, some interviewees proposed the idea of **creating commercial interest for developing new uses for off-patent or generic medicines** by "*changing the rules of the game*", for example by providing additional IP or regulatory protection, introducing prize or reward funds (*e.g.*, the Health impact fund (277)), offering tax incentives or exploring indication-based pricing mechanisms. This idea of introducing new incentives to increase the industry's willingness to invest in repurposing off-patent or generic medicines was discussed in more detail elsewhere in chapter 5 of this dissertation (49,278).

The current study is exploratory in nature and has **three main limitations**. The first limitation is the small number of interview participants representing many different stakeholder groups. To learn valuable insights from this small study sample and reach the point of data saturation, only stakeholders with expertise in either drug repurposing, clinical research or funding mechanisms were included, and the results were complemented with information from the scientific literature as much as possible. The multi-stakeholder approach enabled us to capture diverse opinions about the application potential of the proposed funding mechanisms. A second limitation is the fact that the majority of interview participants are based in Belgium. Nevertheless, more than half of the participants had many years of experience of working in a European or international organisation and context, which is why the results can be extrapolated to the European level. Third, this study applied qualitative research methods, so our results do not allow us to quantify the stakeholders' perspectives or opinions about proposed funding mechanisms. If a new funding mechanism were to be tested in a pilot project, it could be useful to incorporate a quantitative study, for example a survey, involving different stakeholder groups to measure and evaluate the advantages and disadvantages of the studied mechanisms in practice.

CONCLUSION

At present, there is a lot of encouraging science to support the repurposing of off-patent or generic medicines in various disease areas, but the **current pharmaceutical model is not designed to accommodate the development of medicines for which commercial prospects are low**. Additional funding is needed to support and enable not-for-profit actors that are conducting off-patent drug repurposing research for which there is no commercial interest. Even though traditional grant funding was found to be indispensable to fund independent clinical research, interviewees were positive about exploring the value of new funding mechanisms. Additionally, increased collaboration and centralisation at a European and international level is recommended to make clinical research more efficient and reduce the need for additional funding.

PART 3

CLINICAL IMPLEMENTATION OF REPURPOSED MEDICINES

CHAPTER 5

Regulatory framework and recommendations to bring repurposed medicines to cancer patients

This chapter is based on

Verbaanderd C, Rooman I, Meheus L, Huys I.
On-label or off-label? Overcoming regulatory and financial barriers to bring repurposed medicines to cancer patients.
Frontiers in Pharmacology. 2020;10:1664.

ABSTRACT

Repurposing of medicines has gained a lot of interest from the research community in recent years as it could offer safe, timely and affordable new treatment options for cancer patients with high unmet needs. Increasingly, questions arise on how new uses will be translated into clinical practice, especially in case of marketed medicinal products that are out of basic patent or regulatory protection. The aim of this study was to portray the regulatory framework relevant for making repurposed medicines available to cancer patients in Europe and propose specific policy recommendations to address the current regulatory and financial barriers. We outlined two routes relevant to the clinical adoption of a repurposed medicine. First, a new indication can be approved, and thus brought "on-label", via the marketing authorisation procedures established in European and national legislation. Such procedures initiate a detailed and independent assessment of the quality and the benefit-risk balance of a medicinal product in a specific indication, benefiting both prescribers and patients as it reassures them that the scientific evidence is robust. However, the process of marketing authorisation for new therapeutic indications entails a high administrative burden and significant costs while the return on investment for the pharmaceutical industry is expected to be low or absent for medicines that are out of basic patent and regulatory protection. Moreover, most of the repurposing research is conducted by independent or academic researchers who do not have the expertise or resources to get involved in regulatory procedures. A second option is to prescribe a medicine off-label for the new indication, which is managed at the national level in Europe. While off-label use could provide timely access to treatments for patients with urgent medical needs, it also entails important safety, liability and financial risks for patients, physicians and society at large. In view of that, we recommend finding solutions to facilitate bringing new uses "on-label", for example by developing a collaborative framework between not-for-profit and academic organisations, pharmaceutical industry, health technology assessment bodies, payers and regulators.

INTRODUCTION

An increasingly popular anticancer treatment development strategy is the clinical investigation of approved and well-characterized non-cancer medicines for new cancer indications, which is known as drug repurposing (33). Drug repurposing is no longer a new concept. It has gained a lot of interest from the research community over the years as it holds the promise of providing safe, timely and affordable access to new treatment options for patients with unmet medical needs. However, drug repurposing is a broad term covering medicines that are on- or off-patent, shelved or approved, and used "as-is" or reformulated for the new indication (34,35). In addition, various terms or synonyms are used in scientific literature, such as drug repositioning, drug rediscovery, drug reprofiling, drug rescue and drug redirecting, and a formal regulatory definition does not exist (34). For the purpose of this review, drug repurposing is confined to the **research and development of new anticancer indications for marketed medicinal products that are out of basic patent or regulatory protection**.

Key advantages of drug repurposing compared to *de novo* medicine development are the shorter research and development times, the potentially lower development costs and, most importantly, the reduced risk of failure as the safety profile of the medicine is typically well-established (32,59). The opportunities offered by drug repurposing have not gone unnoticed: stories about the success of old 'miracle drugs' in new disease areas have been published by the media on numerous occasions (279,280). Moreover, several not-for-profit, patient and governmental organisations have expressed their interest (53), and the concept has gained recognition amongst researchers, as illustrated by several influential publications in scientific journals of high impact (151,281).

Academia and other research institutes are highly skilled in identifying new candidate molecules for repurposing through computational and experimental screening methods (32,282). They also take the lead in *in vitro* and *in vivo* validation of promising repurposing candidates in human tumour models, often in combination with other repurposed or approved anticancer medicines (53,65). As a result, **the research pipeline with promising candidates for drug repurposing is expanding rapidly** (47,283,284). With more than 280 compounds, the ReDO_DB list of non-cancer medicines with potential new uses in anticancer treatment is extensive (68). About 70 of these medicines are currently being tested in one or more late-stage (*i.e.*, phase II/III, phase III or phase III/IV) clinical trials for the treatment of cancer patients and more than 95% of those late-stage clinical trials have a non-commercial sponsor. Furthermore, drug repurposing is not only gaining momentum in the oncology field, its potential is being recognized **in all areas of medicine**, including neurology, endocrinology, infectious diseases, cardiology and psychiatry (48,50,285–289), and especially in those areas with high medical needs such as rare, paediatric and neglected diseases.

Nevertheless, the substantial increase in scientific knowledge is currently **not reflected by equal changes in clinical practice**, suggesting that the scientific community is facing challenges to bridge the gap between clinical research and practice (70,71). Indeed, **only few success stories** of non-cancer medicines being repurposed for anticancer treatment exist. One example is all-trans-retinoic acid (ATRA), a vitamin A derivate used to treat acne that was authorised in Europe to treat adult patients with newly diagnosed low-to-intermediate risk acute promyelocytic leukaemia in combination with Trisenox (290).

The **aim of this study** was to portray the regulatory framework relevant for bringing repurposed medicines to cancer patients in Europe based on an analysis of the European and national legislation and guidelines, consultations with experts, and a review of scientific and grey literature in this field. We also discuss specific policy recommendations that have been proposed by various stakeholders to address the current regulatory and financial barriers for clinical adoption of new indications for marketed, off-patent medicines.

METHODS

We studied **EU legislation and guidance documents** to identify regulatory pathways and incentives for bringing new uses "on-label". These include Directive 2001/83/EC on medicinal products for human use, Regulation (EC) No 726/2004 on procedures for the authorisation and supervision of medicinal products for human and veterinary use, Regulation (EC) No 1234/2008 on variations to the terms of marketing authorisations, Regulation (EC) No 141/2000 on orphan medicinal products and Regulation (EC) No 1901/2006 on medicinal products for paediatric use. Next, we investigated the impact of the available incentives on the development of new indications in Europe through a search of grey literature (including policy reports from regulatory agencies or institutions, press releases, and thesis manuscripts). The **Community Register of orphan medicinal products for human use** was exported as an Excel file and manually assessed to identify all active European orphan designations for non-cancer medicines in cancer indications (last update in August 2019). We also portrayed off-label use practices, regulations and guidelines in EU member states and countries in the European Economic Area (EEA) through a hand search for previous policy reports and via consultation with experts.

Additionally, we searched for information on current hurdles in the legal and regulatory framework relevant for drug repurposing and on potential solutions in **scientific and grey literature**. Publications in PubMed and Embase databases were identified systematically using a defined search query consisting of MeSH terms and key words used in title and abstract (Appendix E). Only articles published between January 2011 and April 2019, in English, of which the full-text publication was available were included. Inclusion was not restricted to oncology publications only, because challenges and solutions could be similar in other disease domains. Moreover, we selected publications based on reference lists of the identified literature. Grey literature was found through interaction with representatives from industry, non-profit, regulatory, HTA and payer organisations. This grey literature includes policy reports and briefs, media coverage, European and national competent authority websites, European Commission meeting records and thesis manuscripts.

RESULTS

When developing a new therapeutic indication for an authorised medicine that is out of basic patent and regulatory protection, a key question is how this new use will be translated into clinical practice. Here we outline **two options relevant in granting patients access to repurposed medicines**. The first option is to approve the new indication and bring it "on-label" via the regulatory procedures established in European and national legislation. The second option is to allow prescription of the new indication off-label based on national frameworks (Figure 8).

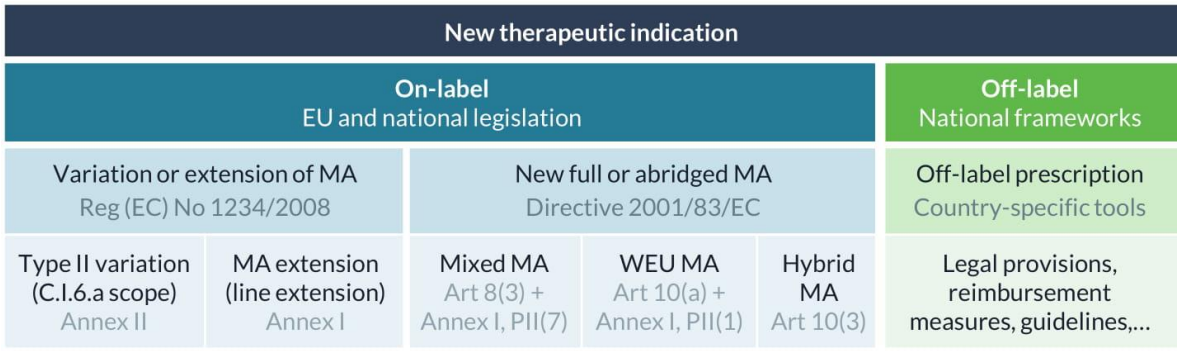

FIGURE 8. REGULATORY FRAMEWORKS RELEVANT FOR NEW THERAPEUTIC INDICATIONS IN EUROPE
Abbreviations: Marketing Authorisation (MA), Well-Established Use (WEU), Commission Regulation (Reg)

BRINGING NEW USES ON-LABEL

EUROPEAN REGULATORY FRAMEWORK FOR MARKETING AUTHORISATION

A marketing authorisation application for a new indication initiates a **detailed and independent assessment of the quality and the benefit-risk balance of a medicinal product in that specific indication**, which is summarized and published in the public assessment report and in the summary of product characteristics (SmPC). Such an assessment benefits both prescribers and patients as it reassures them that the scientific data supporting the new therapeutic indication are robust. Today, the majority of new, innovative medicines are evaluated by the European Medicines Agency (EMA) and authorised via the centralised procedure, resulting in a single marketing authorisation valid in all EU Member States and countries in the EEA. However, some products (especially many older medicines) are authorised at national level via the decentralised, mutual recognition and national procedures, resulting in national marketing authorisations. Regardless of the route, data requirements and standards for marketing authorisation are comparable across the EU.

A **specific European regulatory guideline intended for drug repurposing does not exist but various legal bases are available** to get new therapeutic indications approved and bring them "on-label" (Figure 8) (291,292). First, a marketing authorisation holder can apply for a **type II variation** of its authorised product, more specifically a C.I.6.a scope variation for the addition of a new therapeutic indication or modification of an approved one, under the same marketing authorisation. Variations for extension of indication are quite common in oncology and are typically rewarding for a company as this expands the patient population. For example, paclitaxel, initially indicated for the treatment of breast cancer, was later authorised for the treatment of non-small cell lung cancer and metastatic pancreas adenocarcinoma (293,294). However, certain changes cannot be granted via a variation procedure, for example where a change in indication is accompanied by changes to the strength, pharmaceutical form or route of administration of the medicinal product (292,295). In that case, an **extension of the marketing authorisation** (a line extension) needs to be submitted, which will be assessed according to the same procedure as for the initial marketing authorisation to which it relates. The extension can either be granted as a new marketing authorisation or will be included in the initial marketing authorisation (296). In case the change in therapeutic indication also applies to existing presentations, the application should be presented as a grouping of a line extension and C.I.6.a scope variation (295). All new indications need

to be supported by sufficient (pre-) clinical evidence provided by the applicant, and can be supplemented with literature references if available (296).

In addition, any medicine developer can apply for a **new marketing authorisation** for an existing active substance with a new therapeutic indication. This route would enable a developer to market the product with the repurposed indication under another name, specific for the indication. To make use of scientific data that was published in literature, a **full-mixed marketing authorisation application** can be submitted. This is a stand-alone application in which bibliographical references can be used to support or replace some of the (non-) clinical data in the regulatory dossier. Alternatively, a **well-established use or 'literature-only' application** can be submitted for a well-known active substance if safety and efficacy can be demonstrated by extensive and continued use in the specific indication in the EU over a period of at least 10 years. For this type of application, all test and trial results will be replaced by appropriate scientific literature (with the exception of studies for bridging purposes). For example, mitotane, a well-established medicine that has been used in the treatment of adrenal cortical carcinoma in Europe since 1959, was authorised via this pathway in 2004 based on the results of 220 published studies (297).

Another route that is sometimes mentioned in the context of drug repurposing is called the **hybrid application** route, which is aimed at medicines that differ from their reference medicinal product in therapeutic indication, strength, pharmaceutical form or route of administration (298). This abridged procedure allows cross-referencing to existing data in the registration dossier of the reference medicinal product, but also requires new test and trial data to support the new use. However, in practice, this route is mostly used for applications of generic medicines where there are "minor" differences with the reference medicinal product, for instance for minor changes in therapeutic indications within the same therapeutic field (291). This observation is also in line with the guidance provided in Annex II of Chapter 1 of the Notice to applicants Volume 2A about the procedures for marketing authorisation (299).

In summary, the **legal basis will vary depending on the type of applicant** (*e.g.*, only the marketing authorisation holder can apply for a variation or extension procedure) and on the **amount of data that can be extracted from published literature**. **Scientific and regulatory advice** can be requested at national or European level to better understand the various regulatory pathways and the level of evidence required for marketing authorisation of the new indication (300,301). Another important aspect that needs to be taken into consideration when selecting which regulatory pathway to follow are the available incentives described below.

REGULATORY INCENTIVES FOR MARKETING AUTHORISATION

Each new active medicinal product obtains an eight-year period of data protection followed by a two-year period of marketing protection starting from the date of initial authorisation. Any variations and extensions shall be considered as belonging to the same global marketing authorisation, in particular with regard to data and marketing protection rules. This means that the ten-year exclusivity period can only be granted once per active substance that is the subject of a marketing authorisation held by the same marketing authorisation holder. In order to allow companies to recoup investments for the development of new indications for marketed therapies, some **additional regulatory exclusivities** have been established in Europe (Figure 9) (38,278). First, the marketing authorisation holder can be granted one

additional year of marketing protection for one or more new therapeutic indications, with significant clinical benefit in comparison with existing therapies, applied for during the first 8 years (302). Second, a **non-cumulative period of one year of data exclusivity** can be granted for a new indication for a well-established substance, if significant preclinical or clinical studies were carried out in relation to the new indication (303). However, a report from June 2017 on pharmaceutical incentives and rewards in Europe showed that this last incentive had never been granted for any centrally approved substance (83). In certain cases, medicine developers may choose to **reformulate, protect (*e.g.*, through second medical use patents) and rebrand an established medicinal product to create sufficient legal and strategic protection** from competitors (40–42). For developers other than the original marketing authorisation holder, a new full marketing authorisation application may even offer a ten-year period of data and marketing protection for the repurposed product (304).

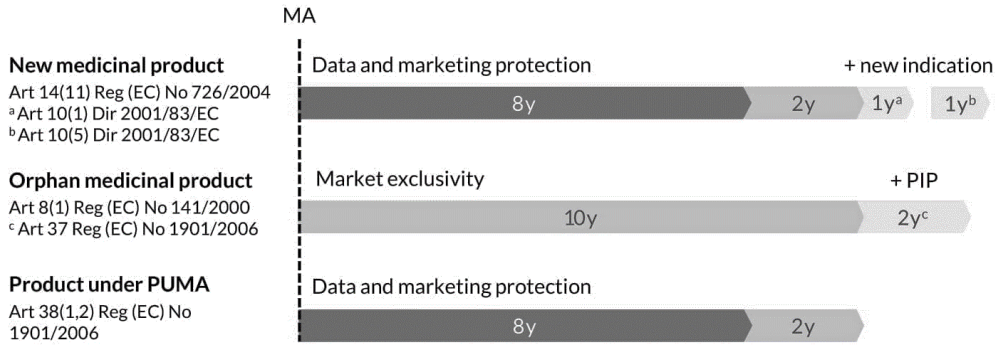

FIGURE 9. REGULATORY EXCLUSIVITIES RELEVANT TO THE DEVELOPMENT OF NEW USES IN EUROPE
Abbreviations: Marketing Authorisation (MA), Paediatric Investigation Plan (PIP), Paediatric-Use Marketing Authorisation (PUMA), Regulation (Reg), Directive (Dir)

Repurposing of existing medicines can be particularly useful in areas with high unmet needs, for example to treat patients with rare diseases (304,305). In fact, studies have shown that about one in five orphan medicinal products are established medicines that were repurposed for a new indication (79). Medicinal products that fulfil the criteria for **orphan designation** (Orphan Regulation (EC) No. 141/2000) are entitled to a **ten-year market exclusivity period**, possibly followed by **two additional years if a paediatric investigation plan (PIP) is completed** (Figure 9). During this exclusivity period, no other marketing authorisation applications can be approved for the same therapeutic indication for a similar medicinal product, including variations or extensions, unless the second medicinal product is safer, more effective or otherwise clinically superior (or one of the other derogations apply). Other incentives for orphan medicinal products include protocol assistance, access to the centralised procedure and fee reductions for regulatory procedures. Thalidomide, a medicine that was withdrawn from the market in the 1960s for its disastrous adverse effects upon use during pregnancy, is a well-known example of a medicine that was successfully repurposed for the treatment of multiple myeloma via the orphan medicinal product pathway (76). Of note, twelve other non-cancer medicines that are currently under investigation for their new use in cancer have obtained an orphan designation in Europe (Table 8).

TABLE 8. EUROPEAN ORPHAN DESIGNATIONS FOR NON-CANCER MEDICINES IN CANCER INDICATIONS

Active substance	Original indication	EU OD indication (cancer)	Designation date	Sponsor
Brivudine	Viral infections	Pancreatic cancer	2010	RESprotect GmbH
Chloroquine	Malaria	Glioma	2014	DualTpharma B.V.
Eflornithine	African trypanosomiasis, hirsutism	Familial adenomatous polyposis	2010	Cancer Prevention Pharma Ltd
		Neuroblastoma	2011	Cancer Prevention Pharma Ltd
		Glioma	2016	Orbus Therapeutics Ltd
+ Sulindac	Inflammatory conditions	Familial adenomatous polyposis	2013	Cancer Prevention Pharma Ltd
Flucytosine	Fungal infections	Glioma	2018	Richardson Associates Regulatory Affairs Ltd
Itraconazole	Fungal infections	Naevoid basal-cell carcinoma syndrome	2017	Mayne Pharma UK Ltd
Ketoconazole	Fungal infections	Granulosa cell tumours	2017	Grupo Español de Tumores Huérfanos e Infrecuentes (GETHI)
Miltefosine	Leishmaniasis	Cutaneous T-cell lymphoma	2008	ExperGen Drug Development GmbH
Naloxone	Opioid overdose	Cutaneous T-cell lymphoma	2012	Winston Laboratories Ltd
Propranolol	Hypertension	Soft tissue sarcoma	2016	The Anticancer Fund
Valproic acid	Epilepsy	Diffuse large B-cell lymphoma	2016	Valcuria AB
+ Carboplatin	Multiple cancer types	Glioma	2018	Dr Ulrich Granzer
Zoledronic acid	Osteoporosis	Glioma	2016	Laboratorio Italiano Biochimico Farmaceutico Lisapharma S.p.A.

Abbreviations: Orphan Designation (OD), Naloxone hydrochloride dihydrate (Naloxone)
Source: Community Register of orphan medicinal products for human use, last update in August 2019

Similar incentives exist for medicines developed exclusively for use in the paediatric population. The EU Paediatric Regulation No. 1901/2006 introduced the **Paediatric-Use Marketing Authorisation (PUMA)** for medicines that have been authorised and can no longer be covered by a supplementary protection certificate (SPC) or a patent (306). A PUMA offers incentives like automatic access to the centralised procedure, a partial fee exemption and a ten-year period of data and marketing protection (Figure 9). Propranolol, a non-selective beta-blocker, is an example of a well-known medicine that was reformulated for use in children with proliferating haemangiomas, authorised via the PUMA pathway and successfully rebranded as Hemangiol in the EU (307,308). However, to this date (October 2019), only six PUMAs have been granted in the EU, even though scientific literature proposes more than 100 repurposing opportunities in paediatrics (55,309).

PRICING, REIMBURSEMENT AND CLINICAL ADOPTION

The next essential step in bringing a treatment to the patient is **setting the price and deciding on the reimbursement of the medicine**, which takes place **at the national level** in the EU and varies across countries (168,310). When a new indication is introduced, the pricing of the existing medicine may be re-evaluated and renegotiated in some countries, like France, Italy and Spain (278). The introduction of a new indication for a product that was already on the market can lead to price cuts because of a combination of price/volume agreements, external reference pricing or budget impact analysis (278). In contrast, a company could ask for an increase in price to compensate for the investments made to develop the new indication, but payers are generally resistant to pay a higher price for a new indication of an existing medicinal product (73,75,311).

Furthermore, **demonstration of cost-effectiveness** is an important factor for reimbursement decisions and for inclusion in national or regional formularies. However, establishing cost-effectiveness of a repurposed medicine may be difficult when comparing it to a medicine comprising the same active ingredient that is already on the market for a different indication and can thus be prescribed off-label for the new indication. This holds especially true in case the price of the repurposed medicine is set significantly higher than the price of the original medicine and in case effectiveness evidence was already available in published literature (312,313). For example, chenodeoxycholic acid (CDCA) was a low-cost medicinal product originally developed to treat gallstones in the 1970s and later extensively used off-label to treat patients with the hereditary metabolic disease cerebrotendinous xanthomatosis (CTX). Since 2017, CDCA is officially authorised in Europe as an orphan medicinal product for the treatment of CTX and marketed by Leadiant Biosciences at a much higher price (314). This price hike led to the medicine not being reimbursed in several EU countries (315).

Ideally, the new indication would also be included in **clinical treatment guidelines** available at the European level (*e.g.*, European Society for Medical Oncology (ESMO) Clinical Practice Guidelines) and/or the national level to support clinical adoption.

CHALLENGES IN BRINGING NEW USES ON-LABEL

Even though repurposing of medicines is considered to be relatively cheap compared to *de novo* medicine development, approval of a new indication can still bring about **high costs** (71,311). These costs include the fees for authorisation applications, scientific advice fees and pharmacovigilance costs for new indications. For example, in 2019, EMA fees for a marketing authorisation application start at €291,800, fees for extension of the marketing authorisation amount to €87,600 and fees for scientific advice range from €43,700 to €87,600 (316). However, the majority of repurposed medicines is likely to go through national, mutual recognition or decentralised procedures for which fees are significantly lower but vary across Member States. In addition, applying for marketing authorisation of a new indication can place a high administrative burden. The product label and pharmacovigilance system need to be updated for a new indication (311) and, in some cases, a risk management plan or a PIP has to be submitted (278).

Pharmaceutical companies often choose not to invest in new therapeutic indications after expiry of basic patent and regulatory protection periods of their approved products (38,278). Patent claims for secondary uses often offer weaker protection compared to the primary basic product patent claims so the

risk of free-riding by competitors is high (281). Developing a new indication outside of a company's therapeutic focus is also high-risk and costly (32,42). Instead, companies may actually benefit from off-label prescribing of their products because it expands the patient population without them having to apply for a variation or extension of the marketing authorisation (281,311). In addition, research has shown that the evidence base supporting new uses for marketed, off-patent medicines in anticancer treatment is largely built through academic or independent research (68). A collaboration between academic or independent researchers and the pharmaceutical industry could potentially facilitate pivotal trials and marketing authorisation procedures for new indications, but convincing pharmaceutical companies to join forces has proven to be quite challenging (47,84).

Research foundations or academic institutions are typically not the marketing authorisation holder of a repurposed medicine, meaning that they cannot apply for a variation to add a new indication to an existing product label (311). However, there is no legal barrier that prevents them from applying for a new marketing authorisation for the medicine in the new indication (79,281,317). While this approach may theoretically result in more affordable repurposed medicines, several barriers exist. Considering the high costs and administrative burden mentioned before, **most non-industry researchers and organisations lack the infrastructure, expertise and resources to fulfil the necessary requirements for obtaining and maintaining a marketing authorisation** (including preparation of regulatory dossier, safety monitoring, provision of up-to-date medical information in SmPC and patient information leaflet, *etc.*) (79,186,311). In addition, academic researchers are encouraged to disseminate their findings through scientific publications, but they are not (systematically) rewarded for engaging in marketing authorisation and market access procedures (318). Current regulatory incentives are tailored to promote development by pharmaceutical companies, while incentives to support further development by the not-for-profit and academic sector are lacking.

PRESCRIBING NEW USES OFF-LABEL

NATIONAL LEGISLATIVE FRAMEWORKS FOR OFF-LABEL USE

As most repurposed medicines are already authorised and marketed for different indications, they could be prescribed off-label to patients with unfulfilled medical needs in some countries (169,319). Off-label use can be defined as **any intentional use of an authorised product not covered by the terms of its marketing authorisation**, for example for another indication, a different patient group, another dose, dose interval or by another route of administration than indicated in the SmPC (169,320). Contrary to the strict legal framework for marketing authorisation, the **actual use of medicinal products in medical practice is not regulated by EU legislation** (as confirmed by the European Court of Justice T-452/14 Laboratoires CTRS v Commission, paragraph 79).

Because there is no EU framework for off-label use of medicines, Member States manage this in different ways. According to a study commissioned by the European Commission, only 10 out of the 21 Member States that participated in this study have specific **policy tools** in place **to manage off-label use** (169). For example, France, Hungary, Italy, Greece and Germany have legal frameworks for off-label use established by their national laws (Table 9). These frameworks vary in scope and stringency, and largely focus on the conditions in which off-label use is allowed and potentially also reimbursed. The conditions relate to the

scientific basis of the off-label use, the need for explicit informed consent by the patients, the severity of the disease (life threatening or not) or the availability of authorised alternative treatments (169,320).

In some countries, **clinical guidelines and policies** are provided to guide off-label use of medicines (*i.e.*, Evidence Summaries: Unlicensed and Off-label Medicines (ESUOMs) in the UK (321)) and off-label treatment options for which robust scientific evidence exists are sometimes included in clinical treatment guidelines and formularies (317,320).

TABLE 9. NATIONAL LEGAL FRAMEWORKS FOR OFF-LABEL USE IN SELECTED EU COUNTRIES

COUNTRY	LEGAL PROVISION	INSTITUTION	REIMBURSEMENT	LEGAL BASIS
France	Temporary recommendations for use (RTU) scheme	National Agency for Medicines and Health Products Safety (ANSM)	Yes, even if authorised alternative medicinal products exist (for economic reasons)	Art L5121-12-1 and Art R5121-76-1 and following of the Public Health Code
Hungary	Individual authorisation for off-label prescribing upon request of treating physician	National Institute for Quality and Organizational Development in Healthcare and Medicines (GYEMSZI)	Yes, but on an individual basis within the named patient-based reimbursement system	Section 25 of Act No. XCV of 2005 and Decree No. 44/2004 of the Ministry for Health Care, Social Affairs and Family
Italy	Permissions for off-label use under certain conditions	Italian Medicines Agency (AIFA)	Yes, if included in AIFA "List 648". Even if authorised alternative medicines exist	Law no. 648/1996, Law no. 94/1998 Art 3(2), Law no. 79/2014
Greece	Permissions for off-label use under certain conditions	National Organization for the Provision of Health Services (EOPYY)	Yes, if included in therapeutic protocols and approved by National Healthcare Council (KESY) or upon individual request of healthcare practitioner	Ministerial Decision No. ΔΥΓ3(α)/οικ. ΓΥ/154 and Article 47 of Law 4316/2014
Germany	Recommendations for off-label prescribing by four "off-label expert panels"	Federal Joint Committee (G-BA)	Yes, if included in part A of Appendix VI of the pharmaceutical directive	Article § 35c(1) of the SGB V

RISKS OF PRESCRIBING NEW USES OFF-LABEL

Even though off-label use could offer timely access to new treatment options, it also entails **important risks for patients, physicians and society at large**. First, prescribers face significant uncertainty about scientific evidence to support an off-label use because the benefit-risk balance was not assessed by competent authorities and robust clinical data may be lacking (278,322). Inconsistencies in off-label use recommendations between treatment guidelines, drug compendia and evidence reviews further complicate treatment decisions (323,324), and so far, only few dedicated data collection systems have been established that could help substantiate the evidence base with real-world data. Another major hurdle for physicians is the risk of legal liability in case a patient experiences any adverse events from using the product outside the SmPC (322,325). Of note, adverse reactions that arise from use of the product outside the terms of the marketing authorisation are already captured by the pharmacovigilance system.

From the patient's perspective, the lack of strong scientific evidence to support off-label use, the lack of information in the patient leaflet and patient materials for the specific indication, the risk of unknown adverse events, and the lack of a risk management plan to protect the patient are key barriers (322,326). Furthermore, not all countries support the reimbursement of off-label use, so some off-label treatments could be unaffordable to patients (278). Another challenge is the risk of suddenly losing a medicine that is used extensively off-label for a certain indication, if the manufacturer decides to take it off the market (70). So even though off-label prescribing of repurposed medicines can be very valuable in individual cases, substantial ethical and legal challenges exist (325).

DISCUSSION AND POLICY RECOMMENDATIONS

The identification of new indications is part of a medicine's life cycle so the more new medicines enter the market, the larger the 'toolbox' for repurposing gets. Consequently, the repurposing pipeline is expected to keep growing over time, which is why we **need to address the regulatory barriers** now. The recommendations below **focus on finding solutions to bring new uses "on-label"** because we consider this approach to be more sustainable in the long term, taking into account the aforementioned risks of off-label prescribing. Moreover, previous studies on managing off-label use of medicines have already proposed a wide range of policy options at different levels (169,317,320,327). The so-called 'soft approaches', such as providing good off-label use practice guidelines, including the new use in existing treatment guidelines and collecting real-world evidence to start knowledge building, were found most relevant to support prescribers and protect patients in the context of off-label use.

INTRODUCING NEW INCENTIVES OR REMOVING CURRENT DISINCENTIVES

Introducing new incentives may **increase industry's willingness to invest in the development of new indications for off-patent medicines**. At the **EU-level**, a first option could be to provide additional or prolonged data and marketing protection periods or improve patent enforceability for second and further medical use claims, however, this could hinder or delay affordable access to medicines (32,71,278,281). A second option could be to offer transferable vouchers that grant priority review for future marketing authorisation applications, like the US Food and Drug Administration (FDA) priority review vouchers (71,247). Priority review would theoretically allow a pharmaceutical company to bring another product in their pipeline to the market sooner, but the value of such a voucher is not yet clear. Third, government or philanthropic organisations could award prizes or special research funds to medicine developers, in particular generic producers or small and medium-sized enterprises (SMEs), or independent/academic researchers for developing new therapeutic indications for off-patent medicines (71,281,317). However, the practical implementation and the value of such prizes or rewards need to be established first.

Alternatively, **country-specific incentives** may be offered, such as tax incentives (*e.g.*, UK research and development (R&D) credits) or a differential pricing system across indications (75,278,317). Differential pricing systems would require the physician to report the indication on their prescriptions for patients, which can be facilitated with e-prescribing software (328). The product could still be prescribed by its generic name for off-patent uses, but also by its brand name for new, patented indications (71,82).

It is uncertain whether the aforementioned incentives would be sufficient to stimulate development of repurposed medicines, and this approach may result in higher medicine prices. A **more sustainable approach** to encourage the development of new indications for marketed therapies could be to remove or at least **reduce the current disincentives for industry**, for instance by providing fee reductions or waivers for scientific advice and/or variation applications. Even though this approach would require some additional public investments in the short term, it may offer significant societal benefits.

CREATING A COLLABORATIVE EUROPEAN FRAMEWORK

The gap between the research that is conducted by non-commercial organisations and the need for marketing authorisation of a new therapeutic indication cannot be bridged by only addressing the (dis)incentives for the pharmaceutical industry. We need a **collaborative, multi-stakeholder, European framework** to streamline the identification of repurposing opportunities supported by adequate and robust data and to accelerate the clinical uptake of repurposed medicines that have proven to be safe and effective (329). For that reason, over the past year, the **European Commission expert group on Safe and Timely Access to Medicines for Patients (STAMP)** has set up a working group to create a visible framework for drug repurposing (330). The aim of this framework is to support a not-for-profit or academic stakeholder, termed a 'Champion', who has evidence and scientific rationale for a new therapeutic indication that meets particular criteria, in bringing this new indication "on-label".

The details of the framework are published elsewhere (331) but here we briefly summarize the **core components**. First, a Champion collects sufficient supporting data for a new indication to an off-patent medicine and requests a scientific advice meeting with European or national authorities. Second, the repurposing regulatory scientific advice provides comments and feedback on the presented data package and on the requirements for future data generation (if any). If required, the Champion conducts further clinical development in compliance with the scientific advice and/or consolidates the available data. During the development, the Champion could seek an immediate or future partnership with one or more marketing authorisation holders. Finally, if the data package is considered sufficient, the marketing authorisation holder(s) seek(s) an extension, variation or a new marketing authorisation using the existing regulatory pathways (330).

In order to test this framework and to assess whether it is able to facilitate an application for a new indication for an off-patent medicine, a **pilot project with real-world repurposing cases** is expected to start in January 2020. However, several **unresolved issues** already come to mind. First, this framework requires a lot of effort and commitment from the Champion, so additional support and incentives for independent or academic researchers to apply for regulatory scientific advice and to collect data intended for regulatory approval are needed (186,212,311). For instance, a fee waiver or reduction for scientific advice could lower the threshold for independent or academic researchers to seek assistance and would consequently facilitate more efficient data generation (79,300). Second, most researchers have no or very limited experience with preparing a scientific advice briefing document, so additional guidance documents and better education on regulatory procedures may be useful (311). The latter could be addressed by the Horizon 2020 Coordination & Support Action on "Strengthening regulatory sciences and supporting regulatory scientific advice" that is currently in preparation. Finally, the outcome of this framework is

uncertain as it fully depends on the willingness of the marketing authorisation holder(s) to apply for a variation, extension or new marketing authorisation. Nonetheless, this type of EU-wide framework to facilitate drug repurposing is definitely encouraging for involved researchers and any unresolved issues can be identified and addressed during the pilot project.

INITIATING LEGISLATIVE CHANGES IN EUROPE

Some stakeholders are convinced that **legislative changes** will be needed. One proposal is to introduce a legal provision in EU legislation that allows third parties, such as research institutes or foundations, to apply directly for a variation or extension of marketed products (311,332). However, the implementation of this approach would require a lot of time and would initiate complicated discussions about the responsibility and legal liability for the marketing authorisation. Another idea is to strengthen the role of the regulatory agencies in bringing new uses "on-label" by requiring them to follow-up on any evidence made available to support new indications for approved medicines. Regulators could encourage (or even enforce) the need for a variation application by marketing authorisation holders based on positive results from clinical trials conducted by third parties. During the STAMP expert meetings, Articles 23 (2), 31 and Annex I (7, 11) of Directive 2001/83/EC and Article 16 (2) of Regulation (EC) No 726/2004 were mentioned as potential legal bases for this type of 'efficacy vigilance' (311). Yet, it soon became clear that this approach would not be sustainable because it raises uncertainties about the responsibility for the evidence and it entails increased legal liability for regulatory agencies. An alternative approach would be for the executive director of the EMA or the Commission representative to request non-binding ("soft") recommendations or advice of the Committee for Medicinal Products for Human Use (CHMP) on all new uses (Article 5 (3) of Regulation (EC) No 726/2004). However, a scientific opinion on a new therapeutic indication by EMA that is not taken up in the marketing authorisation may promote off-label use, which is not in line with their policy.

Legislative actions relevant to drug repurposing have already been proposed in some countries but with limited success so far. In the UK, the Off-Patent Drugs Bill was launched to facilitate drug repurposing by requiring the Secretary of State to seek licences for off-patent medicines in new indications and to request technology appraisals for these medicines from the National Institute for Health and Care Excellence (NICE) but this bill failed in Parliament in 2015 (333). In the US, a bill was introduced in the senate in September 2018, called the 'Making Objective Drug Evidence Revisions for New Labeling Act' or 'MODERN Labeling Act', which could be relevant to drug repurposing (334). The not-for-profit organisation Friends of Cancer Research started the initiative to address outdated generic product labels in the US (171,335). The proposed bill aims to establish a process for the FDA to determine whether the labelling of generic medicines needs modifying, including medicines with relevant accepted uses in clinical practice (supported by evidence that could meet the standards for approval) that are not reflected in the approved labelling.

CONCLUSION

Drug repurposing holds the promise of accelerating access to safe and affordable treatment options, especially for patients with rare, paediatric or neglected diseases. The goal is not to replace *de novo* medicine development but rather to complement it. Even though various regulatory pathways already exist to make repurposed medicines available to cancer patients, important challenges occur in bringing new uses "on-label" (336). To address current challenges, we encourage the development of a European collaborative framework, as proposed by the STAMP expert group, in which academic and not-for-profit organisations, pharmaceutical industry, health technology assessment bodies, payers and regulators can work together on developing new uses for marketed medicines. Interestingly, the **EMA has expressed their support for the development and implementation of such a framework in their regulatory strategy for 2025** (337). The outcome of the planned pilot project to test the proposed repurposing framework will hopefully provide more insights on the outstanding issues for bringing new uses "on-label" and indicate potential next steps for the benefit of public health.

CHAPTER 6

Drug repurposing candidates in oncology - Pilot studies for a European repurposing framework

ABSTRACT

Drug repurposing is an emerging field of drug research and development that may provide timely, affordable and safe new treatment options for patients with unmet medical needs. In March 2016, the topic of repurposing established medicines and active substances became part of the agenda of the European Commission Expert Group on Safe and Timely Access to Medicines for Patients (STAMP). Through a number of *ad hoc* meetings with representatives from patient and consumer organisations, industry, not-for-profit research organisations, health technology assessment bodies and payers, the STAMP group identified many opportunities offered by the repurposing of existing medicines, but also highlighted significant scientific, regulatory and financial barriers. In response to these challenges, the STAMP group started preparing a proposal for a visible supportive framework to a not-for-profit stakeholder (termed "Champion"), who has evidence and scientific rationale for a new indication, with the aim of bringing a new indication "on-label". In preparation of a pilot to test the proposed framework, the present study collected information for nine repurposing candidates in oncology with varying characteristics in terms of available evidence, development stage, type of repurposing and combinations with other medicines. A template was developed to guide evidence generation for the repurposing candidates that required information about the original authorised indication(s) of the candidates, the rationale and unmet medical need in the proposed new indication and the scientific evidence supporting the use of the repurposing candidate in the new indication. Based on the learnings from the present study, the practical implications, the objectives and the long- and short-term deliverables of the pilot were considered. At present, a voluntary virtual observatory group, called the Repurposing Observatory Group (RepOG), is preparing supporting documents to launch the pilot that will test the repurposing framework proposed by the STAMP group.

INTRODUCTION

Drug repurposing is a dynamic field of drug research and development that may provide timely, affordable and safe new treatment options for patients with high unmet needs (32,59,151). The possible benefits of repurposing existing medicines have not gone unnoticed (33,338,339). In March 2016, drug repurposing became part of the agenda of the **European Commission Expert Group on Safe and Timely Access to Medicines for Patients (STAMP)**, which is an expert group under the European Pharmaceutical Committee that involves representatives from all European Member States, countries in the EEA and the EMA. The topic of repurposing established medicines was first introduced to the STAMP group by the representative from the UK, who outlined the different types of repurposing and the available regulatory incentives in Europe (339,340). The subsequent discussions of the STAMP group indicated that, despite the many possible benefits, drug repurposing represents significant scientific, regulatory and financial challenges that need to be addressed to facilitate efficient evidence generation and improve timely access to repurposed medicines for patients. The group discussion primarily focused on **repurposing established, off-patent medicines**, **for which the research is typically carried out by academic or not-for-profit research organisations** and which often results in off-label use of medicines once robust clinical evidence is available (49,70).

In response to the identified challenges, the STAMP group decided to continue and to broaden the discussion by inviting representatives from patient and consumer organisations, industry, not-for-profit research organisations, HTA bodies and payers to participate in an ***ad hoc* brainstorming session**. The objective of this session was to explore the issues and reflect upon the potential solutions to support the introduction of new indications "on-label" through new marketing authorisations or via extension of indications for existing marketing authorisations. External stakeholders also participated in the subsequent meetings of the STAMP group that considered the repurposing of established medicines and active substances (Appendix F comprises an overview of all stakeholder organisations involved in the STAMP meetings from March 2017 to March 2019).

To **better understand the challenges**, a small group, led by the UK with volunteers from the National Competent Authorities (NCAs), EMA and the Anticancer Fund, summarized case studies of the experience of repurposing established medicines (341). This exercise highlighted that researchers from academic and not-for-profit organisations who conduct repurposing research with existing medicines face multiple barriers in bringing new indications "on-label". These researchers generally do not have the knowledge, expertise, resources or intention to apply for and maintain a marketing authorisation, and to fulfil post-marketing responsibilities. Moreover, they often have little experience in designing registration trials, which have to meet strict regulatory requirements, and they may not have access to all relevant data concerning the medicine, in particular the non-clinical data submitted as part of the original authorisation dossier. Engagement with the pharmaceutical industry could facilitate collection of the necessary data and the registration of the new indication. However, due to a lack of incentives and a lack of control over the quality of the data that was generated by third parties, marketing authorisation holders may be reluctant to get involved in drug repurposing research and to extend the therapeutic indications of their authorised products. **Scientific advice** was proposed as a way **to support academic and not-for profit researchers** in designing pivotal clinical trials that meet regulatory standards and generate high-quality data.

Following the discussions on drug repurposing, a working group was established in June 2018 with representatives from the European Commission, selected Member States, the EMA, patient, payer and not-for-profit organisations (including the Anticancer Fund) and the pharmaceutical industry to develop a **proposal for a new framework for the repurposing of established medicines.** The overall aim of this framework is "*to provide a visible supportive framework to a not-for-profit stakeholder (termed Champion), who has evidence and scientific rationale for a new indication […], with the aim of bringing a new indication on-label*" (330). By applying existing regulatory procedures and tools, this framework could facilitate appropriate data generation to support a new therapeutic use for an approved medicine. The framework specifically targets repurposing projects that involve an already authorised medicinal product that is out of basic patent and regulatory protection, in an indication outside its authorisation, where research has shown value to the patient. More precise attributes of the targeted projects under this proposed framework and characteristics of potential "champions" are outlined in the framework proposal and in Appendix G (330).

The repurposing framework comprises a number of **voluntary steps** that already exist within the current regulatory framework, and introduces **scientific and regulatory advice** from regulators (either NCAs or EMA) as a crucial component in the repurposing of established medicines (Figure 10). The champion plays a key role in this framework by generating sufficient supporting data for the new therapeutic indication in preparation of the regulatory scientific advice meeting and by conducting further studies if needed. Moreover, the framework encourages the development of a partnership between the champion and one or more marketing authorisation holders, who can apply for an extension or variation of the marketing authorisation, if the data package is considered sufficient.

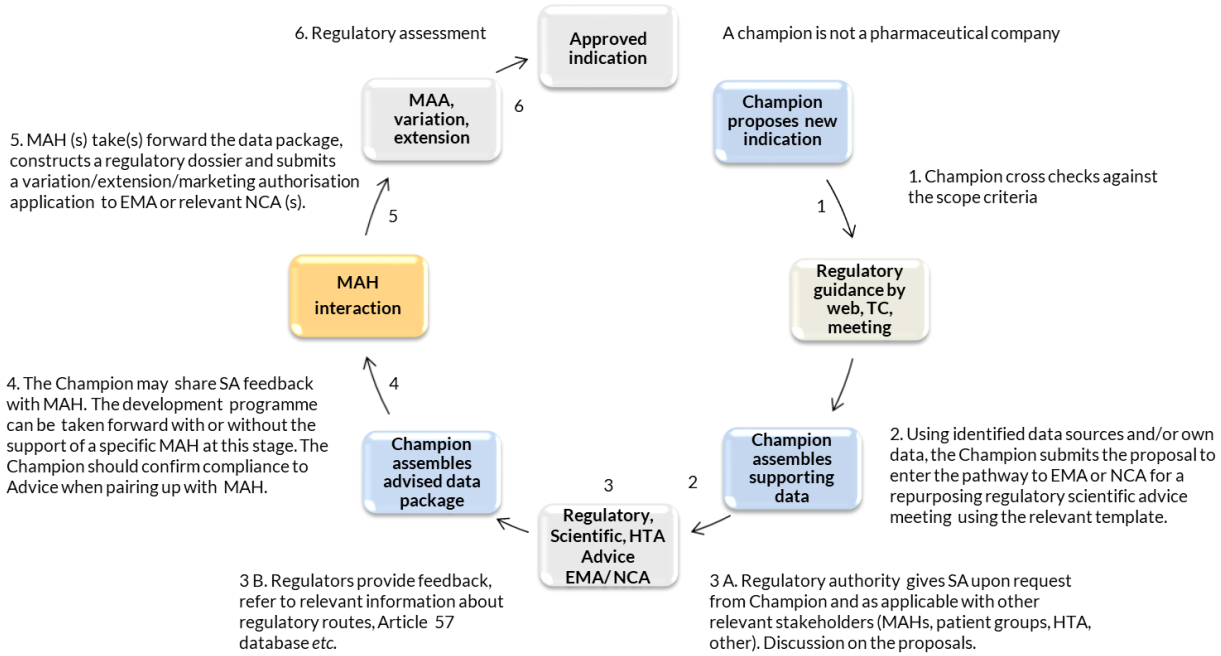

FIGURE 10. PROPOSED FRAMEWORK TO SUPPORT NON-FOR-PROFIT ORGANISATIONS AND ACADEMIA IN DRUG REPURPOSING.

Source: STAMP working group proposal of the repurposing framework, 2019 (330)

Abbreviations: Teleconference (TC), European Medicines Agency (EMA), National Competent Authority (NCA), Scientific Advice (SA), Marketing Authorisation Holder (MAH), Health Technology Assessments (HTAs), Marketing Authorisation Application (MAA)

Finally, the STAMP group considered that it would be important to initiate a **pilot** to assess whether the proposed framework is able to facilitate an application for a new indication for a medicinal product out of basic patent or regulatory protection. To learn from this pilot and conclude on the operational aspects of the repurposing framework, it was decided to create a voluntary virtual observatory group, called the **Repurposing Observatory Group (RepOG)**, which would consist of champion interest groups, industry, regulatory representatives and other stakeholders as appropriate. In addition, the **EU Innovation Network** will play an important role in the repurposing pilot. The specific objectives and long- and short term deliverables of the pilot, as well as the activities and mandate of the RepOG are outlined in the proposal document of the STAMP working group (330).

In preparation of the pilot, the **aim of this study** was to identify and analyse promising repurposing candidates in oncology, to be presented and discussed with the STAMP expert group in March 2019.

METHODS

First, a **number of drug repurposing candidates in oncology** were identified that could potentially serve as pilot cases to test the proposed repurposing framework. This selection was done in consultation with colleagues at the Anticancer Fund who have profound expertise in clinical drug repurposing research as illustrated by the Anticancer Fund's clinical trial portfolio (342) and their involvement in the Repurposing Drugs in Oncology (ReDO) project (45,68). All candidates had to meet the criteria as specified by the framework proposal (Appendix G). Next, a **standardized template** was created with input from members of the STAMP working group to collect comparable information for all pilot cases (Appendix H). **Data collection took place in January 2019.** Various data sources were consulted to collect the required data, including regulatory information documents and databases (public assessment reports, summary of product characteristics, Heads of Medicines Agencies (HMA) MRI Product Index (343), EMA Article 57 database (344)), scientific literature and clinical trial databases (PubMed, clinicaltrials.gov), protocols of the clinical trials supported by the Anticancer Fund and clinical practice guidelines. The proposed template and pilot cases were presented and discussed with representatives from the scientific advice and regulatory affairs departments of the EMA during a teleconference in January 2019 and with all members of the European Commission STAMP Expert Group during a meeting in March 2019.

RESULTS

We purposively selected **nine repurposing candidates in oncology with different characteristics** (Table 10). More specifically, we started by selecting candidates in terms of available evidence and stage of development because candidates with a lot of clinical evidence (one or more phase III trials) require a different type regulatory and scientific support or guidance as opposed to candidates that are still in early development (phase I or II trials). Furthermore, we meant to include examples of "hard repurposing", which means repurposing a medicine from outside of oncology, and "soft repurposing", which refers to medicines that are already used in a cancer indication. We decided to include single agents (potentially in addition to the standard of care) as well as combinations of two or more repurposed medicines. Finally, we selected both nationally authorised products (assessed by NCAs) and centrally authorised products (assessed by EMA) to illustrate possible regulatory implications.

TABLE 10. SUMMARY OF THE SELECTED DRUG REPURPOSING CANDIDATES IN ONCOLOGY

	ACTIVE SUBSTANCE	PROPOSED NEW INDICATION	HIGHEST LEVEL OF EVIDENCE	DEVELOPMENT STAGE [A]	HARD OR SOFT REPURPOSING	COMBI-NATION [B]	EU MARKETING AUTHORISATION
1.	Zoledronic acid	Prevention of breast cancer spreading to the bone in postmenopausal women with primary breast cancer	Meta-analysis of phase III trials	Late	Soft repurposing	No	Centralised procedure
2.	Docetaxel	First-line treatment of metastatic, hormone-sensitive prostate cancer in combination with androgen deprivation therapy	Meta-analysis of phase III trials	Late	Soft repurposing	No	Centralised procedure
3.	Letrozole	Maintenance setting of ER positive epithelial ovarian cancer after surgical debulking and adjuvant chemotherapy	Retrospective studies	Mid	Soft repurposing	No	Mutual recognition and national procedures
4.	Clarithromycin	· Treatment of newly diagnosed multiple myeloma in combination with lenalidomide and dexamethasone · Treatment of refractory multiple myeloma with insufficient response or disease progression on lenalidomide and dexamethasone	Phase II trials	Mid	Hard repurposing	No	Mutual recognition and national procedures
5.	Acetylsalicylic acid and atorvastatin	Treatment of castrate-resistant prostate cancer in combination with standard of care	Observational study with combination	Mid	Hard repurposing	Yes	Mutual recognition and national procedures [C]
6.	Propranolol	Neoadjuvant treatment of resectable angiosarcoma	Case reports	Early	Hard repurposing	No	Mutual recognition and national procedures
7.	Zoledronic acid and sirolimus	Treatment of advanced pretreated osteosarcoma, in combination with metronomic chemotherapy	No evidence of combination	Early	Soft repurposing	Yes	Centralised procedure [C]
8.	Propranolol and etodolac	Perioperative use in pancreatic cancer	Preclinical evidence of combination	Early	Hard repurposing	Yes	Mutual recognition, decentralised and national procedures [C]
9.	CUSP9v3 protocol with 9 repurposed medicines	Treatment of recurrent glioblastoma	Phase I trial with combination	Early	Hard repurposing	Yes	Aprepitant: centralised procedure Other medicines: national procedures [C]

[A] Late= phase III trials completed, Mid= phase III trials ongoing or in preparation, Early= phase I or II trials ongoing or in preparation; [B] Combination of repurposed medicines;
[C] Authorised separately, not as a combination

The results of this study were collected based on a **standardized template** that required information about the product and the original authorised indication(s), the rationale and unmet medical need for the proposed new indication, and a summary of scientific evidence supporting the new indication (*i.e.*, non-clinical data, clinical data and recommendations in clinical practice guidelines if available) (Appendix H).

1. ZOLEDRONIC ACID IN POSTMENOPAUSAL WOMEN WITH PRIMARY BREAST CANCER

Zoledronic acid is a **bisphosphonate** indicated for the prevention of skeletal related events in adult patients with advanced malignancies affecting the bone (pathological fractures, spinal compression, radiation or surgery to bone, or tumour-induced hypercalcaemia) and for the treatment of adult patients with tumour-induced hypercalcaemia. Zoledronic acid was first authorised in Europe in 2001 via the **centralised procedure** (Zometa®, current marketing authorisation holder: Novartis) and today **numerous generic products** are on the market. The authorised pharmaceutical form is a powder or solvent for solution for intravenous use.

The **proposed new indication** for zoledronic acid is the prevention of breast cancer spreading to the bone in postmenopausal women with primary breast cancer. Bisphosphonates are extensively used to prevent fractures in patients with breast cancer who have skeletal metastases, and for the prevention or treatment of osteopenia in women with therapy-induced bone loss (345). In 2015, a large **meta-analysis** showed that bisphosphonate treatment could reduce recurrence and mortality in post-menopausal women with primary breast cancer (346), which was confirmed by a **Cochrane review** in 2017 (347) (Box 6.1). The **exact anticancer mechanisms of bisphosphonates are unknown**, but their ability to prevent or delay bone recurrence is most likely related to their well-known effects on osteoclast activity (348,349).

BOX 6.1 | EVIDENCE SUMMARY: ZOLEDRONIC ACID IN POSTMENOPAUSAL WOMEN WITH PRIMARY BREAST CANCER

A large meta-analysis of individual patient data from 26 RCTs involving 18,766 women around the world with primary breast cancer, of which 11,767 postmenopausal women, was published in the Lancet in 2015 (346). While bisphosphonate treatment had no apparent effect on breast cancer recurrence or mortality among premenopausal women, a definite benefit was shown in women who were postmenopausal at the start of treatment. More specifically, the authors reported that bisphosphonates significantly reduce recurrence (first-event rate ratio (RR): 0.86, 95% confidence interval (CI) 0.78–0.94), distant recurrence (RR: 0.82, 95% CI 0.74–0.92), bone recurrence (RR: 0.72, 95% CI 0.60–0.86) and breast cancer mortality (RR: 0.82, 95% CI 0.73–0.93) in postmenopausal women. A Cochrane review from 2017 also showed a survival benefit from bisphosphonates in postmenopausal women in a subgroup analysis by menopausal status (Hazard Ratio (HR): 0.77, 95% CI 0.66-0.90; 4 studies; 6048 women) (347). Currently, several treatment optimization trials are ongoing to study the effects of different bisphosphonates, formulations, dosing (intervals), and durations of treatment. For example, the REaCT-ZOL phase IV clinical trial sponsored by the Ottawa Hospital Research Institute is comparing a single-dose versus twice-yearly zoledronic acid in patients with early stage breast cancer (NCT03664687).

Based on this meta-analysis and an additional systematic review of scientific literature, the **Cancer Care Ontario (CCO) and American Society of Clinical Oncology (ASCO) guideline** recommends that "*if available, zoledronic acid (4 mg intravenously every 6 months) or clodronate (1,600 mg/d orally) be considered as adjuvant therapy for postmenopausal patients with breast cancer who are deemed candidates for adjuvant systemic therapy*" (350). In 2016, a **European consensus panel** representing 25 clinical oncology centres recommended that "*bisphosphonates (either intravenous zoledronic acid or oral clodronate) are considered as part of the adjuvant breast cancer treatment in this population [postmenopausal women or those receiving ovarian suppression therapy] and the potential benefits and risks are discussed with relevant patients*" (351). In 2017, the **UK National Institute for Health and Care Excellence (NICE)** published a detailed **evidence summary** about the use of adjuvant bisphosphonates in pre- and postmenopausal women with early breast cancer to prevent recurrence and improve survival (352). Despite the large evidence base and the recommendations in various clinical treatment guidelines, zoledronic acid does not have a marketing authorisation for use in the proposed indication and is therefore frequently **prescribed off-label**.

2. DOCETAXEL IN HORMONE-SENSITIVE METASTATIC PROSTATE CANCER

Docetaxel is a **cytotoxic chemotherapeutic agent** indicated for the treatment of breast cancer, non-small cell lung cancer, prostate cancer, gastric adenocarcinoma and head and neck cancer (more detailed therapeutic indication in section 4.1 of the SmPC (353)). Docetaxel was first authorised in Europe in 1995 via the **centralised procedure** (Taxotere®, current marketing authorisation holder: Sanofi Mature IP) and today **numerous generic products** are on the market. The authorised pharmaceutical form is a concentrate and solvent for solution for intravenous use.

The **proposed new indication** for docetaxel is the first-line treatment of metastatic hormone-sensitive prostate cancer in combination with androgen deprivation therapy**.** Docetaxel is a **well-established anti-mitotic agent** that interferes with the normal function of microtubule growth and is already indicated for the treatment of patients with metastatic castrate-resistant prostate cancer in combination with prednisone or prednisolone**.** In 2016, a **meta-analysis of three RCTs** showed that the addition of docetaxel to standard of care also improves survival in men with metastatic hormone-sensitive prostate cancer (354), which was confirmed by a **Cochrane systematic review** (355) (Box 6.2). Based on the meta-analysis of phase III trials, several **clinical treatment and insurance guidelines** recommend the combination of docetaxel and androgen deprivation therapy for the first-line treatment of metastatic, hormone-sensitive prostate cancer. These guidelines include the European Society of Medical Oncology (ESMO) Clinical Practice Guidelines for prostate cancer (356), the European Association of Urology (EAU) prostate cancer guidelines (357) and the US National Comprehensive Cancer Network (NCCN) prostate cancer guidelines (358). However, regardless of the large evidence base, docetaxel does not have a marketing authorisation for use in the proposed indication[1], and is therefore **prescribed off-label** on a case-by-case basis (359,360).

Another treatment regimen, abiraterone acetate plus prednisone, is already authorised for the treatment of metastatic hormone-sensitive prostate cancer. From a public health perspective, it would be interesting

[1] Update: In March 2019, Aventis Pharma S.A. submitted an application for a variation to include the treatment of patients with metastatic hormone-sensitive prostate cancer in combination with androgen-deprivation therapy, with or without prednisone or prednisolone, for Taxotere and Docetaxel Zentiva to the EMA.

to study both treatment regimens in a comparative trial, especially because the overall treatment cost for docetaxel therapy is lower than for abiraterone (359,361). Currently, **a phase III RCT** (PEACE-1) sponsored by UNICANCER is ongoing in several European countries to compare the clinical benefit of androgen deprivation therapy and docetaxel (arm A) versus the combination of androgen deprivation therapy, docetaxel, abiraterone acetate and prednisone (arm B) and both arms with local radiotherapy (arm C & D) in patients with metastatic hormone-sensitive prostate cancer (NCT01957436).

BOX 6.2 | EVIDENCE SUMMARY: DOCETAXEL IN HORMONE-SENSITIVE METASTATIC PROSTATE CANCER

Two phase III clinical trials, STAMPEDE (NCT00268476) and CHAARTED (NCT00309985), support the use of docetaxel in hormone-sensitive metastatic prostate cancer (81,519–521). One phase III trial, GETUG-AFU 15 (NCT00104715), obtained conflicting results and therefore did not recommend docetaxel as part of the first-line treatment in this indication (522,523). In 2016, a meta-analysis of the results from the CHAARTED, GETUG-15 and STAMPEDE trial (2992 participants in total) showed that the addition of docetaxel to standard of care improves survival (HR: 0.77, 95% CI 0.68 - 0.87), and reported an absolute improvement in 4-year survival of 9% (95% CI 5% - 14%) (354). The authors of this study concluded, "*The addition of docetaxel to standard of care should be considered standard care for men with M1 hormone-sensitive prostate cancer who are starting treatment for the first time*". In 2018, a Cochrane systematic review confirmed that the early addition of taxane-based chemotherapy to androgen deprivation therapy for hormone-sensitive prostate cancer probably prolongs overall and disease-specific survival, and delays disease progression, compared to androgen deprivation therapy alone (355). Yet, some real-world evidence studies indicated that the addition of docetaxel to androgen deprivation therapy might be less effective and lead to a higher toxicity rate than shown in phase III clinical trials (524–526).

3. LETROZOLE IN EPITHELIAL OESTROGEN RECEPTOR POSITIVE OVARIAN CANCER

Letrozole is an **aromatase inhibitor** indicated for the treatment of breast cancer in postmenopausal women (more detailed therapeutic indication in section 4.1 of the SmPC (362)). Letrozole was first authorised in Europe in 1996 via the **mutual recognition and national procedures** (Femara®, current marketing authorisation holder: Novartis) and today **numerous generic products** are on the market. The authorised pharmaceutical form are tablets for oral use.

The **proposed new indication** for letrozole is the maintenance setting of oestrogen receptor (ER) positive epithelial ovarian cancer after surgical debulking and adjuvant chemotherapy, for which the current standard of care is to watch and wait for potential recurrence. As the prognosis of advanced epithelial ovarian cancer is poor, new maintenance therapy regimens with a good tolerability are needed to prolong the recurrence-free interval (363). Oestrogen is a key driver of cancer growth in ER positive tumours. By blocking the action of the aromatase enzyme, **aromatase inhibitors such as letrozole inhibit the synthesis of oestrogen** and reduce the growth and spread of cancer. Letrozole is already indicated as a standard therapy in early and advanced ER positive breast cancer patients (364,365) and **preclinical and clinical**

studies provided evidence to support letrozole in the maintenance setting after primary treatment in women with ER positive low-grade and high-grade serous ovarian carcinoma (Box 6.3). At the time of data collection, a **double blind, multicentre phase III RCT was in preparation** by the Swiss Go Trial Group to evaluate the efficacy of adding letrozole (2.5 mg once daily) to the standard maintenance therapy in patients with a primary diagnosis of ER positive epithelial ovarian cancer. The study's primary endpoint is to assess progression free survival of letrozole maintenance treatment compared to the standard of care.

BOX 6.3 | EVIDENCE SUMMARY: LETROZOLE IN EPITHELIAL OESTROGEN RECEPTOR POSITIVE OVARIAN CANCER

Preclinical studies showed that oestrogen stimulates cancer growth in ER positive ovarian tumours and reported aromatase expression in ovarian epithelial normal tissues and in some ovarian epithelial cancer cells and tissues (527–531). *In vitro* studies also indicated an anti-tumour effect of aromatase inhibitors in ovarian cancer cells (532) and an *in vivo* study demonstrated prolonged survival with letrozole treatment (5 mg/kg daily) in a murine model of ovarian cancer with abundant expression of ERα (533). Clinical evidence to support letrozole maintenance therapy after primary treatment in women with low-grade and high-grade serous ovarian carcinoma primarily comes from retrospective studies (363,534–537). However, in patients with relapsed ER positive epithelial ovarian cancer, several phase II trials, retrospective studies and case reports showed clinical benefit of treatment with letrozole (2.5 mg daily) and no serious adverse events were reported (531,534,538–547). Langdon and colleagues summarized that endocrine therapy yields responses in about 10-15% of patients with epithelial ovarian cancer, while disease stabilization is achieved in another 30% (547,548). The use of predictive biomarkers, such as high ERα expression, may help to predict sensitivity to endocrine therapy in ovarian cancer patients and thus may improve the response rate to letrozole therapy (531,547–549). In addition, high grade serous, low grade serous and endometrioid ovarian carcinomas have the highest ER expression so these patients are likely to have the greatest benefit from endocrine therapy (534,547). In the 2018 US NCCN guidelines, letrozole was listed as an option in the adjuvant treatment of low-grade serous endometrioid epithelial carcinoma and for patients who cannot tolerate or have not responded to cytotoxic regimen in the relapsed setting (550).

4. CLARITHROMYCIN IN MULTIPLE MYELOMA

Clarithromycin is a well-known **macrolide antibiotic** indicated for the treatment of a wide variety of bacterial infections caused by clarithromycin-susceptible bacteria (bacterial tonsillitis/pharyngitis, community acquired pneumonia, acute otitis media in children, bacterial sinusitis, acute exacerbation of chronic bronchitis, skin and soft tissue infections, *Helicobacter Pylori* infections). Clarithromycin was first authorised in Europe in 1990 via the **mutual recognition and national procedures** (Klacid® or Klaricid®, current marketing authorisation holder: Mylan) and today **numerous generic products** are on the market (366). The authorised pharmaceutical forms include tablets or granules for suspension for oral use and a powder for solution for intravenous use.

BOX 6.4 | EVIDENCE SUMMARY: CLARITHROMYCIN IN MULTIPLE MYELOMA

In vitro results showed that clarithromycin and thalidomide synergistically inhibit the proliferation of multiple myeloma cells and significantly decrease the production of TNF-alpha and IL-6, two cytokines that are essential for sustaining multiple myeloma growth (551). Moreover, clarithromycin might augment the cytotoxic effects of thalidomide and bortezomib on multiple myeloma cells by attenuating autophagy (552,553). Clarithromycin may also overcome stromal-mediated multiple myeloma resistance to dexamethasone through inhibition of CYP3A4 (554).

Treatment of newly diagnosed multiple myeloma

Several phase II clinical studies showed that clarithromycin as a single agent or in combination with pamidronate is not effective for treating patients with multiple myeloma (555–558). However, a retrospective case-matched analysis (72 patients) demonstrated a significant additive value of adding clarithromycin to lenalidomide and low-dose dexamethasone for newly diagnosed myeloma (559). A number of clinical trials demonstrated clinical benefit of adding clarithromycin to other anticancer treatments in early-stage multiple myeloma (367). Coleman and colleagues evaluated the combination of clarithromycin (500 mg twice daily), thalidomide, and dexamethasone (BLT-D) to treat patients with previously untreated or treated multiple myeloma or Waldenström's macroglobulinemia in a clinical trial. Of the 50 evaluable patients in this study, 93% responded to BLT-D, including 13% complete remissions, 40% near complete responses, 13% major responses, and 27% partial responses (560). Niesvizky and colleagues reported the efficacy of clarithromycin (500 mg twice daily), lenalidomide, and dexamethasone combination therapy (BiRD) for the treatment of symptomatic, newly diagnosed multiple myeloma (NCT00151203) (561,562). Of the 72 patients enrolled in this study, 93% responded to BiRD, including 43% complete responses, 25% very good partial responses, and 25% partial responses after a median follow-up of 6.6 years. The same research group investigated the combination of clarithromycin (500 mg twice daily), lenalidomide, dexamethasone and thalidomide in newly diagnosed symptomatic patients with multiple myeloma (T-BiRD) (NCT00538733) (563). Of the 26 patients in this study, 80% responded to T-BiRD, yet eight patients discontinued due to regimen toxicity.

Treatment of refractory multiple myeloma

In 2013, a case report described the effectiveness of adding clarithromycin to lenalidomide and dexamethasone after long-term use of lenalidomide for refractory multiple myeloma (564). Two retrospective analyses of real-world data of 24 patients and 31 patients with relapsed or refractory multiple myeloma suggested that adding clarithromycin at the time of progression may help to overcome resistance to lenalidomide and dexamethasone in some patients (565,566). A non-randomized clinical study indicated that the BLT-D and BiRD regimens could also be given to multiple myeloma patients after autologous hematopoietic stem cell transplantation (567). A phase II study involving 28 evaluable patients with relapsed and refractory myeloma showed that the combination of clarithromycin (250 mg twice daily), low dose of thalidomide (50 mg at night) and low dose dexamethasone (10 mg for 4 days monthly) was well-tolerated and can offer some clinical benefit (96% overall response rate) (568).

The **proposed new indication** for clarithromycin is the treatment of patients with newly diagnosed multiple myeloma in combination with lenalidomide and dexamethasone, and the treatment of patients with refractory multiple myeloma who have an insufficient response or disease progression on lenalidomide and dexamethasone. Preclinical and clinical studies have shown anticancer activity of clarithromycin in various tumour types, mostly in combination with conventional therapies (367). **Multiple putative mechanisms of action** have been put forward to explain the anticancer effect of clarithromycin (*e.g.*, prolonged reduction of pro-inflammatory cytokines, autophagy inhibition, and anti-angiogenesis) (367). In newly diagnosed multiple myeloma, **several preclinical and phase II clinical studies** demonstrated clinical benefit of administering clarithromycin in combination with lenalidomide and dexamethasone. Moreover, **retrospective analyses of real-world data and a phase II trial** indicated that clarithromycin could also provide clinical benefit to patients with refractory multiple myeloma (Box 6.4).

At the time of data collection, **two phase III RCTs were ongoing** that could provide clarity about the clinical application of clarithromycin in newly diagnosed multiple myeloma (368) [2]. The GEM-CLARIDEX trial is an open-label randomized study sponsored by the PETHEMA foundation in Spain and in the US to examine lenalidomide and dexamethasone with and without clarithromycin in patients with newly diagnosed multiple myeloma (NCT02575144). The second trial is a multicentre, randomized study sponsored by Jinling Hospital in China to explore whether clarithromycin increases responsiveness to cyclo-phosphamide, thalidomide and dexamethasone in newly diagnosed multiple myeloma (NCT02248428).

5. ASPIRIN AND ATORVASTATIN IN CASTRATE-RESISTANT PROSTATE CANCER

Acetylsalicylic acid (aspirin) is a very well-known **nonsteroidal anti-inflammatory drug (NSAID)** with analgesic, anti-pyretic, anti-inflammatory, anti-thrombotic and cardio protective actions. Acetylsalicylic acid has been on the market for over 120 years and is authorised in Europe via the **national procedures** (Aspirin®, original marketing authorisation holder: Bayer). It is available in a variety of pharmaceutical forms, mostly for oral use. Atorvastatin is an established **HMG-CoA reductase inhibitor** indicated for the treatment of hypercholesterolemia and for the prevention of cardiovascular events in adult patients estimated to have a high risk for a first cardiovascular event. Atorvastatin was first authorised in Europe in 1996 via the **mutual recognition and national procedures** (Lipitor®, current marketing authorisation holder: Pfizer). The authorised pharmaceutical forms include tablets for oral use. **Numerous generic products** are on the market for both medicines.

The **proposed new indication** for the combination of acetylsalicylic acid and atorvastatin is the treatment of patients with castrate-resistant prostate cancer, which is defined by disease progression despite androgen depletion therapy, in addition to the standard of care. A substantial body of preclinical, clinical and epidemiologic evidence indicates beneficial effects of both acetylsalicylic acid and atorvastatin individually in various tumour types (369–379), and particularly in the prevention and treatment of prostate cancer (380–387). **Multiple putative modes of action** have been put forward to explain the observed **anticancer effects of statins** (*e.g.*, inhibition of the mevalonate pathway and its downstream

[2] Update: At the ASH Annual Meeting in November 2019, it was reported that the addition of clarithromycin to lenalidomide and dexamethasone in newly diagnosed multiple myeloma patients significantly increases the rate and depth of responses but it is not associated with an improved progression-free survival or overall survival (471).

products) (388–390). However, statins are of particular interest in castrate-resistant prostate cancer as they might reduce androgens within the prostate cancer microenvironment in two ways (391–394). First, cholesterol-lowering statins may disrupt the steroidogenic ability to synthesize androgens from cholesterol in a subpopulation of prostate cancer cells that develop castration-resistance (391,393). Second, statins may inhibit the uptake of the androgenic precursor dehydroepiandrosterone sulfate (DHEAS) by the tumour cells by competitively binding to SLCO transporters (392,394). Furthermore, the **anticancer activity of acetylsalicylic acid** could be associated to **cyclo-oxygenase (COX) and non-COX-dependent pathways** but the exact mechanism remains unknown (370,373,395). Several preclinical and clinical retrospective studies showed anticancer activity and clinical benefit of statin use in castrate-resistant prostate cancer. **Evidence for the combination of acetylsalicylic acid and atorvastatin** primarily comes from ***in vitro* research** in prostate cancer cell lines (Box 6.5).

At the time of data collection, a **phase III, multicentre, international RCT was in preparation** (PEACE-4), sponsored by Gustave Roussy in France, to evaluate the effect on overall survival of adding either acetylsalicylic acid (100 mg daily), atorvastatin (80 mg daily) or the combination of both agents to the standard of care for patients with castrate-resistant prostate cancer starting first line treatment. This study is based on the results from *in vitro* research and on the hypothesis that the cardiovascular effects of acetylsalicylic acid and atorvastatin could also alleviate the long-term cardiovascular side effects of androgen-deprivation therapy, which could further reduce morbidity and mortality (396).

BOX 6.5 | EVIDENCE SUMMARY: ASPIRIN AND ATORVASTATIN IN CASTRATE-RESISTANT PROSTATE CANCER

In vitro studies demonstrated that statins, including atorvastatin, directly inhibit proliferation, migration and colony formation of castrate-resistant prostate cancer cells, especially when combined with abiraterone acetate or docetaxel (391,393). Two retrospective clinical studies reported that statin use is significantly associated with prolonged overall survival and increased prostate-specific antigen (PSA) declines in patients with metastatic castrate-resistant prostate cancer that received abiraterone or enzalutamide (569,570). However, one other study did not observe this effect (571). Two additional retrospective studies showed that statins may prolong time to progression in patients with hormone-sensitive prostate cancer treated with androgen deprivation therapy, also after adjusting for predefined prognostic factors (394,572).

One preclinical study in human prostate cancer cells and xenograft prostate tumours in mice described a beneficial effect of the combination of atorvastatin and acetylsalicylic acid on growth inhibition and apoptosis stimulation in prostate cancer cells, more than treatment with either drug alone (573). A retrospective case-control study at a single academic centre suggested that chronic, concomitant treatment with statins and acetylsalicylic acid has a protective effect on prostate cancer incidence (574). Based on these clinical observations, the same research group performed an *in vitro* study and showed that simvastatin and acetylsalicylic acid have anti-tumorigenic properties in prostate cancer cell lines, which are enhanced when both treatments are administered simultaneously.

6. PROPRANOLOL IN ANGIOSARCOMA

Propranolol is a well-known **beta-blocker** indicated for the treatment of hypertension, angina pectoris, cardiac dysrhythmias, tachycardia, anxiety, and essential tremor, and for long-term prevention of sudden cardiac death. It is also used for the prophylaxis of migraine and upper gastrointestinal bleeding in patients with portal hypertension and oesophageal varices, and as an adjunctive therapy in thyrotoxicosis. Propranolol was first authorised in Europe in 1965 via the **mutual recognition and national procedures** (Inderal®, current marketing authorisation holder: AstraZeneca) and today **numerous generic products** are on the market. In 2014, propranolol was authorised via the **centralised paediatric use marketing authorisation** (PUMA) procedure for treating children with infantile haemangioma (Hemangiol®, current marketing authorisation holder: Pierre Fabre Dermatologie) (307,397). The authorised pharmaceutical forms include tablets or capsules for oral use and an oral solution for paediatric use.

The **proposed new indication** for propranolol is the neoadjuvant setting prior to surgery of resectable angiosarcoma, which is a type of soft tissue sarcoma with a poor survival rate and a high metastatic potential (398,399). The standard of care for localised angiosarcoma is complete surgical resection with or without radiation. Yet, despite optimal management, approximately 50% of patients develop recurrent disease (400). In the locally advanced/metastatic setting, several cytotoxic drugs (*e.g.*, anthracyclines, taxanes and gemcitabine) have shown activity, with varying response rates (401–403). For the treatment of resectable angiosarcoma, there are no studies showing a beneficial role for neoadjuvant systemic therapy with the currently available cytotoxic agents, in terms of prolonged disease-free survival or overall survival. Preclinical and clinical studies have indicated a potential role of propranolol in the treatment of various cancer types, particularly in combination with other agents (399). The anticancer activity of propranolol can be explained through its **direct effect on beta-adrenergic receptors**, which are highly expressed in malignant vascular tumours such as angiosarcoma (404–408). Yet, **other putative modes of action** of propranolol in cancer treatment include the regulation of hematopoietic progenitor cells, anti-angiogenesis and immune modulation (399,409). The hypothesis for the repurposing of propranolol in angiosarcoma is primarily based on evidence from **preclinical studies and a number of case reports** (Box 6.6). Based on a summary of the existing evidence, the Anticancer Fund requested a **European orphan designation** for propranolol as a treatment for soft tissue sarcoma, which was granted in December 2016 (EU/3/16/1805).

In January 2019, a **dose-finding phase I/II clinical trial** of propranolol in combination with metronomic fixed-dose oral cyclophosphamide in 24 patients with locally advanced or metastatic angiosarcoma was ongoing in France (NCT02732678). A **phase II trial** with propranolol in the treatment of metastatic soft tissue sarcoma was expected to start recruiting mid-2019 in Egypt (NCT03108300). The primary endpoint of this trial is to assess progression free survival in 50 patients with pathological proof of malignant soft tissue sarcoma treated with a combination of anthracyclin-based chemotherapy and propranolol (40 mg twice daily). Moreover, at the time of data collection, the Netherlands Cancer Institute - Antoni van Leeuwenhoek Hospital was developing a study protocol for a **neoadjuvant window of opportunity phase II study** to explore the efficacy of propranolol monotherapy (40-80 mg 2-3 times a day, if tolerated) in cutaneous angiosarcoma.

BOX 6.6 | EVIDENCE SUMMARY: PROPRANOLOL IN ANGIOSARCOMA

Preclinical studies showed that propranolol inhibits tumour cell viability, proliferation, tumour growth and mitogenic signalling in angiosarcoma cell lines and animal models (399,406,575). The anti-proliferative effect of propranolol was shown to be dose-dependent, where the dose that is needed for the anti-angiogenic effect is beneath the threshold of toxic concentrations and shows no vascular-disrupting activity of normal endothelial cells (408). Furthermore, preclinical studies have demonstrated synergy between propranolol in combination with vinblastine, cisplatin, busulfan, vincristine, 5-FU, and paclitaxel in *in vitro* angiosarcoma models (405,406,408).

Banavali *et al*. described a case of relapsing metastatic angiosarcoma treated with a combination of metronomic chemotherapy, celecoxib and 40 mg propranolol twice daily (576). They observed a quick complete response that lasted for 20 months, the patient ultimately died of progressive disease. In a subsequent report of the same group, propranolol and vinblastine-based metronomic chemotherapy led to 100% response in 7 patients with advanced angiosarcoma (405). Furthermore, two other case reports provided promising evidence for the use of propranolol in combination with standard therapy in angiosarcoma (577,578). Only two cases were described in which a patient with angiosarcoma was treated with propranolol monotherapy (407,579). Galván *et al*. reported that after 12 months, the cardiac angiosarcoma decreased in size, and metastatic nodules stabilized or resolved with no evidence of hyper-metabolic activity (579). Chow *et al*. reported a reduction in the proliferative index (evaluation before and after 1 week of propranolol monotherapy) of the tumour by approximately 34% (407).

7. ZOLEDRONIC ACID AND SIROLIMUS IN ADVANCED PRETREATED OSTEOSARCOMA

Sirolimus is an **immunosuppressant agent** indicated for the prophylaxis of organ rejection in adult patients at low to moderate immunological risk receiving a renal transplant and for the treatment of patients with sporadic lymphangioleiomyomatosis with moderate lung disease or declining lung function. Sirolimus, also called rapamycin, was first authorised in Europe in 2001 via the **centralised procedure** (Rapamune®, current marketing authorisation holder: Pfizer) and there are **no generic products** on the market. The authorised pharmaceutical forms include coated tablets and a solution for oral use. The product characteristics of zoledronic acid were previously described (see pilot case 1).

The **proposed new indication** for the combination of zoledronic acid and sirolimus is the treatment of patients with advanced pretreated osteosarcoma in addition to metronomic chemotherapy. The standard treatment for osteosarcoma typically involves surgery and (neo-) adjuvant chemotherapy (anthracyclines, platinum salts, ifosfamide and methotrexate given in combination in different protocols). Upon relapse, combination protocols are recommended when complete surgery of the metastases is considered achievable, but patients with metastatic and recurrent osteosarcoma have a very poor prognosis. A large body of preclinical and clinical evidence indicates that **targeting the mTOR complex using mTOR inhibitors like sirolimus** could be a valuable approach for treating osteosarcoma (410–414). Some preclinical data suggest a benefit of **zoledronic acid** used alone or in combination with other anticancer agents in osteosarcoma, but the **exact anticancer mechanism remains unknown** (Box 6.7).

Nevertheless, to our knowledge, the **combination** of methotrexate and cyclophosphamide given together with sirolimus and zoledronic acid was **not yet investigated in preclinical or clinical studies**.

BOX 6.7 | EVIDENCE SUMMARY: ZOLEDRONIC ACID AND SIROLIMUS IN ADVANCED PRETREATED OSTEOSARCOMA

Preclinical studies showed that alterations in the mTOR signalling pathway are associated with osteosarcoma tumorigenesis and the formation of metastases, and that combining mTOR inhibition with other anticancer agents could have a synergistic effect on both the tumour microenvironment and cancer cells in advanced osteosarcoma (580–585). Early clinical trials showed anticancer activity and safety of sirolimus, alone or in combination with anticancer therapies (586–588). In a phase II trial, sirolimus (4 mg daily) showed little activity when combined with oral cyclophosphamide in 49 patients with heavily pretreated sarcoma (NCT00743509) (589). However, this study included only five patients with osteosarcoma and the dose of cyclophosphamide assessed in this study (200 mg daily) may have precluded any positive immunological effect. Metronomic low-dose cyclophosphamide may be more effective in treating patients with advanced cancers (590). An open-label, phase II trial assessing the mTOR inhibitor ridaforolimus as a single agent in patients with distinct subtypes of advanced sarcomas showed positive results regarding clinical benefit response and progression free survival (NCT00093080, NCT00112372) (591). Moreover, a single-arm phase II trial demonstrated anticancer activity and safety of gemcitabine plus sirolimus for treating patients with relapsed, unresectable osteosarcoma (NCT02429973) (592). A study regarding off-label use of targeted therapies in osteosarcomas, using the national registry of the French sarcoma group (GSF-GETO), reported benefit and acceptable toxicity of sirolimus in the treatment of refractory osteosarcomas (593).

In vitro studies showed that bisphosphonates have a direct effect on the proliferation, migration, invasiveness and survival of osteosarcoma cells (594–600). Studies in murine models of osteosarcoma demonstrated a reduction in lung metastases and prolonged survival upon administration of bisphosphonates in high doses (0.1 mg/kg at least twice weekly) (596,597,601). However, conflicting results have been reported with regard to the efficacy of zoledronic acid in clinically relevant doses (0.08 - 0.1 mg/kg given once) against pulmonary metastases in murine and rat osteosarcoma models (598,602–604). Additionally, preclinical studies showed synergistic effects of the combined use of zoledronic acid with other anticancer agents (paclitaxel, gemcitabine, cisplatin, doxorubicin, ifosfamide) on osteosarcoma growth (605–607), and with mTOR inhibition (everolimus) (608). One clinical study reported encouraging progression free survival with zoledronic acid as a single agent in four consecutive patients with metastatic osteosarcoma (609). A phase I trial established that zoledronic acid can be safely combined with conventional chemotherapy with an maximum tolerated dose of 2.3 mg/m^2 (max 4 mg) for treating patients with metastatic osteosarcoma (NCT00742924) (610). Yet, a multicentre, open-label, phase III RCT involving 318 newly diagnosed high-grade osteosarcoma patients was terminated after the second interim analysis because the combination of zoledronic acid with chemotherapy and surgery did not improve event-free survival (NCT00470223) (611).

Currently, an **open-label phase I trial** is ongoing in France sponsored by the Institut Bergonié to investigate metronomic chemotherapy combined with zoledronic acid and sirolimus in patients with solid tumours with bone metastasis and advanced pretreated osteosarcoma (METZOLIMOS, NCT02517918). This study consists of two parts, namely a dose escalating study to assess two dose levels of sirolimus when prescribed in combination with metronomic cyclophosphamide, methotrexate and zoledronic acid followed by an expansion cohort once the maximum tolerated dose is established.

8. PERIOPERATIVE USE OF PROPRANOLOL AND ETODOLAC IN PANCREATIC CANCER

Etodolac is a **NSAID** indicated for the management of acute pain and for acute or long-term use in rheumatoid arthritis and osteoarthritis. Etodolac was first authorised in Europe around 1987 via the **decentralised and national procedures** but the brand product (Lodine®, original marketing authorisation holder: Wyeth pharmaceuticals) was discontinued. As a result, etodolac is only available as a generic product in a limited number of countries. The authorised pharmaceutical form is a capsule or tablet for oral use. The product characteristics of propranolol were previously described (see pilot case 6).

The **proposed new indication** for the combination of propranolol and etodolac is the perioperative use in pancreatic cancer. The majority of patients with pancreatic ductal adenocarcinoma, which is the most common form of pancreatic cancer, are diagnosed at an advanced stage. Only about 15 to 20 percent of patients show no sign of metastasis at diagnosis and are eligible for surgical resection followed by adjuvant chemotherapy but the five-year overall survival of these patients is still low (about 20%), almost half of the patients relapse within the first year after surgery. Pancreatic cancer recurrence appears to be stimulated by perioperative psychological and surgical stress. **Simultaneously targeting catecholamines (stress hormones) and prostaglandins around the time of surgery** could therefore be an interesting treatment approach (415). Preclinical studies indicated that chronic psychological stress and catecholamines (norepinephrine and epinephrine) promote tumour cell proliferation, migration and invasion in a concentration-dependent manner via beta-adrenergic signalling, which provided a rationale for blocking beta-adrenergic signalling with a non-selective beta-blocker such as propranolol to prevent cancer recurrence (416–423). The anticancer activity of etodolac may be explained through the inhibition of COX2 enzymes, which are typically overexpressed in pancreatic tumour cells and are implicated in tumour development and progression through synthesis of prostaglandins (424,425). Several preclinical studies showed anticancer activity of propranolol or etodolac in pancreatic cancer cell lines and animal models (Box 6.8). Moreover, the combination of propranolol and etodolac together with other anticancer agents demonstrated clinical benefit and tolerability in patients with metastatic pancreas adeno-carcinoma and advanced hepatocellular carcinoma. **Evidence for the combined perioperative use of etodolac and propranolol** for reducing tumour metastasis comes from **preclinical animal studies and two pilot clinical trials in breast and colorectal cancer** (Box 6.8).

At the time of data collection, **a phase II, randomized clinical trial was in preparation** by the University of Heidelberg to investigate the safety, feasibility and generate first efficacy data of perioperative propranolol (20 or 40mg twice daily) and etodolac (400mg twice daily) in patients with operable cancer of the pancreatic head planned for elective pancreatoduodenectomy (426).

BOX 6.8 | EVIDENCE SUMMARY: PERIOPERATIVE USE OF PROPRANOLOL AND ETODOLAC IN PANCREATIC CANCER

In vitro and animal studies indicated that blocking beta-adrenergic signalling with a non-selective beta-blocker such as propranolol can inhibit early development of pancreatic cancer and metastasis formation (416–422,612,613). Moreover, preclinical *in vitro* and *in vivo* studies showed that COX2 inhibitors such as celecoxib, aspirin or etodolac can suppress pancreatic cancer growth and invasion, mostly in combination with other therapies (424,614–617).

In one clinical trial, 23 patients with metastatic pancreas adenocarcinoma were randomized to receive either nab-paclitaxel plus gemcitabine (GemNab), which is the standard of care, or GemNab after one week of propranolol and etodolac (PEGemNab) (618). This study reported an additional 5.4 months in overall survival and 4.6 months in progression free survival of the PEGemNab arm compared to the control arm, and no serious adverse events were reported. Similar results were reported in a small randomized study (20 patients) that combined sorafenib with propranolol and etodolac for advanced hepatocellular carcinoma (NCT01265576) (619).

The combined perioperative use of propranolol and etodolac, rather than either treatment on its own, improved recurrence-free survival and resistance to postoperative metastasis in mammary adenocarcinoma, melanoma, lung carcinoma and colon cancer rodent models (620–623). Additionally, two phase II proof-of-concept biomarker trials that explored the perioperative use of propranolol and etodolac in breast and colorectal cancer patients reported long-term safety and potential efficacy of the treatment, as demonstrated by a reduction of multiple tumour and circulating biomarkers associated with cancer progression and metastasis (NCT00502684, NCT00888797) (624–626).

9. COMBINATION OF NINE REPURPOSED DRUGS IN GLIOBLASTOMA

The **Coordinated Undermining of Survival Paths (CUSP)9v3 protocol** is a combination of metronomic temozolomide with nine repurposed drugs: aprepitant (a neurokinin 1 receptor inhibitor), minocycline (a tetracycline antibiotic), auranofin (a gold complex), disulfiram (an aldehyde dehydrogenase inhibitor), ritonavir (a protease inhibitor), itraconazole (a triazole antifungal agent), captopril (an angiotensin-converting-enzyme inhibitor), sertraline (a selective serotonin reuptake inhibitor) and celecoxib (a COX inhibitor). Only **aprepitant** is authorised via the **centralised procedure** in Europe, **all other medicines** are authorised via the **mutual recognition, decentralised or national procedures**. All medicines are on the market as **generic products**, except for auranofin, for which there is currently only one marketing authorisation holder in Europe (Vianex, Greece).

The **proposed new indication** for the CUSP9v3 regimen is the treatment of recurrent glioblastoma. Available treatment regimens for glioblastoma consist of surgery, radiation and chemotherapy using temozolomide. Yet, only 15 to 20% of patients are still alive five years after first treatment indicating that there is a clear unmet medical need for more and better options for patients with recurrent disease. The CUSP9v3 protocol is an innovative and non-conventional treatment regimen first proposed by Dr Marc-

Eric Halatsch and Dr Richard Kast. These medicines all have a well-established safety and toxicity profile and were selected based on experimental data indicating their potential anticancer activity. The **rationale** behind the combination of nine repurposed drugs is that **each drug would inhibit one or more essential growth-enhancing pathways used by glioblastoma**, thus increasing the effectiveness of temozolomide (427). Kast and Halatsch hypothesized that the combined action of the CUSP9 treatment regimen may "*block signaling at, or the activity of, AKT phosphorylation, aldehyde dehydrogenase, angiotensin converting enzyme, carbonic anhydrase -2,- 9, -12, cyclooxygenase-1 and -2, cathepsin B, Hedgehog, interleukin-6, 5-lipoxygenase, matrix metalloproteinase -2 and -9, mammalian target of rapamycin, neurokinin-1, p-gp efflux pump, thioredoxin reductase, tissue factor, 20 kDa translationally controlled tumor protein, and vascular endothelial growth factor*" (428). The combination of drugs in the original CUSP9-protocol was well tolerated when given on a **compassionate use basis** to patients with glioblastoma (428). A **phase I proof-of-concept clinical trial** with ten patients was completed and showed that the CUSP9v3 protocol is safe (NCT02770378) (429). Next, efficacy needs to be evaluated in a larger randomized clinical study.

DISCUSSION

To represent different repurposing scenarios, we deliberately selected **nine repurposing candidates with varying characteristics in terms of available evidence, development stage, type of repurposing and combinations with other medicines.** For example, some candidates already had a lot of clinical evidence to support their new use (*e.g.*, zoledronic acid in postmenopausal women with primary breast cancer, docetaxel in hormone sensitive metastatic prostate cancer), while others are still in the earlier stages of development (*e.g.*, CUSP9v3 protocol in glioblastoma, propranolol in angiosarcoma). Moreover, we included examples of "hard repurposing" (*e.g.*, clarithromycin, an antibiotic, in multiple myeloma), and "soft repurposing" (*e.g.*, letrozole, already approved for breast cancer, in epithelial ovarian cancer). Finally, we included examples of single repurposed medicines that can potentially be added to the standard of care (*e.g.*, docetaxel in hormone sensitive metastatic prostate cancer), as well as combinations of two or more repurposed medicines (*e.g.*, acetylsalicylic acid and atorvastatin in castrate-resistant prostate cancer, zoledronic acid and sirolimus in advanced pretreated osteosarcoma).

For some of the candidates in this study, the **mechanism of action** is evident (*e.g.*, inhibition of oestrogen synthesis by letrozole), whereas for others the exact mechanism remains unknown or multiple putative mechanisms have been identified. In fact, contrary to the present paradigm of targeted therapies, many of the 'older' medicines such as propranolol, clarithromycin and acetylsalicylic acid have multiple targets (*i.e.*, polypharmacology) (10,45). Since repurposed medicines are available on the market and typically used for other indications, the **initial rationale for a new use frequently derives from real-world observations and epidemiological studies** (*e.g.*, acetylsalicylic acid and atorvastatin in castrate-resistant prostate cancer) (106). Furthermore, almost all candidates in this study are either added to the standard of care or used in combination with other repurposed medicines. This observation is hardly surprising because **combination treatments are standard in oncology practice** so a repurposed medicine is unlikely going to be effective as a monotherapy. In fact, evidence suggests that many repurposed medicines could enhance the anticancer activity of existing anticancer treatments, such as chemotherapeutic drugs, radiotherapy and immunotherapy, and are therefore most effective when administered in combinations (45,68).

All candidates described in this study might entail significant **patient and public health benefits.** First, as a result of their **wide availability**, these medicines can readily be tested in clinical trials for their new use. Second, all candidates have **well-established toxicity and pharmacokinetics profiles** owing to their long-term clinical use in the originally autorised indications (59,72). It should be noted though that the safety and toxicity profile of repurposed medicines should be evaluated carefully on a case-by-case basis, especially when the product is administered in a different dose, dose interval, route of administration or in combination with other medicines. A common misconception is that repurposed medicines are safe. Yet, the reports of serious side effects of the well-established antimalaria drugs chloroquine and hydroxy-chloroquine in the treatment of COVID-19 highlight that safety, tolerability and potential toxicity of repurposed medicines should be considered cautiously in the new context. Third, all but one candidate (sirolimus) are available as generic products so they are relatively **affordable** compared to new anticancer medicines that enter the market. Fourth, all but two candidates (zoledronic acid and docetaxel) are available as tablets or capsules for oral use and therefore relatively **easy to administer to patients**.

In our opinion, all candidates outlined in this study could **benefit from regulatory and scientific advice** to efficiently generate a robust data package for marketing authorisation of the new indication once clinical benefit is established (300). Regulatory and scientific advice could help to assess whether additional studies are required to confirm the repurposing hypothesis and could facilitate the design of planned studies to ensure that they meet the strict regulatory requirements of registration trials. Such an advice procedure may also be an opportunity to discuss the relevance of real-world evidence (*e.g.*, data from observational studies or retrospective analyses of patient registries and payer databases) as a complement to RCTs to demonstrate clinical benefit of a repurposing candidate on a case-by-case basis. It should be noted that after we collected the data for this study and presented the proposed candidates to the STAMP group, Aventis Pharma S.A. submitted an application for a variation to include the treatment of patients with metastatic hormone-sensitive prostate cancer in combination with androgen-deprivation therapy for Taxotere and Docetaxel Zentiva to the EMA (430). On 19 September 2019, the EMA Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion recommending a change to the terms of the marketing authorisation for Taxotere (docetaxel) and Docetaxel Zentiva (431). This positive outcome obviates the need for regulatory or scientific advice for this specific candidate as it is now authorised in the new indication. In addition, in November 2019, the clinical investigators of the phase III GEM-CLARIDEX trial reported that the addition of clarithromycin to lenalidomide and dexamethasone in newly diagnosed multiple myeloma patients was not associated with improved progression-free survival or overall survival (109). Based on the negative results from this phase III trial, further investigations regarding clarithromycin in multiple myeloma will likely be discontinued.

During the STAMP meeting in March 2019, it was agreed that it is up to the Anticancer Fund (as a potential champion) to select and submit one or more of the candidates proposed in this study to become part of the **repurposing pilot**, preferably in consultation with the principal investigators of the planned or ongoing clinical trials. The pilot will also be open to submissions from other champions in all disease areas. To participate in the repurposing pilot, champions will be able to submit their candidate project(s) to the competent authority of their choice, *i.e.*, the EMA or a NCA participating in the project. The **template** that was created and used to guide evidence generation in this study (Appendix H) was considered relevant by the STAMP group, and is being developed further by the members of the RepOG as a "Drug Repurposing

Submission Form" for the pilot. Additionally, the RepOG is developing a **Q&A document** that will be made available upon the launch of the repurposing pilot to clarify the practical aspects (*e.g.*, eligibility criteria and selection process of candidate projects, procedural steps and timelines). The STAMP group considered that it would be ideal to include at least one candidate supported by advanced clinical evidence and one candidate in an early development stage. Moreover, while this study highlighted the importance of combinations therapies (especially in the oncology field), the STAMP group considered that it would be more practical, from a regulatory perspective, to only include drug repurposing projects with a single compound in the pilot. Finally, it was decided that the pilot should primarily focus on conditions for which no or few medicines are currently authorised or which are associated with high morbidity and/or mortality despite available medicines. In view of these considerations, the use of propranolol in the neoadjuvant setting prior to surgery of resectable angiosarcoma could be considered as the most appropriate candidate to be submitted as a pilot candidate.

Despite the many benefits offered by the proposed framework, this study highlighted **several remaining barriers** that could limit the willingness of champions to participate. First, the framework requires a lot of effort and financial commitment from the champions (*e.g.*, fees for scientific advice, costs of follow-up studies if needed), while there are few incentives for them to engage in this project, aside from the main important potential benefit to their patients. However, it should be noted though that there will be no fee for the pre-entry phase submission of the pilot (*i.e.*, when the champion submits its project for first consideration) and several NCAs provide fee reductions or waivers for scientific advice to non-profit applicants. Second, only the marketing authorisation holder can apply for a variation or extension of indication of an authorised product (Commission Regulation (EC) No 1234/2008). Consequently, the champion needs to identify and approach the right contact person within the pharmaceutical company that holds the original marketing authorisation, which may be particularly difficult and time-consuming. In recognition of this challenge, European industry umbrella organisations are putting together a list of specific contact points for repurposing projects within the pharmaceutical companies in their network. Third, the outcome of this framework entirely depends on the willingness of a pharmaceutical company to submit the data package to the regulators for a variation, extension, or new marketing authorisation. Moreover, concerns have been raised about potential increases in the prices of repurposed medicines after the addition of the new indication. However, industry representatives mentioned that, in most cases, it would not be possible to get a higher price for a repurposed medicine that is already on the market for a different indication, and that this would not be their intention. Still, champions may consider drafting an agreement with the marketing authorisation holder to establish certain prerequisites (in compliance with competition law) and to ensure that the company does not maximise profits based on research that was performed with public funding.

This study clearly demonstrated the need to find sustainable solutions to facilitate the clinical research and implementation of repurposed medicines for cancer patients with urgent medical needs, but it has two important **limitations**. First, even though drug repurposing is gaining momentum in all disease areas (*i.e.*, neurology, endocrinology, cardiology, psychiatry, orphan and paediatric diseases, and infectious diseases (48–51)), candidates in this study were selected based on the expertise of the Anticancer Fund and were restricted to oncology. The purposive selection of candidates also makes it impossible to do a quantitative analysis of the characteristics of the cases that were included. Second, the evidence outlined in this study

was searched through multiple scientific literature databases and clinical trial registries using systematic search queries, however, this study was explorative in nature with the aim to identify and analyse promising repurposing candidates that could be further elaborated in a pilot. As a result, the evidence outlined in this study may not be exhaustive. Moreover, due to time-related and logistical constraints, the data collection was performed by a single person as opposed to multiple researchers in parallel and the studies included in the evidence summaries were not scored based on their quality (432).

CONCLUSION

Following the STAMP meeting in March 2019, a proposal was completed to establish the framework to support not-for-profit organisations and academia in bringing a new indication "on-label". This framework specifically targets repurposing projects that involve an already authorised medicinal product that is out of basic patent and regulatory protection in an indication outside its authorisation, where research has shown value to the patient. In July 2019, the Pharmaceutical Committee of the European Commission endorsed the proposal for the repurposing framework. In preparation of the pilot to test the proposed framework, the present study developed a template to guide evidence generation (Appendix H) and described nine promising repurposing candidates for which there is some clinical evidence or scientific rationale available to support a new use in an oncological indication. At present, the RepOG is preparing supporting documents (including a Q&A guidance document and a pilot submission form) for the launch of the pilot, which was originally planned for March 2020 but is postponed due to the COVID-19 outbreak.

CHAPTER 7

Patient and HCP perspectives on clinical adoption of repurposed medicines in Belgium

Manuscript in Preparation

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Patient and healthcare professional perspectives on clinical adoption of repurposed medicines.

ABSTRACT

Repurposing approved and well-characterised drugs for new indications is an emerging treatment development strategy in many disease areas. In oncology, drug repurposing holds the promise of providing safe, timely and affordable treatment options for patients with unmet needs. Yet, previous research has highlighted a number of challenges with regard to the translation of repurposed medicines into clinical practice and described these from the perspective of academia, industry, regulators, HTA bodies and payers. The present study aimed to explore the patient and health care professional (HCP) perspectives on specific aspects of the clinical implementation of repurposed medicines for anticancer treatment in Belgium via semi-structured interviews. Furthermore, pragmatic solutions to facilitate drug repurposing in cancer research and clinical practice were identified and discussed during focus group discussions with the same stakeholder groups. Overall, patients and HCPs were largely in favour of exploring new uses for existing medicines in preclinical and clinical research in oncology. However, HCPs mentioned that, since many repurposing candidates are off-patent, there are no financial incentives for industry to conduct clinical trials or to apply for regulatory approval of the new indication. Off-label prescribing can be a viable alternative for the safe and timely treatment of patients in case robust clinical evidence is available. However, off-label use also entails important financial, ethical and legal concerns. To address the current regulatory, financial and evidentiary challenges that hinder the development and clinical implementation of repurposed medicines, we explored the application potential and feasibility of several pragmatic solutions that have been put forward. While patients and HCPs recognized the need for and relevance of the proposed solutions, they highlighted a number of unresolved issues that remain to be addressed.

INTRODUCTION

With an estimated 9.6 million deaths in 2018**, cancer is one of the leading causes of death worldwide** (1,3,4,29)**.** Widespread research efforts have led to a better understanding of the disease mechanisms and the identification of new targets for anticancer treatment. However, new medicinal products first have to undergo an extensive period of preclinical and clinical testing, followed by marketing authorisation, pricing and reimbursement procedures. In fact, studies have shown that it takes about 5 to 15 years to develop a single anticancer drug (16). Even though the pipeline of oncology drugs in late-stage development is continuously expanding, the pharmaceutical industry is faced with productivity issues due to high attrition rates of new oncology drugs in clinical trials (11,433). Furthermore, **the economic impact of cancer** has significantly increased in recent years. In 2018, the total cost of cancer was about €199 billion in Europe (27). One of the key contributing factors to the increased global expenditure on cancer are the high prices of new oncology drugs, especially of novel biological and targeted therapies (28). These prices are putting great pressure on national healthcare budgets and delay or hinder access to new treatment options for patients (16,18,19,29–31). In view of these challenges, there is a **high medical need to develop safe, effective and affordable anticancer treatments**.

An increasingly popular anticancer treatment development strategy is the **clinical investigation of approved and well-characterised drugs for new anticancer indications**, which is called **drug repurposing** (33). Repurposing existing medicines has **several advantages** over developing new chemical entities (59). A first key advantage is the availability of data regarding the safety, toxicity and pharmacokinetics of approved medicines, as this could reduce the research and development time and the risk of failure in clinical trials (45). Where approximately 30% of new candidate drugs fail in clinical research because of safety issues, this problem is largely avoided with repurposed drugs (97). Besides, costs of research and development of repurposed medicines are expected to be lower because preclinical and phase I safety trials do not have to be repeated (72,338). Moreover, many of the drugs that are investigated in the context of drug repurposing are relatively affordable, owing to the availability of generic products (68,70).

Drug repurposing is **not a new concept**. In fact, seeking additional oncological indications for approved anticancer drugs is common practice in oncology, as illustrated by the approval of numerous new indications for Keytruda (pembrolizumab) since its initial marketing authorisation. Yet, drug repurposing also refers to finding new anticancer indications for approved drugs that were originally developed outside of the oncology field (44,48,63–67). The ReDO_DB database currently lists **over 300 non-cancer drugs that have shown some evidence of anticancer activity** based on data from peer-reviewed studies, medical case reports, observational studies and clinical trials (69). In 2018, more than 70 of these drugs were being tested in at least one phase III or IV clinical trial in cancer patients (68).

Despite the extensive research activity in oncology and the advantages compared to *de novo* drug development, thus far, only few of the drugs identified as potential repurposing candidates found their way into routine clinical use. Previous research has identified several **scientific, regulatory and financial challenges** for the clinical research and implementation of repurposed medicines, in particular for off-patent drugs, and explored these from the perspective of academia, industry, regulators, HTA bodies and payers (39,75,282,339). However, the opinion and experience of cancer patients and health care professionals (HCP) with regard to drug repurposing in oncology is largely missing in this discussion.

In view of that, the **aim of this study** was to explore the patient and HCP perspectives on specific aspects of the clinical implementation of repurposed medicines for anticancer treatment in Belgium and to explore proposals that could facilitate drug repurposing in oncology research and practice.

METHODS

Belgian cancer patients and HCPs (more specifically oncologists and hospital pharmacists) were invited to participate in a **semi-structured interview** to explore their perspectives on specific aspects of the clinical research and implementation of repurposed medicines for anticancer treatment. Study participants were selected through patient and professional organisations and networks via purposive sampling. Prior knowledge about drug repurposing was not a requirement to be included in this study. In total, 33 cancer-specific patient organisations and 53 HCPs (primarily oncologists) in Belgium were contacted via e-mail and received an information sheet describing the objectives and design of the study. An **interview topic guide** was developed per stakeholder group based on background information from scientific literature and previous studies of this PhD project (Appendix I & J). Questions differed slightly depending on the stakeholder group but related to the following main topics: i) opinion of and experience with repurposed medicines in clinical research and practice, ii), marketing authorisation of new therapeutic indications, iii) off-label prescribing of repurposed medicines, iv) communication towards patients about repurposed medicines, v) potential recommendations for clinical implementation of repurposed medicines.

The interviews took place between October and December 2019 and were performed by three researchers with a background in pharmaceutical and biomedical sciences. Before the start of this study, two pilot interviews were conducted to optimize the interview guide and standardize the interview approach. Next, the interviews were conducted in pairs or individually by the researcher team, either face-to-face in the workplace of the participant or via phone or video call. The interviews were carried out in Dutch and lasted about 20 to 60 minutes each. All interviews were audio-recorded with written informed consent from the study participants, transcribed *ad verbatim* and pseudonymized to protect participants' personal information and ensure confidentiality. The interview transcripts were analysed based on the **framework analysis method** using the NVivo qualitative data analysis software (102,103).

The same participants were invited to a follow-up **focus group discussion** (FGD) per stakeholder group to discuss and seek consensus on proposals for facilitating the implementation of drug repurposing in clinical practice, based on ideas and recommendations from scientific literature or from the previous interviews. Each FGD was led by two researchers from the research team. A topic guide and visual presentation of the proposals were used to guide the discussion (Appendix K). The FGD with HCPs took place on 10 February 2020 and the FGD with patients on 4 March 2020, both at Campus Gasthuisberg of the University of Leuven (Belgium), and lasted approximately two hours each. Similar to the interviews, the FGDs were audio-recorded, transcribed *ad verbatim*, and analysed based on the framework analysis approach, using the NVivo software (102,103).

The study protocol was **approved by the Ethics Committee of UZ Leuven in Belgium in September 2019**. Citations used in this manuscript were translated from Dutch to English as accurately as possible to represent participants' views.

RESULTS

In this study, we conducted **twelve semi-structured interviews** with Belgian representatives from two stakeholder groups, namely HCPs primarily specialized in oncology (N = 6) and cancer patients (N = 6). In addition, **two follow-up FGDs** were organised with the same stakeholder groups, HCPs (N = 5) and patients (N = 3) (Table 11. Characteristics of study participants).

TABLE 11. CHARACTERISTICS OF STUDY PARTICIPANTS

HEALTH CARE PROFESSIONALS						
ID	PROFESSIONAL BACKGROUND	#YEARS ACTIVE	CURRENT ORGANISATION	GENDER	INTVW	FGD
1	Gastroenterologist/oncologist	> 20 y	University hospital	M	Yes	Yes
2	Medical oncologist (head, neck, neuro)	> 20 y	University hospital	M	Yes	Yes
3	Hospital pharmacist	± 5 y	University hospital	F	Yes	No
4	Haematologist	> 20 y	University hospital	M	Yes	No
5	Gastroenterologist/oncologist	> 20 y	University hospital	M	Yes	Yes
6	Medical oncologist (immune therapy)	± 10 y	University hospital	F	Yes	No
7	Medical doctor	> 20 y	Research foundation	M	No	Yes
8	Hospital pharmacist	> 20 y	University hospital	M	No	Yes

PATIENTS							
ID	PRIMARY CANCER	1^{ST} DIAG-NOSIS	HIGHER EDUCATION	AGE	GENDER	INTVW	FGD
A	Breast cancer	2018	Yes (PhD)	60	F	Yes	No
B	Hodgkin lymphoma	2015	Yes (LLM)	37	F	Yes	No
C	Breast cancer	1996	No	62	M	Yes	Yes
D	Breast cancer	2015	No	63	F	Yes	No
E	Colorectal cancer	2013	Yes (MSc)	50	M	Yes	Yes
F	Prostate cancer	2002	Yes (PhD)	68	M	Yes	Yes

Abbreviations: Interview (INTVW); Focus Group Discussion (FGD); Master of Laws (LLM); Doctoral degree (PhD); Master of Science (MSc)

OPPORTUNITIES FOR DRUG REPURPOSING IN ONCOLOGY

All HCPs in this study knew the concept of drug repurposing and broadly described it as the use of existing medicines for new therapeutic indications. Several HCPs referred to the development and commercialisation of thalidomide for the treatment of multiple myeloma as a well-known success story of drug repurposing in oncology. HCPs provided some examples of repurposed medicines that are **prescribed off-label in clinical practice**: acetylsalicylic acid for the chemoprevention of colorectal cancer, celecoxib for hereditary non-polyposis colorectal cancer (or Lynch syndrome), amitriptyline for the treatment of cancer patients experiencing neuropathy, olanzapine for the treatment of chemotherapy-induced nausea and vomiting, and zoledronic acid as adjuvant treatment in primary breast cancer. Moreover, HCPs had knowledge of various repurposing candidates with potential anticancer effects that are **currently under investigation in clinical trials,** *e.g.*, vitamin D and losartan in pancreatic cancer, eflornithine in combination with chemotherapy in anaplastic astrocytoma, valproic acid in glioblastoma multiforme, and metformin and cimetidine for the treatment of a variety of cancer types.

Four patients indicated that their **treating physician had prescribed a repurposed drug off-label** as part of their anticancer treatment regimen (*e.g.*, zoledronic acid in primary breast cancer, bendamustine in Hodgkin's lymphoma) or for symptomatic relief (*e.g.*, an antidepressant for hot flashes of a breast cancer patient, an unidentified off-label treatment for low anterior resection syndrome (LARS)). However, three patients decided not to take the prescribed medication for different reasons: a lack of consensus on the benefit-risk balance amongst treating physicians (zoledronic acid), fear of addiction (antidepressant) or because the symptoms remained tolerable without additional treatment (LARS).

The **immediate availability,** the **overall affordability** (especially for off-patent or generic medicines) and the **many years of clinical experience** leading to well-established safety and toxicity profiles were the most important benefits of drug repurposing according to HCPs and patients in this study. HCPs stated that medicines originally developed for non-cancer indications could primarily play a role as (neo) adjuvant therapy to improve the efficacy of other anticancer treatments or to help prevent recurrence. HCPs and patients also cited several examples of repurposed drugs used for supportive care in cancer. Furthermore, previous research suggests that drug repurposing is especially important for identifying new treatments for patients with rare cancers or patients who do not, or no longer, respond to the standard treatment options (45,188,207,221,434–437). HCPs and patients confirmed these to be areas with high medical needs for which commercial incentives to develop *de novo* drugs are generally lacking.

All HCPs and patients were in favour of exploring **drug repurposing opportunities in preclinical and clinical research in oncology** as this could benefit both patients and society, especially given the rising pressure on national healthcare budgets. HCPs noted that the repurposing of anticancer treatments from one cancer to another, based on similarities in disease mechanisms, already happens quite frequently in clinical practice. On the other hand, some oncologists remained a bit sceptical about using drugs originally developed for a non-cancer indication in anticancer treatment because, so far, there are few success stories to illustrate its potential.

> *"I am a bit sceptical, critical, but open to the idea. […] Of course it is always interesting if this could lead to active medicines, both economically and for the patient." (HCP 1)*

> *"I must say [drug repurposing] is an attractive domain because the cost of the new anticancer medicines has risen by 30% in recent years, to more than a billion euros, so where will this end? In that sense, I think this is now the ideal climate to think about drug repurposing but without actually creating unrealistic expectations." (HCP 4)*

Overall, HCPs clearly stated that claims of anticancer activity of repurposed medicines should be **evidence-based** and there should be a **clear scientific rationale or proven mechanism of action**, particularly for medicines that were originally developed outside of the oncology field.

With regard to the clinical development of repurposed medicines, HCPs mentioned that **phase I trials** to demonstrate safety and tolerability are typically not required because of the many years of clinical experience. However, a patient and oncologist pointed out that the safety and toxicity of a product may be different when used in a new disease setting (especially in heavily pretreated patients), in case the dose or route of administration needed to change for the new use, or when administered in combination with other treatments. **Phase II clinical trials** are usually performed with a small number of patients to establish proof-of-principle, followed by **a phase III randomized controlled trial** (RCT) with a sufficiently large sample size and predefined clinical endpoints to demonstrate safety and efficacy of the repurposed drug in the patient population. HCPs were largely of the opinion that **standards for efficacy and safety of repurposed medicines should be identical to those of *de novo* medicines**. However, one oncologist mentioned that lower efficacy gains might be accepted compared to other anticancer treatments if the drug is known to be safe and is relatively cheap.

CLINICAL IMPLEMENTATION OF REPURPOSED MEDICINES

REGULATORY APPROVAL OF A NEW INDICATION

An application for a marketing authorisation of a new therapeutic indication is an important step in the clinical adoption of repurposed medicines because this initiates an **in-depth assessment by regulatory authorities of the benefits and risks** of a medicine in a certain indication. Moreover, marketing authorisation is typically a prerequisite for the **reimbursement** of the treatment and the **inclusion in clinical treatment guidelines** (49,72,304). However, according to HCPs in this study, pharmaceutical developers are hardly interested to invest in expensive and time-consuming clinical research and marketing authorisation procedures to develop new therapeutic indications for medicines for which appropriate regulatory and intellectual property incentives are lacking.

> *"A disadvantage, I think, is that there is a lack of interest from the industry. Usually, those products are owned by a company, but the patent has expired and the product price is very low. In such cases, we sometimes see that, even though data become available to support a certain medication, it is not developed further because no one is interested in commercializing it for that new indication." (HCP 2)*

The **lack of return on investment for repurposing off-patent drugs** is a key issue that has been raised by many different stakeholders in recent years (10,38,49,53,71,84,171,311,438). As a result, new therapeutic indications for medicines that are out of patent or regulatory protection are mainly studied in **non-commercial or independent clinical trials** sponsored by researchers from academia, research institutes or non-profit collaborative groups (68).

"A drawback is that the interest of the companies that market the medication is relatively limited, given that there is no longer any profit perspective. You usually have to set up your own initiatives, academic or local initiatives within a certain country, to demonstrate that the medication is effective in that indication with limited toxicity." (HCP 5)

Nonetheless, several oncologists emphasized that academic or independent researchers generally do not have the resources to initiate **large phase III confirmatory trials that are required for regulatory approval** and they do not have the time or expertise to take the lead in marketing authorisation procedures. Moreover, they would still need to find an **industry partner to apply for a marketing authorisation** for an extension of indication of an approved drug (296).

"The current context has become so expensive that no one can afford it, certainly not the academic community, and the companies that could do it, will have no return on investment." (HCP 2)

OFF-LABEL PRESCRIBING FOR A NEW INDICATION

While bringing a new indication "on-label" via marketing authorisation procedures is the standard and preferred approach for implementing a repurposed drug into clinical practice, HCPs and patients were of the opinion that **off-label prescribing can be a viable alternative for the safe and timely treatment of patients** in case robust clinical evidence is available but incentives are lacking.

"I think that the majority of patients wouldn't mind off-label use. Patients often feel the regulations as a barrier. Not as an added value." (Patient E)

Off-label use of medicines is **common in many disease areas**, especially in paediatric and rare diseases, and is **allowed or simply not regulated in most countries worldwide** (86,439–443). Off-label use is defined as any intentional use of an authorised product not covered by the terms of its marketing authorisation and therefore not in accordance with the summary of product characteristics (SmPC) (169). It includes the prescription of a product for a new indication, a different patient group, another dose or dose interval, or the use of a different method of administration (169,319,320). In Europe, the actual use of medicines in medical practice is managed at the national level. Consequently, **various policies are in place in the different European countries** to manage and even reimburse off-label use of medicines (49,169,320).

HCPs and patients pointed out that **off-label prescribing is very common in oncology** and is particularly important for treating patients with unmet medical needs. In view of that, HCPs were positive about the **Belgian legal framework** that gives clinicians the **therapeutic freedom** to prescribe medicines as they see fit, on the condition that the medicine has a valid marketing authorisation for another indication in Belgium and adequate data is available to demonstrate patient benefit. HCPs strongly emphasized the need for a **plausible scientific rationale and robust human data** to demonstrate efficacy and safety of a medicine in the new indication. Ideally, the off-label use should be supported by **positive outcomes from one or more phase III RCTs, and included in clinical treatment guidelines.**

"You have to demonstrate that the drug is effective and safe in clinical studies […]. More specifically, in phase III research, not a series of 100 patients in a phase 2 study. The latter may detect a trend or plausible effect but you really have to do a randomized trial." (HCP 1)

On the other hand, oncologists and patients noted that **individual clinical circumstances** could have an **impact on the level of evidence** they would require before prescribing or taking an off-label repurposed drug. For example, in case there are no other treatment options available, most patients indicated that they would be willing to take a repurposed drug if the risk of adverse events is low and if there is a strong scientific rationale, even if there is no or very limited evidence to support clinical benefit. HCPs stated that they would prefer to have some evidence from phase II trials or at least from case reports that shows safety and possible benefit in the new indication before prescribing a medicine for such an exceptional use.

> *"If the risk of side effects is high, there is also a greater need for evidence. If there are few complications, what is there to lose?" (Patient E)*

To prevent misuse of off-label prescribing (for example by conducting unauthorised clinical experiments), both HCPs and patients emphasized that the **off-label use should always be in the best interest of the patient**. Patients should be well informed about any potential adverse events of the off-label use and toxicity and efficacy should be monitored closely. Ideally, the outcome of an off-label treatment should be published as a case report to learn from clinical experiences. If early clinical results are promising, HCPs and patients were of the opinion that a **formal clinical trial should be initiated** to generate high-quality data regarding the safety, efficacy, clinical benefits and risks of the repurposed medicine.

> *"The problem is that we usually do not have that data and then it is difficult to defend [off-label use] because you are actually experimenting on humans, which is not allowed. The only alternative is to start a trial, which requires funding." (HCP 2)*

Another ethical and financial concern regarding off-label use of repurposed medicines is the potential **lack of reimbursement of the treatment** as this increases out-of-pocket expenses for patients and restricts access to treatments for patients with limited financial resources (49,278). However, several European countries have measures for reimbursement of off-label use at the national level (169,320). In Belgium, there is no specific policy in place but HCPs explained that the Belgian reimbursement schemes indirectly provide mechanisms to reimburse off-label use of medicines categorized in "chapter 1", as clinicians are not required to specify the therapeutic indication for those products (444). Moreover, patients assumed that clinicians sometimes circumvent the system by prescribing medicines for an approved indication instead of the off-label use.

Still, **several patients had experience with treatments that were prescribed off-label and not reimbursed in Belgium** (*e.g.*, zoledronic acid for the prevention of recurrence in primary breast cancer, hormone therapy for male breast cancer), resulting in a situation where the patient is confronted with a difficult trade-off between the potential benefit and the financial burden of a treatment. Patients and HCPs noted that the available evidence to support the off-label use of a medicine is an important factor in this decision, as well as the patient's financial situation and the price of the drug. With regard to the price of the medicine, HCPs mentioned that the typical repurposing candidates in oncology (*e.g.*, metformin, aspirin, and beta-blockers) are relatively cheap compared to standard anticancer treatments, and that patients are often willing to pay for such treatments themselves. If treatment costs are too high (*e.g.*, off-label use of an immunotherapy), clinicians said they sometimes request free samples from pharmaceutical developers. Finally, one patient had experience with pharmaceutical compounding as a more affordable approach to get access to expensive treatments that are not reimbursed for a certain indication.

Furthermore, off-label use of medicines raises concerns about the **physician's liability in case of an adverse reaction** (322,325,445). All HCPs and several patients in this study confirmed that physicians are responsible for the choice of treatment so off-label prescribing should be considered carefully on a case-by-case basis. Still, all HCPs stated that the liability risk would not stop them from prescribing a medicine off-label, if robust scientific data is available to support this decision. In some cases, clinicians would consider referring the question to an independent ethics committee and/or to request a written informed consent of the patient, especially for medicines that are administered in the hospital setting. Of note, one oncologist presumed that, since so many products are used outside the terms of the marketing authorisation in oncology, clinicians do not always realize when they are prescribing off-label.

A final challenge highlighted by one of the oncologists was the **risk of losing an effective off-label treatment** in case it is withdrawn from the market for its original indication or in case of drug shortages.

COMMUNICATION TOWARDS PATIENTS ABOUT REPURPOSED MEDICINES

In general, HCPs and patients were of the opinion that providing **clear and correct information about repurposed medicines** is important to address any potential concerns of patients and to ensure treatment compliance. According to HCPs, the origin and scientific rationale for a treatment is of less relevance to cancer patients, as long as there is sufficient evidence of clinical benefit and safety in their cancer subtype. However, the different indications listed in a SmPC may lead to confusion and could necessitate additional information (*e.g.*, antidepressant for the treatment of neuropathy). Moreover, the history of a drug may also give rise to patients' concerns (*e.g.*, thalidomide in multiple myeloma).

> *"Patients mainly want to know whether it is a product that [the doctors] have clinical experience with or whether it is a completely new product that [the doctors] have no experience with." (HCP 4)*

Patient and HCPs explained that the **need for information is particularly high in case of off-label use of medicines,** as the patient needs to understand the risks to be able to make an informed treatment decision in consultation with the treating physician. Important aspects that should be discussed with the patient are the available evidence to support safety and efficacy of the medicine in the new indication, the cost of the proposed treatment, the out-of-pocket expenses for the patient and any potential adverse events and risks associated with the off-label use. Overall, HCPs noted that the **need for information increases along with the uncertainty about the efficacy and safety of the treatment**. Moreover, HCPs said that they adapt the amount of information based on a patient' willingness to be informed.

> *"There are two types of patients: those patients who want to know everything and immediately consult "Dr Google" upon leaving the doctor's office […] and those patients who don't want to know everything. […] It is up to a healthcare provider to estimate whether a specific patient needs additional information or not. (Patient C)*

Patients and HCPs mentioned that **proposing a treatment plan that involves off-label use of a medicine can be difficult**, especially if the treatment is not reimbursed or carries significant risks due to a lack of solid evidence. On the one hand, patients were of the opinion that **transparency is key** and that they should be informed and given a choice if there is a potential repurposed drug, even if the treatment is off-label and not reimbursed. On the other hand, patients emphasized that clinicians should **avoid creating**

false hope by prescribing medicines off-label for which there is insufficient data. Both patients and HCPs noted that clinicians should carefully consider the patient's willingness to be informed about "experimental" treatments before proposing a specific treatment plan.

Most patients and HCPs agreed that there is no need to raise awareness about the concept of drug repurposing to the general public. **Information should only be given directly to patients on a case-by-case basis**, preferably by the oncologist or treating physician. Patients were of the opinion that a folder or website in lay language could be useful to recapitulate the information that was given. However, both patients and HCPs acknowledged that this is not practical, as information is rapidly outdated (owing to the continuous scientific advances) and treatment decisions are highly dependent on individual patient characteristics and previous treatments. Additionally, HCPs expressed concerns about information that is disseminated via patient organisations' websites, online discussion forums or "Dr Google", as this information is open to misinterpretation by patients and not always scientifically validated. Finally, HCPs in this study had little experience with patients requesting access or information about repurposed medicines (with the exception of aspirin, vitamin D and celecoxib), but one oncologist assumed that some patients take over-the-counter medicines based on information they find online, without informing their treating physician.

PROPOSALS TO FACILITATE CLINICAL IMPLEMENTATION OF REPURPOSED MEDICINES

In recent years, several **pragmatic solutions** have been put forward to address the current regulatory, financial and evidentiary challenges that hinder the development and clinical implementation of repurposed medicines (49,71). In the present study, we explored the **perspectives of HCPs and patients on the application potential and feasibility** of these proposed solutions via two FGDs.

1. DEVELOP A COLLABORATIVE FRAMEWORK TO BRING NEW USES "ON-LABEL"

A first proposal is to introduce a framework in which academia, non-profit organisations, pharmaceutical industry and regulators can work together on developing new uses for approved medicines that are out of basic patent and regulatory protection. More specifically, the **framework for repurposing established medicines proposed by the European Commission expert group on Safe and Timely Access to Medicines for Patients (STAMP)** (49,330) was presented to HCPs and patients during the FGDs. The aim of this framework is to support a not-for-profit or academic stakeholder, termed a "Champion", who has evidence and scientific rationale for a new therapeutic indication, in bringing this new indication "on-label". The framework puts forward **scientific and regulatory advice from regulators** as a means to evaluate the available evidence and to determine whether additional studies need to be performed. In this framework, the champion is responsible for generating the data package in preparation of the regulatory scientific advice meeting and, if needed, for conducting further studies (for which they would need to secure public or philanthropic funding). The Champion is encouraged to seek an immediate or future partnership with one or more marketing authorisation holders who can apply for an extension or variation of the marketing authorisation if the data package is considered sufficient. Currently, a **pilot is in preparation** to test this framework and to assess whether it is able to facilitate a marketing authorisation application for a new indication for an off-patent medicine.

Patients in the FGD were positive about the proposed framework, as it could facilitate the clinical research and adoption of repurposed medicines. However, they expressed the need for **patient involvement in the selection of pilot projects** to test this framework. In contrast, HCPs highlighted **several shortcomings of the proposed framework**. The biggest of which is that the financial and administrative burden is entirely placed on the champion (*e.g.*, costs related to executing the clinical trials, generation of the data package, costs for the scientific advice fees), while possible benefits of a positive outcome would accrue to the marketing authorisation holder. In view of this, HCPs suggested that fees for scientific advice should be waived for academic or independent researchers, which is already done by several competent authorities, or that such fees should be included in research grants provided by public funding bodies. A second hurdle is that academic researchers lack the expertise to request scientific advice and would need additional training in regulatory science. The EU funded Coordination and Support Action on Strengthening Training of Academia in Regulatory Science (CSA STARS) could help to tackle this hurdle. Third, the successful outcome of this framework is fully dependent on the cooperation of the marketing authorisation holder. HCPs suggested that early engagement between the champion and the marketing authorisation holder could reduce this uncertainty. However, collaboration between academia and industry may be hindered by a climate of mutual distrust. In fact, during the FGD, patients noted that academic researchers often blame the industry for solely pursuing "the bottom line", while the industry criticizes academic research for being slow and of inferior quality (*i.e.*, not meeting the standards for regulatory approval).

2. INTRODUCE LEGAL CHANGES TO ENABLE REGULATORY APPROVAL OF NEW USES

Taking into account the aforementioned limitations of the STAMP framework, a second proposal could be to **change the legislation** at the national or European level to enable independent researchers in bringing new uses "on-label", without the need for cooperation of the original marketing authorisation holder. For example, a legal provision could be introduced that allows **third parties (*e.g.*, academic or non-profit researchers) to apply for a marketing authorisation of an extension of indication for an already approved drug**. While HCPs and patients were in favour of finding alternative solutions for obtaining marketing authorisation for new indications of approved medicines in case the marketing authorisation holder is not interested, they noted that a product label is always associated with a specific product and owned by the marketing authorisation holder. Therefore, allowing a third party to apply for a marketing authorisation of an extension of indication would raise difficult discussions about the post-marketing responsibilities related to the new indication (*e.g.*, pharmacovigilance, submission of benefit-risk data to regulatory authorities, paediatric requirements…). Moreover, access to the treatment may be lost in case the marketing authorisation holder decides to withdraw the product from the market at some point.

Alternatively, a legal change could be introduced to **require regulatory agencies to follow-up on evidence made available to support new indications for approved medicines** and encourage (or enforce) marketing authorisation holders to change their product label accordingly (similar to the UK Off-Patent Drugs Bill introduced in 2015, which was withdrawn due to a lack of support from the UK Government (446)). Yet, patients indicated that such a change in the mandate of regulatory agencies could give rise to conflicts of interest (*i.e.*, when a regulatory agency both collects and evaluates evidence to support a new use). In recognition of this, it was suggested that the evidence and data package should be generated by an independent agency (*e.g.*, a medical society) and evaluated by a regulatory authority.

3. CREATE INCENTIVES TO ENCOURAGE MARKETING AUTHORISATION OF NEW USES

A third proposal is to introduce **additional incentives for the pharmaceutical industry** to apply for marketing authorisation of new therapeutic indications for their approved medicines that are out of basic patent and regulatory protection (49). Examples of potential incentives at the national and/or European level include: additional regulatory exclusivities, tax incentives, transferable vouchers that grant priority review for future marketing authorisation applications, special research funds to reward repurposing efforts, a differential pricing system across indications, and fee reductions or waivers for scientific advice and/or variation applications (49). HCPs and patients expressed **concerns** that some of these **incentives might evoke high drug prices**, disproportionate to the development costs. In addition, impact of some incentives may be low due to the possibility of off-label prescribing (*e.g.*, differential pricing system across indications). HCPs also commented that most repurposing research efforts are currently initiated and led by academic groups, raising the question of who actually deserves additional incentives.

Alternatively, patients in the FGD suggested creating a **consortium of all producers of a certain drug or active substance** to share the administrative and financial burden associated with developing new uses, within the terms of competition laws. Such a consortium would address the free-rider problem by generic competitors in off-patent drug repurposing as it allows the individual cost-benefit analysis of the involved companies to be positive, certainly in cases where there is already a competing "on-label" drug.

4. PROMOTE INDEPENDENT CLINICAL RESEARCH WITH REPURPOSED MEDICINES

To reduce the scientific uncertainty associated with off-label use of medicines, a fourth proposal is to promote and enable **independent clinical research** with repurposed medicines that seem promising but lack robust evidence. First, **additional public funding** could be provided to conduct independent clinical trials, especially confirmatory phase III RCTs, with repurposed medicines. Yet, HCPs emphasized that clinical trials are very expensive, usually last up to several years and have a high risk of failure. Therefore, it is important to identify and prioritise the research projects with the highest potential benefit. At present, several government-sponsored initiatives already exist in Belgium to support non-commercial clinical research (*e.g.*, KCE Trials programme, FWO TBM (Applied Biomedical Research with a Primary Social finality) projects) but HCPs indicated that the amount of funding provided by these initiatives is limited compared to the substantial research grants provided in other countries, for example by the US NIH.

Second, HCPs and patients expressed a need for **increased harmonisation and centralisation** of clinical research at the European level to reduce fragmentation of research. Currently, many exploratory phase II clinical trials are initiated to test the off-label use of medicines. However, these trials are often not sufficiently powered to show statistically significant results (*e.g.*, due to difficulties in patient recruitment) (85), or they are not followed by a confirmatory trial, thus increasing medical uncertainty (447). Moreover, many of these studies have been initiated without seeking scientific and regulatory advice and can therefore be of limited design quality. HCPs indicated the need for a coordinating body to accomplish the harmonisation on a supranational level but this would again require substantial public or philanthropic funds. Moreover, they highlighted potential regulatory hurdles for organising and conducting clinical trials at the European level. Yet, the European Clinical Trial Regulation (Regulation (EU) No 536/2014), which entered into force in 2014 but still needs to come into application, may help to overcome these hurdles.

Third, more **innovative clinical trial designs such as adaptive platform trials** could be introduced to make clinical research with repurposed medicines more efficient. An adaptive platform trial can be defined as a clinical trial with a single master protocol in which multiple treatments are evaluated simultaneously (259,448). HCPs indicated that adaptive platform trials offer several advantages over traditional RCTs, such as the ability to stop futile interventions early, reduced competition for patients between multiple clinical trials running in parallel, and the opportunity to show comparative effectiveness between multiple treatments. Moreover, platform trials can be either exploratory (phase II-III) or confirmatory (phase III-IV), and can include both commercial and non-commercial arms. HCPs highlighted the example of the STAMPEDE trial, which is a multi-arm multi-stage platform trial in the UK and Switzerland that aims to evaluate multiple therapeutic strategies in the management of prostate cancer (NCT00268476) (449,450). In the area of drug repurposing, the STAMPEDE trial is currently investigating whether adding the antidiabetic drug metformin to the current standard-of-care for non-diabetic men with prostate cancer can improve overall survival. Even though the benefits of platform trials are quite compelling, several stakeholders pointed out that their complicated design brings about a distinct set of statistical, financial and regulatory challenges, which are discussed elsewhere (259,451).

5. ENABLE COLLECTION OF REAL-WORLD EVIDENCE FOR REPURPOSED MEDICINES

A fifth proposal is to develop **a framework that routinely collects real-world experiences and generates real-world evidence** on the efficacy and safety of medicines that are used off-label in clinical practice. Several systems that gather individual patient data are already in place, such as electronic health records (EHRs), patient registries (*e.g.*, the Belgian Cancer Registry) and payer databases. Moreover, innovative computational tools are available to extract, integrate and analyse patient data from those different sources. HCPs and patients strongly supported the proposal to find new ways to collect and leverage real-world data concerning off-label use of medicines but **several aspects should be taken into consideration** in order for this approach to be successful.

A first consideration is that real-word data may not be "fit-for-purpose" to generate robust evidence of safety and efficacy of a medicine in a new indication (due to a heterogeneous target population, various real-world endpoints, many confounding variables, publication and reporting bias, missing safety data, *etc.*). Moreover, while payer databases comprise a lot of information with regard to medicine use, procedures, hospital visits and diagnostic codes, they typically lack information about the clinical efficacy of a treatment. Consequently, there is **a need for improved quality control and adequate governance of the data in EHRs, patient registries and payer databases** to attain reliable outcomes. Stakeholders mentioned that additional public investments would be required to optimize the integration, standardization, transparency and interoperability of the current systems at the national and even at the European level. A second consideration is the lack of incentives for HCPs to properly register and report off-label use of medicines in EHRs or patient registries. While HCPs recognized the value of entering patient data into disease registries, they emphasized that this places a heavy administrative burden and requires resources, which are not available in all treatment centres. Consequently, **better incentives are needed to encourage (or enforce) physicians** to enter correct patient data in disease registries. A third consideration are privacy- and General Data Protection Regulation (GDPR)-related concerns and uncertainties about the need for consent of patients to collect and re-use real-world clinical data.

Furthermore, the **CURE ID app**, which enables sharing of off-label treatments for infectious diseases, was briefly discussed as a potential solution to learn from clinical experiences (197,452). This internet-based repository was developed by the US Food and Drug Administration (FDA) and the National Institutes of Health (NIH) and allows HCPs to report novel uses of existing drugs for difficult-to-treat infectious diseases. While HCPs in this study thought this was an interesting concept, they indicated **several caveats**. First, considering the legal liability of physicians, HCPs noted that the reports of off-label use should be anonymous. Yet, the need for anonymity could compromise the quality of the reports. Second, applying this approach to oncology would require many alterations due to the distinct nature of these disease domains. Third, HCPs were concerned that this approach would significantly increase the administrative burden and time investment per patient for the treating physician.

6. INCLUDE REPURPOSED MEDICINES IN CLINICAL TREATMENT GUIDELINES

A sixth and final proposal is to systematically include **new indications in existing treatment guidelines** in case sufficient high-quality evidence is available but incentives to bring the new use "on-label" are absent. HCPs suggested that lessons could be learned from the US approach to include off-label uses in the insurance-based recommendations or drug compendia, such as the **National Comprehensive Cancer Network (NCCN) guidelines**, that aim to arbitrate appropriate use of medicines. More specifically, inclusion in these guidelines reduces the legal liability incurred by physicians and allows for insurance coverage of off-label use for patients. Such an approach addresses some of the key limitations of off-label use and partly alleviates the need for marketing authorisation of the new indication. Evidently, the Belgian health insurance system is different from the US system and there is no European or Belgian organisation with the same mission as the NCCN. Nonetheless, opportunities could be explored to increasingly include off-label indications in **existing treatment guidelines produced by the European or Belgian Society of Medical Oncology** (ESMO or BSMO) based on high-quality evidence, which could reduce the scientific and legal uncertainty for physicians. Moreover, these guidelines could encourage clinicians to register and report follow-up data regarding off-label use of medicines.

However, HCPs highlighted several **potential shortcomings** with regard to the inclusion of off-label use in clinical treatment guidelines. First, HCPs mentioned that, where NCCN guidelines provide a range of potential therapeutic options, clinical treatment guidelines provide specific recommendations for the practical management of the patient. Accordingly, clinical treatment guidelines are less likely to include an off-label use in case there is an "on-label" alternative. For example, the inclusion of the antipsychotic drug olanzapine in clinical guidelines for the off-label treatment of chemotherapy-induced nausea and vomiting took a very long time, despite available evidence of clinical superiority compared to the "on-label" alternative (metoclopramide) in the given indication (453). Second, due to the rigorous (and time-consuming) methodology applied by most clinical treatment guideline committees, they are only updated every 2 to 5 years, limiting their ability to answer the needs of the rapidly changing oncology field. Third, an ethical dilemma may arise when including an off-label use in treatment guidelines at the European level. On the one hand, country-specific policies regarding off-label use and reimbursement may prevent accessibility to patients in certain European countries. On the other hand, the medical and patient community deserve to be informed about all evidence-based treatments, regardless of national policies.

DISCUSSION

Scientific literature describes numerous examples of existing medicines that could be repurposed for new anticancer indications (44,48,63–67). However, the scientific community is facing significant challenges to translate these opportunities into clinical practice (53,70,71). The present study aimed to explore patient and HCP perspectives on specific aspects of the clinical implementation of repurposed medicines for anticancer treatment in Belgium via semi-structured interviews. Furthermore, pragmatic solutions to facilitate drug repurposing in cancer research and practice were identified and discussed during FGDs with the same stakeholder groups.

Most stakeholders agree that the **end goal of drug repurposing efforts should be to obtain regulatory approval for the new therapeutic indication** as this offers a number of advantages over off-label prescribing. More specifically, marketing authorisation reduces concerns of patients, provides legal and medical certainty for clinicians, facilitates reimbursement of the treatment, increases adoption in clinical treatment guidelines, permits a fair comparison to other "on-label" treatments, and enables access to treatment for all patients. Unfortunately, in case of off-patent medicines, commercial incentives to apply for marketing authorisation of new indications are often lacking. Both HCPs and patients emphasized that regulatory issues or commercial interests should not hinder access to effective treatments for patients with urgent medical needs, and therefore viewed off-label prescribing as a viable alternative pathway under certain circumstances.

This study also uncovered an important **catch-22 regarding the evidence generation and clinical translation of repurposed medicines**. On the one hand, therapeutic freedom allows clinicians to treat patients with urgent medical needs by prescribing medicines off-label. Yet, off-label use implies a degree of medical uncertainty and legal liability for physicians. On the other hand, clinicians can decide to enrol patients in prospective clinical studies to build the evidence base regarding repurposed medicines, which benefits future patients and society at large. However, the high costs and efforts associated with clinical trials prove to be a major barrier for physicians, and patients may prefer getting the treatment off-label instead of participating in a RCT because they might end up in the control arm. Consequently, from an individual clinician and patient perspective, the immediate benefits of off-label use will likely outweigh the long-term incentives for conducting or participating in a clinical trial. But then again, routine off-label use discourages the clinical research that is needed to reduce medical uncertainty and to eventually apply for marketing authorisation of a new indication, thus maintaining the status quo.

To optimize the clinical implementation of repurposed medicines, we explored a number of **pragmatic solutions** that tackle the current challenges at different levels. **The first three proposals specifically aim to enable marketing authorisation of new therapeutic indications** for approved medicines for which commercial incentives are lacking. The most practical and advanced proposal, which already obtained wide support from various European stakeholders, is the framework developed by the European Commission expert group STAMP that provides a structure to support a not-for-profit or academic stakeholder in bringing a new indication "on-label". Yet, one of the main limitations of this framework is that the outcome is fully dependent on the willingness of the marketing authorisation holder to cooperate and apply for a marketing authorisation for an extension of indication of their approved medical product once sufficient evidence is available. Two additional proposals were explored to address this limitation.

First, legal changes could be introduced to allow a third party (*e.g.*, academic researchers or non-profit organisations) to seek an extension of indication for a marketing authorisation of an approved medical product, or to require government or regulatory agencies to follow-up on available evidence and encourage (or enforce) marketing authorisation holders to adapt their product label. Second, additional incentives could be introduced to incentivize the pharmaceutical industry to apply for marketing authorisation of new indications for their approved medicines. While both of these proposals may help to address the limitation of the STAMP framework, they also give rise to a distinct set of financial, legal and ethical questions that would need to be explored further. The **fourth and fifth proposals aim to facilitate evidence generation for repurposed medicines** and to reduce the scientific uncertainty associated with off-label use of medicines. More specifically, the fourth proposal relates to the need for additional public funding to support and enable more efficient independent clinical research with off-patent repurposed medicines. The fifth proposal emphasises the need for investments to optimize and harmonize the infrastructure to generate real-world evidence on the efficacy and safety of medicines that are used off-label in clinical practice. The **sixth proposal aims to reduce the scientific and legal uncertainty associated with off-label prescribing** by systematically including off-label use in existing clinical treatment guidelines in case high-quality evidence is available but commercial incentives are lacking. As mentioned previously, routine off-label use is not an ideal scenario but, given the current pharmaceutical model, it may be the only way to treat patients with urgent medical needs.

While the current study provides several new insights into the patient and HCP perspective on drug repurposing in oncology, it has **four important limitations**. First, this study included a relatively small number of participants. Yet, since the patient and HCP perspective on drug repurposing has not been examined so far, interesting new insights could be derived from this study. Second, the study population is limited to Belgian stakeholders, which limits the extrapolation of the results to other (especially non-EU) countries. However, due to this focus on Belgium, more in-depth insights could be generated. Additionally, the proposals that were discussed during the FGDs could be relevant to address similar issues in other countries worldwide. Third, all patients in this study were active in a patient organisation or involved in one or more advisory boards of research or regulatory organisations, thus making them more experienced in drug research and development compared to the average patient. However, their experience allowed for a more elaborate and in-depth discussion about the subject. Furthermore, all but one HCP in this study were associated with a university hospital, so their perspective might differ from HCPs in the non-academic setting. Fourth, this study applied qualitative research methods only (*i.e.*, semi-structured interviews and FGDs), meaning that the participants' perspectives cannot be quantified. To prioritise and select the most feasible solutions to enable the clinical implementation of repurposed medicines, a follow-up consensus seeking experiment could be performed with a large panel of experts.

CONCLUSION

While drug repurposing holds the promise of providing safe, affordable and timely treatment options for cancer patients, the clinical adoption of approved, off-patent medicines for new therapeutic indications is facing scientific, regulatory and financial challenges. This study clarified the perspectives of patients and HCPs on the use of repurposed medicines in oncology practice, more specifically with regard to regulatory approval and off-label prescribing, and explored a number of pragmatic solutions for addressing the current challenges:

1. Develop a **collaborative framework** to support a not-for-profit or academic stakeholder, who has evidence and scientific rationale for a new therapeutic indication, in bringing this new indication "on-label" (*i.e.*, STAMP framework for repurposing established medicines (330)).
2. Introduce **legal changes** at the national or European level to enable third parties (academic researchers, non-profit organisations or others), governments or regulatory authorities in seeking marketing authorisation for new therapeutic indications in case sufficient evidence is available.
3. Create **additional incentives for the pharmaceutical industry** to apply for marketing authorisation of new therapeutic indications for approved medicines that are out of basic patent and regulatory protection.
4. Promote and enable **independent clinical research** (especially confirmatory RCTs) with repurposed medicines that are promising but lack robust evidence.
5. Develop a framework to routinely collect **real-world experiences** and generate real-world evidence on the efficacy and safety of medicines that are used off-label in clinical practice.
6. Include **new indications in existing treatment guidelines** in case sufficient high-quality evidence is available but incentives to bring the new use "on-label" are absent.

Nonetheless, the feasibility and adequacy of the proposed solutions should be explored further, taking into account the perspectives of all stakeholders (*i.e.*, pharmaceutical industry, academia and non-profit organisations, regulators, HTA bodies, payers, HCPs and patients).

PART 4

CONCLUDING DISCUSSION

CHAPTER 8

General discussion of findings & recommendations to address the challenges in drug repurposing

GENERAL DISCUSSION

Drug repurposing holds the promise of providing safe, timely, affordable and effective new treatment options for cancer patients with unmet medical needs. However, so far, only few of the many drugs that were identified as potential repurposing candidates in oncology have found their way into routine clinical use. Indeed, the medical community is facing substantial **scientific, regulatory, legal and financial challenges with regard to the clinical research and adoption of repurposed medicines, especially for authorised medicines that are out of basic patent and regulatory protection** (70,71). In this project, we aimed to address the following question: "How can we overcome the current challenges that hinder the clinical research and implementation of repurposed off-patent medicines?"

The **first objective** was to investigate data sharing initiatives, partnerships and new funding mechanisms that could **facilitate the research and development of repurposed medicines**. This objective was addressed in **Part 2** of this dissertation in Chapters 3 and 4.

Chapter 3 focuses on one of the key advantages of drug repurposing compared to *de novo* development, which is the existence of non-clinical and clinical data for existing medicines. In this chapter, via a literature review and semi-structured interviews, we explored how the large amount of available data can be used to facilitate the research and development in drug repurposing. This study demonstrated that **existing non-clinical, clinical and real-world data can be applied in each stage of the repurposing process**, namely for the identification and prioritisation of candidates, the validation and selection of the best candidate(s), the translation of the repurposing hypothesis into clinical research and finally for the clinical adoption of a successfully repurposed medicine. However, the mere existence of this data is not enough, the data should also be available, accessible and of sufficient quality. Therefore, we carried out a series of interviews on the topic of **data sharing via open access databases and public-private partnerships (PPPs)**. A number of web-based databases and platforms to share drug-, disease- or target-related data relevant to drug repurposing already exist (Table 5). Yet, stakeholders highlighted that sharing of clinical trial and patient data remains sensitive, primarily because of privacy-related concerns and commercial motives. Interviewees indicated that they would prefer to share data in controlled access models, based on a formal agreement and with a clear objective, instead of providing data through open access sources. Accordingly, interviewees were positive about PPPs for sharing data, resources and expertise, although it was noted that a positive business case is generally needed to engage private partners in a PPP, which is often not the case for the repurposing of medicines that are out of basic patent and regulatory protection.

Chapter 4 addresses the lack of funding and economic incentives to test repurposing hypotheses in confirmatory phase III RCTs, which is a significant financial challenge for off-patent drug repurposing. To address this challenge, we studied **several funding mechanisms for independent clinical trials** and explored stakeholder views on their feasibility in Europe via semi-structured interviews. The most straightforward and common mechanism is **traditional grant funding** that can come from different sources (*e.g.*, government agencies, philanthropy, pharmaceutical companies). Interviewees highlighted the importance of public funding in all research areas where market failure predominates, including the repurposing of off-patent medicines, however, they recognized that public funds are limited and should therefore be allocated to research that addresses the highest unmet needs in healthcare. **Crowdfunding**

was discussed as an alternative way to raise funds. However, interviewees indicated that crowdfunding would not be sustainable to support large RCTs as the amount of funding required surpasses the willingness to pay of "the crowd" and because it gives rise to several ethical and practical issues. Another model that has been successful in several areas of drug development is the **multi-stakeholder PPP**. Even though several precompetitive PPPs have been established to identify and develop repurposing opportunities for shelved experimental assets (37,180), interviewees were of the opinion that this model would not be viable to fully fund clinical research to repurpose off-patent, generic or biosimilar medicines due to a lack of financial incentives for private stakeholders. A fourth and final model that was explored in this study is the **pay-for-success or Social Impact Bond (SIB) model** that leverages private investments to develop public health services or interventions. Only few interviewees had prior knowledge of the SIB model but they considered it a model with great potential that warrants further exploration. All new funding mechanisms require initial public or philanthropic investments to cover the implementation and transaction costs and are typically associated with some risks. While those challenges should definitely be considered, interviewees were of the opinion that it should not prevent new funding mechanisms from being tested in a pilot project to fund independent clinical research. Finally, this study also emphasized the need to **improve collaboration and centralisation at a European or supranational level** to make clinical research more efficient and to maximize the value of the limited public funding.

The **second objective** was to portray the **regulatory framework** relevant for making repurposed medicines available to patients in Europe and to explore solutions that have been proposed to **overcome regulatory and financial barriers for clinical adoption** of repurposed medicines. This objective was addressed in **Part 3** of this dissertation in Chapters 5, 6 and 7.

In **Chapter 5**, we explored two routes relevant to the clinical adoption of a repurposed medicine in Europe. First, a **new indication can be approved, and thus brought "on-label"**, via various legal bases established in the European and national legislation. A marketing authorisation application for a new therapeutic indication initiates an independent assessment of the benefits and risks of a medicinal product in that specific indication and is typically a prerequisite for the reimbursement and the adoption of the treatment in clinical practice guidelines. This study outlined available regulatory incentives to promote marketing authorisation of new indications (*e.g.*, one additional year of marketing protection or data exclusivity, incentives for orphan and paediatric medicines (Figure 9)). However, where these incentives do not apply, pharmaceutical companies typically choose not to invest in new therapeutic indications for medicines that are out of basic patent and regulatory protection, as this entails a high administrative burden and significant costs while the return on investment is expected to be low or absent. A second route is **off-label prescribing of a medicine for the new indication**, which is managed at the national level in Europe. While off-label use could provide timely access to treatments for patients with urgent medical needs, it also entails important ethical, legal and financial concerns for patients, physicians and society at large. Finally, to **overcome the current regulatory barriers and bring new uses "on-label"**, Chapter 5 introduces a number of **proposed solutions**, which were elaborated upon in **Chapter 6 and 7**.

Chapter 6 focuses on one specific solution, namely the **repurposing framework proposed by the European Expert Group STAMP**. This framework is based on scientific and regulatory advice to support a champion who has evidence and scientific rationale for a new indication and wants the indication to be

brought "on label". In preparation of a **pilot to test the proposed framework**, we collected information for nine repurposing candidates in oncology with varying characteristics in terms of available evidence, development stage and combinations with other medicines. We also developed a template to guide evidence generation for the repurposing candidates. One or more of the proposed candidates in this study could be submitted for inclusion in the repurposing pilot, but the pilot will also be open to submissions from other champions in all disease areas. At the time of writing this dissertation, the Repurposing Observatory Group (RepOG) is preparing supporting documents for the launch of the official call for the submission of pilot candidates, which was originally planned for March 2020 but was postponed due to the COVID-19 outbreak. Late June, the RepOG agreed to resume the activities.

In **Chapter 7**, we investigated **cancer patient and HCP perspectives on specific aspects of the clinical implementation of repurposed medicines** for anticancer treatment in Belgium via semi-structured interviews. Interviewees agreed that the ultimate goal of each repurposing project should be to obtain regulatory approval for the new indication as this offers a number of advantages over off-label prescribing. Nonetheless, given the current regulatory and financial barriers in off-patent drug repurposing, off-label use might be the only route to deliver repurposed medicines to patients with urgent medical needs in a timely manner. To overcome the barriers that hinder the development and clinical implementation of repurposed medicines, we explored the **feasibility of several pragmatic solutions** by organising two focus group discussions with cancer patients and HCPs who are primarily specialized in oncology.

RECOMMENDATIONS

The **third and final objective** was to integrate the knowledge obtained from all previous studies and to propose **pragmatic policy recommendations** for addressing the current challenges in the clinical research and implementation of repurposed medicines, taking into account different stakeholder perspectives. These recommendations aim to capitalize on the economic and societal benefits of drug repurposing, as this treatment development strategy holds the promise of contributing to more sustainable health care systems in the long term.

RECOMMENDATIONS FOR THE RESEARCH AND DEVELOPMENT OF REPURPOSED DRUGS

SUPPORT DATA SHARING AND OPEN SCIENCE INITIATIVES IN DRUG REPURPOSING

Data availability is considered one of the key advantages of repurposing existing medicines. However, various data are dispersed among many different sources, in non-standardized formats, and are often of unconfirmed quality. To make optimal use of existing data, there is a **need to develop reliable and accessible international platforms and research infrastructure to facilitate data sharing and optimize data governance.** These platforms should collect, integrate and annotate data from various sources and convert it to standardized, searchable formats. Instead of developing new platforms, there are several existing open science initiatives that can be used or adapted to accommodate for drug repurposing (*e.g.*, the Biomedical Data Translator program launched by NIH NCATS (195)).

Furthermore, the **development of international data sharing agreement templates and licenses** could encourage and accelerate data sharing by reducing the administrative burden to researchers. Global standards regarding "open data licensing" could be adopted (*e.g.*, Creative Commons Licenses (454,455)).

The **role of real-world data** to generate and validate research hypotheses is gaining momentum in drug repurposing (*e.g.*, retrospective analyses of patient data from insurance or payer databases, medical records or patient registries). Consequently, there is a **need to facilitate access to real-world data and to optimize the integration, standardization, transparency and interoperability of the current systems for real-world data collection at the national and at the European level**. Furthermore, a framework or platform could be developed to routinely collect real-world experiences on the safety and efficacy of medicines that are used off-label in clinical practice (*e.g.*, similar to CURE ID app for infectious diseases (197)). Of note, better **incentives** are needed to **encourage physicians to enter correct patient data in disease registries and electronic health records**, especially to capture data on off-label use of medicines, given the legal liability incurred by the physician.

Finally, **innovative technologies to integrate and mine big data already exist** (*e.g.*, machine learning and artificial intelligence) and could be applied more efficiently to existing data included in the aforementioned platforms to generate hypotheses and build the evidence base for drug repurposing.

PROMOTE INDEPENDENT CLINICAL RESEARCH WITH REPURPOSED MEDICINES

Due to a lack of commercial prospects, off-patent medicines are mainly studied in independent clinical trials initiated and led by researchers from academia, research institutes or collaborative research groups. While these researchers conduct many phase I and II proof-of-concept studies, public and philanthropic funds are often insufficient to support large (and expensive) pivotal phase III trials. Consequently, there is a **need to promote and enable independent clinical research**, which can be achieved in several ways.

First, **additional public funding** could be provided to conduct independent clinical trials with repurposed medicines, especially confirmatory phase III RCTs. Given that clinical trials are very expensive and have a high risk of failure, it is important to adopt a robust method for allocating the limited public funds to the research projects with the highest potential benefit to patients and society.

Second, while public funding is indispensable to support independent clinical research, the feasibility of **new funding mechanisms**, as described in Chapter 4, could be explored in one or more pilot projects.

Third, there is a clear need for **increased harmonisation and centralisation** of clinical research at the European level in order to reduce fragmentation of independent research and maximize the value of limited resources. Accordingly, one or more coordinating centres should be established to accomplish this harmonisation on a supranational level. Collaborative initiatives such as the US Clinical Trials Transformation Initiative (CTTI), the European Clinical Research Infrastructure Network (ECRIN) or multinational disease-specific research organisations (*e.g.*, EORTC) could be instrumental in this effort. There is also a need to encourage academic researchers to seek advice and to engage with regulators early in the clinical development plan, including seeking scientific advice on the design of phase I and II studies.

Fourth, **innovative clinical trial designs such as adaptive platform trials** could be promoted to make clinical research with repurposed medicines more efficient. An adaptive platform trial offers several advantages over traditional RCTs, such as the ability to stop futile interventions early, reduced competition for patients between multiple clinical trials running in parallel, and the opportunity to show comparative effectiveness between multiple treatments. Moreover, platform trials can be either exploratory (phase II-III) or confirmatory (phase III-IV), and can include both commercial and non-

commercial arms. Nevertheless, a number of statistical, financial and regulatory concerns need to be addressed to unlock the full potential of these innovative trial designs (259,451).

Finally, solutions should be explored to **alleviate the administrative and financial disincentives** that discourage clinical investigators to initiate or engage in non-commercial clinical research, as described in Box 1.1 of Chapter 1 (*e.g.*, supply of trial medication free of charge, provision of administrative support in clinical trials units of university hospitals). Moreover, academic performance indicators should increasingly take into account the achieved societal benefit of research, instead of focusing primarily on the amount and impact of scientific publications.

RECOMMENDATIONS FOR CLINICAL IMPLEMENTATION OF REPURPOSED MEDICINES

DEVELOP A COLLABORATIVE FRAMEWORK TO BRING NEW USES "ON-LABEL"

Researchers from academic or non-profit organisations, who conduct most clinical drug repurposing research, generally do not have the knowledge, expertise, resources, legal mandate or intention to apply for and maintain a marketing authorisation, and to fulfil post-marketing responsibilities. Marketing authorisation holders are often reluctant to extend the therapeutic indications of their authorised products using data that was generated by third parties due to a lack of incentives and a lack of control over the quality of the data, for which they would become responsible regardless of who carried out the trial (456). To avoid problems with marketing authorisation applications based on academic or independent trials, a **collaborative European framework** is needed that stimulates (early) dialogue between academia and non-profit organisations, pharmaceutical industry and regulators. This framework should support academic or independent researchers in designing and conducting pivotal clinical trials that generate high-quality data for marketing authorisation.

The **European Commission expert group STAMP created a framework to support a not-for-profit or academic stakeholder**, termed a "Champion", who has evidence and scientific rationale for a new therapeutic indication, in bringing this new indication "on-label" (described in Chapter 6 of this dissertation). The framework puts forward **scientific and regulatory advice from regulators** as a means to evaluate the available evidence and to determine whether additional studies need to be performed. In this framework, the champion is responsible for generating the data package in preparation of the regulatory scientific advice meeting and, if needed, for conducting further studies (for which they would need to secure public or philanthropic funding). The Champion is encouraged to seek an immediate or future partnership with one or more marketing authorisation holders who can apply for an extension or variation of the marketing authorisation if the data package is considered sufficient. Currently, a pilot is in preparation to test this framework and to assess whether it is able to facilitate a marketing authorisation application for a new indication for an off-patent medicine.

Yet, solutions should be explored to overcome a number of shortcomings of the proposed framework. First, **additional support and incentives are needed to encourage the participation of independent and academic researchers** in this framework, as it requires a lot of effort and commitment from their part. One option is to waive scientific advice fees for academic or independent researchers, which is already implemented by some competent authorities (*e.g.*, EMA recently announced that applicants from the academic sector are eligible to receive free protocol assistance for developing orphan medicines as of 19

June 2020), and to include regulatory fees in research grants provided by public funding bodies. Moreover, additional guidance documents and better education on regulatory procedures could be offered as most researchers have no or very limited experience with preparing a scientific advice briefing document (311). The latter could be addressed by the Horizon 2020 Coordination & Support Action on "Strengthening regulatory sciences and supporting regulatory scientific advice". Finally, the successful outcome of this framework is fully dependent on the cooperation of the marketing authorisation holder to apply for a variation, extension or new marketing authorisation. While early engagement between the champion and the marketing authorisation holder could reduce this uncertainty, **alternative solutions should be explored for when the marketing authorisation holder is unwilling to cooperate**.

INTRODUCE LEGAL CHANGES TO BRING NEW USES "ON-LABEL"

One solution to tackle the aforementioned limitation of the STAMP framework could be to **change the legislation** at the national or European level to enable independent researchers in bringing new uses "on-label", without the need for cooperation of the original marketing authorisation holder. For example, a legal provision could be introduced that allows **third parties (*e.g.*, academic or non-profit researchers) to apply for a marketing authorisation of an extension of indication for an already approved drug**. However, in this legal provision, questions should be addressed about the legal liability and post-marketing responsibilities related to the new indication because a product label is always associated with a specific product and owned by the marketing authorisation holder.

Alternatively, a legal change could be introduced to **require regulatory agencies to follow-up on evidence made available to support new indications for approved medicines** and encourage (or enforce) marketing authorisation holders to change their product label accordingly. A change in the mandate of regulatory agencies may result in a need for additional public resources. Of note, the risk of potential conflicts of interest should be addressed by this legal provision (*i.e.*, when a regulatory agency both collects and evaluates evidence to support a new use). A similar provision was included in the Off-Patent Drugs Bill that was introduced before Parliament in the UK in 2015, however, this bill was withdrawn due to a lack of support from the UK Government (446).

CREATE NEW INCENTIVES TO ENCOURAGE BRINGING NEW USES "ON-LABEL"

Another solution to encourage marketing authorisation applications of new therapeutic indications for approved medicines that are out of basic patent and regulatory protection is to introduce **additional incentives for the pharmaceutical industry**. We described possible new incentives that could be introduced at the national and/or European level in Chapter 5 (*e.g.*, additional regulatory exclusivities, tax credit incentives, transferable vouchers that grant priority review for future marketing authorisation applications, special research funds to reward repurposing efforts, a differential pricing system across indications, and fee reductions or waivers for scientific advice and/or variation applications) (49). However, various stakeholders have expressed concerns that some incentives might evoke high drug prices, disproportionate to the development costs. The Commission staff working document evaluating the orphan and paediatric regulations in Europe, published in August 2020, also highlighted the issue of high prices for repurposed orphan drugs: "*The fact that the current regulatory framework for the Orphan Regulation contains no provisions to safeguard the affordability and accessibility of orphan medicines, even when*

no significant R&D investments have been made, may be regarded as a significant inefficiency. However, the absence of data on the costs of development for such products makes it difficult to objectively estimate what would constitute an appropriate reward". Consequently, further research is needed into the actual costs of developing repurposed drugs and the appropriate incentives and rewards that could encourage pharmaceutical developers to invest in drug repurposing.

Alternatively, **consortia could be created that involve all producers of a certain drug or active substance** (both originator and generic/biosimilar developers) to share the administrative and financial burden associated with developing new uses, within the terms of competition laws. Such consortia would address the free-rider problem by generic or biosimilar competitors in off-patent drug repurposing.

MANAGE AND IMPROVE OFF-LABEL USE OF REPURPOSED MEDICINES

Given the current pharmaceutical model, off-label use is often the only available route to rapidly treat patients with urgent medical needs. When high-quality evidence is available but incentives to apply for regulatory approval are lacking, solutions should be explored to facilitate the **reimbursement of the off-label use and the inclusion in existing treatment guidelines or national formularies**. Additionally, the medicine should be **registered in the WHO Essential Medicines List** to prevent the drug from being withdrawn from the market. Finally, to reduce the scientific and legal uncertainty associated with off-label prescribing and to build the evidence base, **follow-up data regarding the efficacy and safety of off-label use** should be collected in a central repository, preferably at a supranational level.

STRENGTHS AND LIMITATIONS OF THE PROJECT

This dissertation provides a **comprehensive overview** regarding the research and development of repurposed medicines, from candidate selection to clinical adoption. We used **qualitative research methods** to generate new insights and applied a **multi-stakeholder approach** to develop an overarching understanding from different perspectives on various aspects and challenges of drug repurposing as a treatment development strategy. Moreover, one of the key strengths of this project is the **close collaboration with the colleagues at the Anticancer Fund** who have profound expertise in drug repurposing research as illustrated by their clinical trial portfolio (342) and their involvement in the Repurposing Drugs in Oncology (ReDO) project (45,68). The Anticancer Fund is a Belgian Foundation of Public Utility that is dedicated to expanding the range of treatment options available to cancer patients, regardless of commercial value. This collaboration allowed the PhD candidate to learn from their experience and make use of the broad network that the Anticancer Fund has built in this field, which includes key European and global stakeholders in the healthcare sector (academic groups and research institutes, regulators, policymakers, payers, patient and professional organisations, pharmaceutical industry associations, *etc.*). Additionally, the involvement of the PhD candidate in the policy and regulatory science activities of the Anticancer Fund allowed for a more pragmatic approach towards formulating policy recommendations with a patient-centric and societal view.

This project's **main limitation** is that it is **exploratory** in nature and therefore could not always achieve an in-depth understanding of the **numerous sub-topics** that were broached. In fact, most studies uncovered

many additional research questions that warrant further exploration. Several follow-up research projects are proposed in the section on 'Future research'.

Chapters 3, 4 and 7 applied **qualitative research methods** (*i.e.*, semi-structured interviews and focus group discussions) that allow an in-depth investigation of stakeholder perspectives on specific topics. Semi-structured interviews were chosen as only little information was available about the extent and the causes of the legal, regulatory and financial challenges in drug repurposing at the start of the PhD project. Moreover, semi-structured interviews allowed us to purposively select study participants with specific knowledge about the topics we were interested in, which were relatively new to the scientific community and the general public. In Chapter 3 and 4, study participants were identified through conference proceedings, author lists of scientific publications and the network of the research group. In chapter 7, study participants were selected through patient and professional organisations and networks, and prior knowledge about drug repurposing was not a requirement in this study. The semi-structured interviews and focus group discussions helped us to better understand the multifaceted policy problems that impede research and development of repurposed drugs and allowed us to propose a number of pragmatic policy recommendations to address the current challenges. However, qualitative research also suffers some important limitations. First, results are not generalizable outside of the study sample and the number of study participants per stakeholder group was rather small in each of the studies due to time constraints and low response rates. Second, qualitative studies do not allow the quantification of stakeholder perspectives on the different aspects that were discussed. Third, qualitative research is subject to bias in the different stages of the research (*e.g.*, biased questions, biased study sample, biased in analysis and bias in reporting). To reduce this bias and to maximize the validity of the results of the interviews and focus group discussions, we prepared and followed a topic guide for each study, which was pilot tested. Interviews and focus group discussions were audio recorded and transcribed *ad verbatim*. Qualitative data was analysed in different stages using the Framework Method described by Gale *et al.* (102) and the Qualitative Analysis Guide of Leuven (QUAGOL) guideline by Dierckx de Casterlé *et al.* (457). Additionally, the 32-item Consolidated criteria for reporting qualitative research (COREQ) checklist was applied to facilitate the reporting of the study methods, results and findings (458).

Another limitation is that even though drug repurposing is gaining momentum in various disease areas, the scope of this project was focused on oncology. Nonetheless, most findings and policy recommendations could also be relevant to other disease areas. Moreover, while the challenges in drug repurposing play at a global level, we concentrated our efforts on the European and Belgian context. Finally, this project focused primarily on overcoming the challenges associated with the repurposing of authorised medicines that are out of basic patent and regulatory protection. However, as explained in Chapter 1, there are a number of other repurposing scenarios that face a distinct set of challenges, which were not addressed.

FUTURE RESEARCH

While this PhD project provided a comprehensive overview of wide range of challenges in drug repurposing, it also uncovered **many additional research questions** that warrant further exploration. A number of specific proposals for future research are summarized below.

First, additional clinical data and evidence is needed to demonstrate the value of drug repurposing for cancer patients. So far, only a handful of non-cancer agents have been successfully repurposed and approved in oncology. Yet, the interest of the scientific community in the repurposing of non-cancer drugs for the treatment of cancer patients has increased significantly in recent years, as illustrated by the growing number of published preclinical and clinical studies and repurposing talks at scientific conferences, and the many ongoing late-stage clinical trials that investigate repurposed drugs in cancer patients (68). In January 2020, Corsello and colleagues identified about 50 non-oncology drugs that selectively inhibit subsets of cancer cell lines in a manner predictable from the molecular features of the cell lines (459). Moreover, the ReDO project reviewed and summarized the evidence of anticancer activity for a range of non-cancer drugs, including diclofenac, nitroglycerin, itraconazole, clarithromycin, cimetidine, mebendazole, propranolol, (hydroxy-) chloroquine and selective phosphodiesterase 5 inhibitors. This project also created a database of about 300 non-cancer medicines with potential anticancer effects based on data from peer-reviewed studies (*in vitro*, *in vivo* or human research), medical case reports, observational studies and clinical trials (www.redo-project.org/db). The identified candidate drugs have shown to fight cancer in various ways (*e.g.*, directly targeting the tumour cells, influencing the tumour microenvironment). At present, **additional research is needed to provide clinical evidence that repurposed drugs can improve outcomes for cancer patients. However, several aspects should be considered to increase the chances of success**. First, given the limited resources, future studies should focus on identifying criteria to prioritize the strongest repurposing candidates for testing in clinical trials (*e.g.*, robust scientific rationale, evidence from preclinical studies, toxicity). Second, lessons should be learned from clinical studies with repurposed drugs that failed to improve outcomes for cancer patients (*e.g.*, a lack of efficacy, toxicity, insufficient power, slow accrual, *etc.*)(460). To avoid poorly designed or underpowered studies that add on uncertainty, only well-designed trials should be conducted based on robust scientific rationale (*e.g.*, studies that include predictive biomarkers for patients' selection). Joint scientific advice from regulators and HTA bodies may help to safeguard robust trial designs. Finally, as mentioned previously, the application potential of innovative clinical trial designs could be explored further to optimize drug repurposing research (e.g., multi-arm multi-stage trials, pragmatic clinical trials)."

Second, a **systematic analysis of the proportion of approved and marketed medicines that obtained a marketing authorisation for a new therapeutic indication after first approval could be performed to quantify drug repurposing in practice**. The following aspects could be studied for repurposed medicines: the legal basis for the marketing authorisation, the time after first approval of the original marketing authorisation, the type of applicant, the non-clinical and clinical evidence submitted to support the marketing authorisation application, relevant incentives (patent protection and regulatory exclusivities) and whether the new indication belongs to the same or a different therapeutic domain.

Third, during the course this PhD project, it became clear that there is a **lack of transparency regarding the actual costs and investments needed to develop new therapeutic indications for existing drugs.** Further research to estimate the actual research and development spending on repurposed medicines could be valuable to determine the appropriate incentives and rewards to incentivize pharmaceutical developers to invest in drug repurposing. Such an analysis could facilitate the creation of incentive schemes that balance the need for affordability and accessibility for society and the need for appropriate return on investment for pharmaceutical developers.

Finally, an analysis that cross-references real-world patient data from insurance or payer databases with medical records and/or patient registries could be useful to gain insight into off label use of medicines in clinical practice and possibly generate new repurposing hypotheses.

LESSONS LEARNED FROM COVID-19

Over the past months, the **global COVID-19 pandemic** highlighted the significant potential of repurposed drugs to help tackle urgent global health threats in a timely and affordable manner. Pharmaceutical and life science companies, academic researchers, not-for-profit organisations, philanthropy, public funding bodies and regulators worldwide joined forces to answer the urgent demand for COVID-19 treatments. Interestingly, the **data-driven and experimental approaches** described in Chapter 3 of this dissertation were widely applied to quickly identify repurposing candidates for COVID-19 (87). Moreover, a **number of wide-ranging, international initiatives to facilitate sharing and access to research data** were established to halt the virus' progression (*e.g.*, COVID-19 Data Portal, COVID-19 Data Exchange).

Numerous regional, national and international clinical trials investigating a wide-array of repurposing candidates have been registered in clinical trial registries at an unprecedented rate (at least 870 ongoing trials with repurposed drugs as of July 2020) (96). However, questions have been raised about whether conducting that many "small" clinical trials is a good use of resources (461). Various stakeholders have expressed concerns about the risk of duplication of research, the competition for patients and research funds, the ethical issue of enrolling so many patients in individual control groups and the ability of these trials to support robust regulatory and treatment decision-making (462). Indeed, this pandemic emphasized the **need for better coordination in clinical research at the international level**, which was also highlighted in Chapter 4 of this dissertation (462). The EU "ERAvsCorona" action plan was launched to provide rapid dedicated funding and infrastructure to support large, EU-wide clinical trials for the management of coronavirus patients. In addition, key stakeholders underscored the **value of adaptive platform trials** for accelerating the identification of effective COVID-19 treatments (462,463). Examples of such trials investigating repurposed drugs for COVID-19 include the international "Solidarity" trial launched by the WHO and the UK-based "RECOVERY" trial led by the University of Oxford.

While **off-label prescribing of existing medicines** was widely applied as a way to rapidly treat patients with urgent medical needs, the COVID-19 pandemic also **brought to light several of the pitfalls of off-label use** described in chapters 5 and 7 of this dissertation. First, the serious adverse events related to (hydroxy-) chloroquine use in COVID-19 demonstrated that off-label or unregulated use of unproven treatments can be dangerous, even when the drug has been on the market for a long time. Second, COVID-19 highlighted the dilemma between learning (test a drug in an RCT) and doing (treat the patient with an off-label drug), which was discussed in Chapter 7 of this dissertation (464). To be able to learn from real-world experiences and potentially reduce the need for future clinical studies, **real-world efficacy and safety data regarding off-label use of medicines should be collected in a central repository** (465).

Regulators also took action to aid research and development of COVID-19 treatments. For one, **regulatory taskforces and international workshops** were established to overcome regulatory challenges emerging from the pandemic (*e.g.*, COVID-19 EMA pandemic Task Force). In addition, **early dialogue**

between researchers and regulators was encouraged in order to generate high-quality data needed for the development and the marketing authorisation of repurposed and *de novo* treatments for COVID-19.

It is apparent that, when rapid action is needed, the financial and regulatory barriers that typically impede off-patent drug repurposing can be largely removed. **Yet, it remains to be seen whether the lessons learned from COVID-19 will be translated to the repurposing of medicines in other disease areas.**

FUTURE PERSPECTIVES

In recent years, drug repurposing caught the attention from policymakers and regulators globally. **In Europe**, drug repurposing became part of the agenda of the **European Commission Expert Group on STAMP**, which is an expert group under the European Pharmaceutical Committee that involves representatives from all European Member States, countries in the EEA and the EMA. This resulted in the establishment of the "**Proposal for a framework to support not-for-profit organisations and academia (institutions and individuals) in drug repurposing**". **A pilot to test this framework will be launched soon** (330,339). Furthermore, the EMA has expressed their commitment to support the development and implementation of a repurposing framework as part of the agency's **"Regulatory science to 2025" strategy** (337,466). More specifically, the agency proposed to: "i) enhance scientific and regulatory advice on evidence generation and marketing authorisation application submission; ii) develop methodological principles for third-party data-pooling, relevant real-world data and historical nonclinical datasets; iii) translate experience with EMA's registry pilot to guide real-world data collection; iv) explore utility of low-intervention clinical trials for evidence generation for drug repurposing". In February 2020, **European experts in oncology published an awareness call** for bringing new indications on-label for "old" drugs (467):

> *"Can we make progress and get more label extensions for evidence-based beneficial treatments? This is a scenario most commonly difficult in low-cost, off-patent generics or drugs close to an end of their initial patent, which have been shown to provide meaningful patient benefit in new clinical contexts. The new clinical use, when based on high-level evidence, should lead to an updated EMA approved indication. How can we get there?"*

On the **national level**, a **number of initiatives** have been taken to support drug repurposing as well. For example, in the UK, potential routes for repurposed medicines are offered in the Early Access to Medicines Scheme, in the Accelerated Access Collaborative and in the report on "Facilitating adoption of off-patent, repurposed medicines into NHS clinical practice" created by Academy of Medical Research Charities (317,339). In the Netherlands, several programmes focus on harnessing the opportunities offered by drug repurposing and aim to address its challenges (*e.g.*, the Drug Rediscovery topic in the Goed Gebruik Geneesmiddelen programme of ZonMw, Fair Medicine, the drug rediscovery platform (DRUP) of the Oncode Institute (468)).

In the **US**, the NIH NCATS and its Cures Acceleration Network Review Board (CANRB) partnered with the FDA and the Reagan-Udall Foundation to hold a **multi-stakeholder workshop** in December 2019, titled "Repurposing Off-Patent Drugs: Research and Regulatory Challenges". The aim of this workshop was to identify and prioritize the problems relevant to repurposing off-patent drugs and to start **creating a research agenda** to seize the opportunities offered by off-patent drug repurposing and accommodate the

challenges (469). At the 2019 WHO "**World Conference on Access to Medical Products: Achieving the SDGs 2030"** in New Delhi, **policy recommendations, collaborative initiatives and regulatory approaches for drug repurposing** were discussed as well (470).

Finally, the EU currently shows a strong commitment on tackling cancer on all fronts. This is reflected by the **Europe's Beating Cancer Plan** launched in February 2020 that aims to take action at every key stage of the disease: prevention, diagnosis, treatment and survivorship. Additionally, the **Mission on Cancer** is one of the five missions under the Horizon Europe Framework Programme for Research and Innovation (2021-2027) that aims to deliver solutions to major challenges for Europe. Furthermore, the EU is launching a **new EU pharmaceutical strategy** that aims to improve and accelerate patients' access to safe and affordable medicines and to support innovation in the EU pharmaceutical industry. **In view of these ambitious plans, there is now an ideal climate in Europe to consider the aforementioned policy recommendations and accommodate for drug repurposing as a timely and affordable treatment development strategy for cancer patients with urgent medical needs.**

GENERAL CONCLUSION

The recommendations proposed in this dissertation are pragmatic and are intended to overcome the financial and regulatory challenges that impede the clinical research and implementation of repurposed medicines that are out of basic patent and regulatory protection. Nevertheless, these recommendations do not address the fundamental issue underlying the challenges in drug repurposing, namely that the **current pharmaceutical model is not designed to accommodate the development of treatments with potentially high patient value for which commercial prospects are low**.

Indeed, due to the lack of commercial prospects, **the re-use of "old" drugs for new indications is typically not considered "sexy" or innovative,** especially not compared to the many targeted therapies that are being developed in oncology. This not only discourages investments by pharmaceutical companies, but also negatively affects the capacity of drug repurposing projects to attract research grants or to obtain backing from key-opinion-leaders, oncologists and regulators. Yet, the lack of commercial value of repurposing off-patent medicines is also the reason for its high potential societal value and public health benefit, especially given the strained healthcare systems worldwide.

A final issue in drug repurposing is that it involves **many different stakeholders, yet nobody owns "the problem of new uses"**. While the current project focused on the oncology field, there is a clear need for concerted actions and collaboration between stakeholders across all disease areas at the EU or even global level to overcome the barriers for drug repurposing and thus tap into its potential for providing safe, timely, affordable and effective new treatment options for patients with unmet medical needs.

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APPENDICES

Appendix A. Chapter 3 - Interview topic guide

THEME	QUESTION(S)
Introduction	1. Could you please elucidate your background/interest/field of research?
Candidate selection for repurposing	2. According to you, which data are required to efficiently identify new indications for existing drugs? 3. Which data sources could be applied or are already being applied to identify new indications for existing drugs?
Marketing authorisation of new indications	4. In your opinion, which data are required to apply for a marketing authorisation for a new indication for an existing drug with the competent authorities? 5. Which data sources could be used in such an application for a new indication? *Sub question:* Are there certain quality standards to be met? (*E.g.*, use of real-world evidence or results from Randomized Controlled Trials (RCTs)?
Data sharing	6. According to you, what is the importance of sharing previously mentioned data with other researchers in the context of drug repurposing? 7. Which data, applicable in the context of drug repurposing, would you be willing to provide through databases? *Sub question:* Would you be willing to share these data publicly? 8. Which advantages do you foresee in introducing collaborations between the public and the private sector, for example through PPPs, in relation to the sharing of data in drug repurposing? *Sub question:* Why did your organisation opt to participate in such a collaboration? **OR** What is keeping you from participating in such a collaboration?

Appendix B. Chapter 3 - Literature search

MEDLINE search (January 31, 2020)

(("Drug Repositioning"[Mesh] OR "Repurposed drug*"[tiab] OR "Repositioned drug*"[tiab] OR "Drug repurposing"[tiab] OR "Drug repositioning"[tiab] OR "Drug reprofiling"[tiab] OR "Drug redirecting"[tiab] OR "Drug rediscovery"[tiab] OR "Drug retasking"[tiab]) OR (("Pharmaceutical Preparations"[Mesh] OR "Drug*"[tiab] OR "Medicine*"[tiab] OR "Medication*"[tiab] OR "Medicinal product*"[tiab] OR "Pharmaceutical product*"[tiab] OR "Medicament*"[tiab]) AND ("Repositioning"[tiab] OR "Repurposing"[tiab] OR "Rediscovery"[tiab] OR "Redirecting"[tiab] OR "Reprofiling"[tiab] OR "Retasking"[tiab] OR "Re-profiling"[tiab] OR "Re-tasking"[tiab]))) AND (("Public-Private Sector Partnerships"[Mesh] OR "Partnership*"[tiab] OR "Cooperation*"[tiab] OR "Co-operation*"[tiab] OR "Collaboration*"[tiab]) OR ("Databases, Pharmaceutical"[Mesh] OR "Database*"[tiab] OR "Data base*"[tiab] OR "Open Source"[tiab] OR "Platform*"[tiab]))

Criteria: Articles published between January 2015 and January 2020, in English, of which the full-text publication was available

EMBASE search query (November 6, 2019)

('Repurposed drug*':ti,ab OR 'Repositioned drug*':ti,ab OR 'Drug repurposing':ti,ab OR 'drug repositioning'/exp OR 'Drug repositioning':ti,ab OR 'Drug reprofiling':ti,ab OR 'Drug redirecting':ti,ab OR 'Drug rediscovery':ti,ab OR 'Drug retasking':ti,ab) OR (('Drug*'/exp OR 'Drug*':ti,ab OR 'Medicine*':ti,ab OR 'Medication*':ti,ab OR 'Medicinal product*':ti,ab OR 'Pharmaceutical product*':ti,ab OR 'Medicament*':ti,ab) AND ('Repositioning':ti,ab OR 'Repurposing':ti,ab OR 'Rediscovery':ti,ab OR 'Redirecting':ti,ab OR 'Reprofiling':ti,ab OR 'Retasking':ti,ab OR 'Re-profiling':ti,ab OR 'Re-tasking':ti,ab)) AND (('Partnership*':ti,ab OR 'Cooperation*':ti,ab OR 'Co-operation*':ti,ab OR 'Collaboration*':ti,ab) OR ('Database*':ti,ab OR 'Data base*':ti,ab OR 'Open Source':ti,ab OR 'Platform*$':ti,ab))

Criteria: Articles published between January 2015 and November 2019, in English, of which the full-text publication was available

Article selection and inclusion

# Articles	Database
Total	MEDLINE: 578 Embase: 64
After title & abstract screening	MEDLINE: 80 Embase: 16
After full-text screening	MEDLINE: 65 Embase: 7

Appendix C. Chapter 4 - Literature search

MEDLINE search (November 25, 2019)

(("Drug Repositioning"[Mesh] OR "Repurposed drug*"[tiab] OR "Repositioned drug*"[tiab] OR "Drug repurposing"[tiab] OR "Drug repositioning"[tiab] OR "Drug reprofiling"[tiab] OR "Drug redirecting"[tiab] OR "Drug rediscovery"[tiab] OR "Drug retasking"[tiab]) OR (("Pharmaceutical Preparations"[Mesh] OR "Drug*"[tiab] OR "Medicine*"[tiab] OR "Medication*"[tiab] OR "Medicinal product*"[tiab] OR "Pharmaceutical product*"[tiab] OR "Medicament*"[tiab]) AND ("Repositioning"[tiab] OR "Repurposing"[tiab] OR "Rediscovery"[tiab] OR "Redirecting"[tiab] OR "Reprofiling"[tiab] OR "Retasking"[tiab] OR "Re-profiling"[tiab] OR "Re-tasking"[tiab]))) AND ("Fund*" [tiab] OR "Financ*" [tiab]) NOT fundamental

Criteria: Articles published between January 2010 and November 2019, in English, of which the full-text publication was available

Embase search (November 26, 2019)

('Repurposed drug*':ti,ab OR 'Repositioned drug*':ti,ab OR 'Drug repurposing':ti,ab OR 'drug repositioning'/exp OR 'Drug repositioning':ti,ab OR 'Drug reprofiling':ti,ab OR 'Drug redirecting':ti,ab OR 'Drug rediscovery':ti,ab OR 'Drug retasking':ti,ab) OR (('Drug*'/exp OR 'Drug*':ti,ab OR 'Medicine*':ti,ab OR 'Medication*':ti,ab OR 'Medicinal product*':ti,ab OR 'Pharmaceutical product*':ti,ab OR 'Medicament*':ti,ab) AND ('Repositioning':ti,ab OR 'Repurposing':ti,ab OR 'Rediscovery':ti,ab OR 'Redirecting':ti,ab OR 'Reprofiling':ti,ab OR 'Retasking':ti,ab OR 'Re-profiling':ti,ab OR 'Re-tasking':ti,ab)) AND ('fund*':ti,ab OR 'financ*':ti,ab) NOT fundamental

Criteria: Articles published between January 2010 and November 2019, in English, of which the full-text publication was available

Article selection and inclusion

# Articles	Database
Total	MEDLINE: 101 Embase: 76
After title & abstract screening	MEDLINE: 45 Embase: 13
After full-text screening	MEDLINE: 14 Embase: 2

Appendix D. Chapter 4 - Interview topic guide

THEME	QUESTION(S)*
Introduction	1. Could you please elucidate your [*professional background/field of research*]?
Need	2. In your opinion, is there a need for new finance models to support non-commercial/independent clinical research, such as clinical trials with off-patent repurposed drugs? 3. Who should be responsible for fundraising and allocating funds for non-commercial scientific projects?
Knowledge/ Experience	4. Could you name one or more existing finance models that may be used for financing clinical research? 5. What is your experience with [*PPPs/SIBs/crowdfunding/other*]?
Stakeholders	6. Who are the main stakeholders involved in [*PPPs/SIBs/crowdfunding/ other*]? 7. Is there a need to involve additional stakeholders? If yes, who?
Advantages, disadvantages and risks	8. What are the advantages of these new finance models? • More specifically of [*PPPs/SIBs/crowdfunding/other*]? 9. What are the disadvantages and risks of these new finance models? • More specifically of [*PPPs/SIBs/crowdfunding/other*]? 10. In your opinion, do the advantages outweigh the disadvantages and risks?
Current role	11. What is the current role of these finance models in Belgium/Europe? • Can you name any examples of new finance models used in practice, preferably in the health care sector?
Future perspectives	12. What needs to change in order to optimize the implementation of new finance models, more specifically [*PPPs/SIBs/crowdfunding/other*], in Belgium/Europe?

** Information between square brackets was adapted depending on area of expertise of each interviewee.*

Appendix E. Chapter 5 - Literature search

Search query: A AND (B OR C OR D)

A. Drug repurposing

(("Drug Repositioning"[Mesh] OR "Repurposed drug"[tiab] OR "Repurposed drugs"[tiab] OR "Repositioned drug"[tiab] OR "Repositioned drugs"[tiab] OR "Drug repurposing"[tiab] OR "Drug repositioning"[tiab] OR "Drug reprofiling"[tiab] OR "Drug redirecting"[tiab] OR "Drug rediscovery"[tiab] OR "Drug retasking"[tiab]) OR (("Pharmaceutical Preparations"[Mesh] OR "Drug"[tiab] OR "Medicine"[tiab] OR "Medication"[tiab] OR "Medicinal product"[tiab] OR "Pharmaceutical product"[tiab] OR "Medicament"[tiab]) AND ("Repositioning"[tiab] OR "Repurposing"[tiab] OR "Rediscovery"[tiab] OR "Redirecting"[tiab] OR "Reprofiling"[tiab] OR "Retasking"[tiab] OR "Re-profiling"[tiab] OR "Re-tasking"[tiab])))

B. Marketing authorisation

(("Legislation, Drug"[Mesh] OR "Legislation as Topic"[Mesh:noexp] OR "Legislation"[tiab] OR "Legislations"[tiab] OR "Regulation"[tiab] OR "Regulations"[tiab] OR "Legal rule"[tiab] OR "Legal rules"[tiab] OR "Drug law"[tiab] OR "Drug laws"[tiab] OR "Drug legislation"[tiab] OR "Legal requirements"[tiab] OR "Regulatory"[tiab] OR "Legal"[tiab] OR "Directive"[tiab] OR "Government Agencies"[Mesh:noexp] OR "Government Agencies"[tiab] OR "Regulatory agencies"[tiab] OR "Policy Making"[Mesh] OR "Policy making"[tiab] OR "Policy makers"[tiab] OR "Regulators"[tiab] OR "Market authorization"[tiab] OR "Market authorisation"[tiab] OR "Marketing authorization"[tiab] OR "Marketing authorisation"[tiab] OR "Market approval"[tiab] OR "Marketing approval"[tiab] OR "Drug approval"[tiab] OR "Drug licensing"[tiab] OR "Drug license"[tiab] OR "Market access"[tiab] OR "Label extension"[tiab] OR "Label extensions"[tiab] OR "Extension application"[tiab] OR "Extension applications"[tiab] OR "Variation application"[tiab] OR "Variation applications"[tiab] OR "Variations application"[tiab] OR "Type 2 variation"[tiab] OR "Type 2 variations"[tiab] OR "Extension of indication"[tiab] OR "Extensions of indication"[tiab])

C. Regulatory incentives

("Regulatory exclusivities"[tiab] OR "Regulatory exclusivity"[tiab] OR "Data protection"[tiab] OR "Marketing protection"[tiab] OR "Data exclusivity"[tiab] OR "Market exclusivity"[tiab] OR "Orphan regulation"[tiab] OR "Orphan medicinal products"[tiab] OR "Orphan medicinal product"[tiab] OR "OMPs"[tiab] OR "OMP"[tiab] OR "Orphan drug"[tiab] OR "Orphan drugs"[tiab] OR "Orphan drug designation"[tiab] OR "Orphan designation"[tiab] OR "Orphan exclusivity"[tiab] OR "Pediatric regulation"[tiab] OR "Paediatric Regulation"[tiab] OR "PUMA"[tiab] OR "Paediatric-use marketing authorisation"[tiab] OR "Paediatric-use marketing authorisations"[tiab] OR "Pediatric exclusivity"[tiab])

D. Off-label use

("Off-Label Use"[Mesh] OR "Off-Label Use"[tiab] OR "Off Label Use"[tiab] OR "Off-Label Uses"[tiab] OR "Off-Label Prescribing"[tiab] OR "Off Label Prescribing"[tiab] OR "Unlabeled Indication"[tiab] OR "Unlabeled Indications"[tiab] OR "Unlicensed use"[tiab]))

Appendix F. Chapter 6 - Stakeholder meetings on drug repurposing

Chaired by the commission expert group on safe and timely access to medicines for patients ("STAMP")

MEETING	DATE	PARTICIPATING STAKEHOLDER ORGANISATIONS
6th	13 March 2017	Anticancer Fund EUnetHTA Joint Action 3 European Confederation of Pharmaceutical Entrepreneurs (EUCOPE) European Consumer Organisation (BEUC) European Federation of Pharmaceutical Industries and Associations (EFPIA) European Organisation for Rare Diseases (EURORDIS) International Rare Diseases Research Consortium (IRDIRC) Medicines for Europe National Health Care Institute Netherlands (Zorginstituut Nederland)
7th	27 June 2017	Anticancer Fund European Federation of Pharmaceutical Industries and Associations (EFPIA) Medicines for Europe
8th	8 December 2017	Anticancer Fund European Federation of Pharmaceutical Industries and Associations (EFPIA) Medicines for Europe European Society for Paediatric Oncology (SIOPE)
9th	8 June 2018	Anticancer Fund Belgian Healthcare Knowledge Centre (KCE) European Confederation of Pharmaceutical Entrepreneurs (EUCOPE) European Consumer Organisation (BEUC) European Federation of Pharmaceutical Industries and Associations (EFPIA) European Organisation for Rare Diseases (EURORDIS) European Patients' Forum (EPF) European Social Insurance Platform (ESIP) European Society for Paediatric Oncology (SIOPE) International Association of Mutual Benefit Societies (AIM) Medicines for Europe Pharmaceutical Group of the European Union (PGEU) Standing Committee of European Doctors (CPME)
10th	3 December 2018	Anticancer Fund Belgian Healthcare Knowledge Centre (KCE) European Confederation of Pharmaceutical Entrepreneurs (EUCOPE) European Consumer Organisation (BEUC) European Hospital Healthcare Federation (HOPE) European Federation of Pharmaceutical Industries and Associations (EFPIA) European Organisation for Rare Diseases (EURORDIS) European Patients' Forum (EPF) European Social Insurance Platform (ESIP) European Society for Paediatric Oncology (SIOPE) International Association of Mutual Benefit Societies (AIM) Medicines for Europe Pharmaceutical Group of the European Union (PGEU)
11th	15 March 2019	Anticancer Fund Belgian Healthcare Knowledge Centre (KCE) European Confederation of Pharmaceutical Entrepreneurs (EUCOPE) European Federation of Pharmaceutical Industries and Associations (EFPIA) European Organisation for Rare Diseases (EURORDIS) European Patients' Forum (EPF) European Social Insurance Platform (ESIP) International Association of Mutual Benefit Societies (AIM) Medicines for Europe Pharmaceutical Group of the European Union (PGEU) Standing Committee of European Doctors (CPME)

Appendix G. Chapter 6 - Core components of the targeted repurposing projects

Source: *Proposal for a framework to support not-for-profit organisations and academia (institutions and individuals) in drug repurposing* (330)

The following attributes should be considered for the repurposed medicinal product(s) targeted under this proposed framework, in particular, for a future repurposing pilot:

1. The proposed new indication for an authorised active substance should be in a condition distinct to the currently authorised indication(s) listed in section 4.1 of the relevant summary of product characteristics (SmPC) of a medicinal product in the European Union (EU) (nationally or centrally authorised, including EEA countries)
2. The targeted indication should be in an area where important public health benefits / Union interests are likely to be achieved
3. There should be a valid marketing authorisation granted in a Member State or in the European Union for the medicinal product containing the concerned active substance
4. Relevant authorised medicinal products containing the concerned active substance should be out of basic patent / supplementary protection certificate (SPC) protection, and data and market exclusivity periods
5. A Champion takes the initiative and is willing and able to take forward the roles and responsibilities required of the framework whose goal is to facilitate the bringing of the new indication to a label. A Champion can be for example a person or entity from a charity or patient group/academic unit/learned society/research funder or payer (generally seen as not- for-profit organisations) with a particular interest in repurposing an authorised medicinal product for a new indication, and who has data evidence/scientific rationale to do so. In principle, Champions based both within and outside the EU are eligible.

   A Champion is typically characterised by the following:

   a. Is not a pharmaceutical company or is not financed or managed by private profit organisations (PPO) in the pharmaceutical sector, nor has concluded any operating agreements with any PPO concerning their sponsorship or participation to the specific research project at the time of entry into the framework
   b. Is able to coordinate and / or foster the research programme up until the point of full industry engagement
   c. Is initially responsible for liaising and leading the interactions with regulatory authorities and industry / other stakeholders such as patient groups
   d. Is transparent regarding interactions with relevant pharmaceutical company(s)
   e. Files the initial request for scientific/regulatory advice on the basis of the available data
   f. Where feasible and appropriate, provides information to the MAH during the MAA submission / process (*e.g.*, regarding GCP compliance of the clinical trial(s), responses to questions from regulatory authorities)
6. There should be some supportive clinical evidence. It could include documentation from clinical trials, off label use, registry data, or reported case studies.

In summary, the repurposing framework is defined by the aim to foster the authorisation of a new indication to unprotected off-patent medicinal product where some data have already been generated.

Appendix H. Chapter 6 - Template for the repurposing pilot cases

AVAILABLE PRODUCT INFORMATION (IN EU)	
Active substance	
Authorised indication(s) (section 4.1 SmPC)	
Authorised pharmaceutical form(s)	
Authorisation details (Article 57 database*)	
NEW THERAPEUTIC USE	
Proposed indication	
Unmet medical need or significant public health benefit	
Rationale for use / Mechanism of action	
EVIDENCE SUMMARY	
Non-clinical data (*in vitro*, *in vivo*)	
Clinical trial data and case reports	
Real world data (observational studies, registry data)	
Inclusion in clinical guidelines	
REMARKS	
REFERENCES	

Abbreviations: Summary of Product Characteristics (SmPC)

* https://www.ema.europa.eu/en/human-regulatory/post-authorisation/data-medicines-iso-idmp-standards/public-data-article-57-database

Appendix I. Chapter 7 - Interview topic guide (Patient)

THEME	QUESTION(S) & PROBES	
Demographics	1.	Could you please briefly introduce yourself? • Age, education, disease history
Drug repurposing	2.	What is your experience with repurposed medicines (or do you know other cancer patients who have had any experience)? • If yes, which medicines and in which context? • Hypothetical: If there is a new drug on the market that is approved for indication A and there is a repurposed drug, also approved for indication A with the same effectiveness and safety profile. Would you prefer one to the other? Why (not)? • What if one is much more expensive than the other is?
	3.	Repurposed medicines are often explored for treating patients with rare cancers or patients who have no other treatment options left. What is your opinion about this?
Off- vs. on-label use	4.	Are you familiar with the different steps in the research and development of medicines, including market access? • If not, interviewer should provide additional information.
	5.	An advantage of repurposed medicines is that they are already available on the market and can therefore be prescribed “off-label” for a new therapeutic indication. What is your view on off-label use?
	6.	According to you, what scientific evidence is required before a medicine can be prescribed off-label?
	7.	How important is the reimbursement of a treatment to you?
	8.	In your opinion, is it important to bring new indications "on-label" through a marketing authorisation procedure? Why (not)? • What are the potential advantages and disadvantages? • Would you prefer on-label to off-label use? Why (not)?
Communication	9.	How important is it to inform patients about potential treatment options with off-label repurposed medicines, according to you?
	10.	What specific aspects of drug repurposing should be explained?
	11.	Through which communication channels would you prefer to be informed about drug repurposing? • *e.g.*, via oncologist, patient organisation, flyers, website, videos ...
Future perspective	12.	In your opinion, what measures could or should be taken to improve the clinical implementation of repurposed drugs in oncology?

Appendix J. Chapter 7 - Interview topic guide (HCP)

THEME	QUESTION(S) & PROBES
Demographics	1. Could you please briefly introduce yourself? • Current function, years of clinical experience
Drug repurposing	2. How would you describe the concept of drug repurposing? • Interviewer should correct/clarify if needed
	3. What is your opinion about drug repurposing? • What are the advantages and disadvantages? • Hypothetical: If there is a new drug on the market that is approved for indication A and there is a repurposed drug, also approved for indication A with the same effectiveness and safety profile. Would you prefer one to the other? Why (not)? • What if one is much more expensive than the other is?
	4. Do you have experience in prescribing (or delivering) repurposed medicines for the treatment of cancer patients? • Could you give one (or more) examples of medicines that were originally developed for a non-cancer indication that are currently being <u>used</u> in practice for the treatment of cancer patients? • Are you aware of drugs that were originally developed for a non-cancer indication and are currently being <u>researched</u> for the treatment of cancer patients? If yes, which?
	5. Repurposed medicines are often explored for treating patients with rare cancers or patients who have no other treatment options left. What is your opinion about this?
Off- vs. on-label use	6. An advantage of repurposed medicines is that they are already available on the market and can therefore be prescribed "off-label" for a new therapeutic indication. What is your view on off-label use of medicines?
	7. According to you, what scientific evidence is required before a medicine can be prescribed off-label?
	8. How important is the reimbursement of a treatment to you?
	9. How important is the physician's liability in off-label prescribing?
	10. Are there any other aspects that may be important when prescribing repurposed drugs off-label?
	11. In your opinion, is it important to bring new indications "on-label" through a marketing authorisation procedure? Why (not)? • What are the potential advantages and disadvantages? • Would you prefer on-label to off-label use? Why (not)?
	12. Academic or independent researchers (PI-driven clinical trials) conduct the majority of clinical studies with off-patent repurposed drugs. What role could these researchers play in marketing authorisation procedures?

Communication	13.	How important is it to inform patients about potential treatment options with off-label repurposed medicines, according to you?
	14.	How would you explain the concept of drug repurposing and off-label use to patients?
	15.	Through which communication channels would you prefer to inform patients about drug repurposing? *e.g.*, via oncologist, patient organisation, flyers, website, videos ...
	16	Have you ever received any questions from patients about the possibility of including repurposed medicines in their treatment?
Future perspective	17.	In your opinion, what measures could or should be taken to improve the clinical implementation of repurposed drugs in oncology?

Appendix K. Chapter 7 - Focus group discussion topic guide (Patient & HCP)

PART 1

Challenge: Regulatory barriers for clinical adoption of repurposed medicines

Repurposing of medicines has gained a lot of interest from the research community in recent years as it could offer safe, timely, and affordable new treatment options for cancer patients with high unmet needs. However, increasingly questions arise on how new uses will be translated into clinical practice.

Q1: Should new therapeutic indications for approved medicines be authorised by the regulatory authorities or should they be prescribed off-label?

Q2: What is your opinion about the following recommendations for bringing new uses "on-label"?

- Introduce new incentives for the pharmaceutical industry to apply for marketing authorisation of new therapeutic indications for their approved medicines (additional regulatory exclusivities, patent protection, tax incentives, regulatory fee waivers, etc.)
- Create a collaborative framework in which academia, physicians, not-for-profit organisations, pharmaceutical industry, health technology assessment bodies, payers, and regulators can work together on developing new uses for approved medicines (*e.g.*, European STAMP framework)
- Introduce a change in the pharmaceutical legislation that would require regulatory agencies to follow-up on any evidence made available to support new indications for approved medicines

Q3: What is your opinion about the following recommendations for optimizing off-label use of repurposed medicines?

- Systematically include off-label uses in existing treatment guidelines based on efficacy and safety from independent clinical research
- Collect real-world evidence about efficacy and safety of off-label use in clinical practice via electronic health records or an app similar to the CURE ID-app launched by the US FDA.
- Other suggestions?

PART 2

Challenge: Lack of commercial interest to invest in drug repurposing clinical trials

Q4: What is your opinion about the following recommendations to address this challenge?

- Provide additional funding to conduct independent clinical research with repurposed medicines (especially confirmatory phase III RCTs)
- Explore more efficient clinical trial designs (*e.g.*, platform trials, crowdsourcing for real-world patient data)
- Other suggestions?

Challenge: Lack of acceptance of repurposed medicines by the medical and patient community

Q5: Based on your experience, do you think acceptance of repurposed medicines in clinical practice would be an issue if there were sufficient data to support the new use?

SUMMARY

Cancer is a disease that affects many people's lives. At present, there is an urgent medical need for high-quality translational research to develop safe, effective and affordable treatments for cancer patients. **Repurposing existing medicines for new oncological indications** has been put forward as an innovative but largely untapped solution to address current medical needs**.** Drug repurposing is a treatment development strategy that seeks to use existing medicines for new medical indications rather than developing *de novo* molecules.

Part 1 of dissertation comprises two chapters. **Chapter 1** provides a general introduction into the field of drug repurposing and clarifies the definitions, terminology, benefits, opportunities and current research activities in oncology. Moreover, this chapter introduces key regulatory and financial challenges with regard to the clinical research and adoption of repurposed medicines that are authorised and out of basic patent and regulatory protection.

Chapter 2 describes the scope, objectives and research design of this project. The **overall aim of this PhD project** was to investigate the challenges that hinder the clinical research and implementation of drug repurposing and to explore possible solutions for unlocking the full potential of this strategy. This aim was translated in three separate objectives.

The **first objective** was to investigate data sharing initiatives, partnerships and new funding mechanisms that could facilitate the research and development of repurposed medicines. This objective was addressed in **Part 2** of this dissertation in Chapters 3 and 4.

Chapter 3 focuses on one of the key advantages of drug repurposing compared to *de novo* development, which is the existence of non-clinical and clinical data for existing medicines. Via a literature review and semi-structured interviews, we explored how the large amount of available data can be used to facilitate the research and development in drug repurposing. This study demonstrated that existing non-clinical, clinical and real-world data can be applied in each stage of the repurposing process, namely for the identification and prioritisation of candidates, the validation and selection of the best candidate(s), the translation of the repurposing hypothesis into clinical research and finally for the clinical adoption of a successfully repurposed medicine. However, the mere existence of this data is not enough, the data should also be available, accessible and of sufficient quality. Therefore, we carried out a series of interviews on the topic of data sharing via open access databases and public-private partnerships (PPPs). While drug-, disease- or target-related data relevant to drug repurposing are already shared through a number of web-based databases, interviewees highlighted that sharing of clinical trial and patient data is more sensitive, primarily because of privacy-related concerns and commercial motives. Interviewees indicated that they would prefer to share data in controlled access models, instead of providing data through open access sources. Interviewees were positive about PPPs for sharing data, resources and expertise, although it was noted that a positive business case is generally needed to engage private partners in a PPP, which is often not the case for the repurposing of medicines that are out of basic patent and regulatory protection.

Chapter 4 addresses a significant financial challenge for off-patent drug repurposing, namely the lack of funding and economic incentives to test repurposing hypotheses in confirmatory phase III RCTs. To address this challenge, we studied several funding mechanisms for independent clinical trials and explored

stakeholder views on their feasibility in Europe via semi-structured interviews. The most straightforward and common mechanism is traditional grant funding, typically provided by government agencies, philanthropy and sometimes pharmaceutical companies. Crowdfunding was discussed as an alternative way to raise funds. However, interviewees indicated that crowdfunding would not be sustainable to support large RCTs as the amount of funding required surpasses the willingness to pay of "the crowd" and because it gives rise to several ethical and practical issues. Another model that has been successful in several areas of drug development is the multi-stakeholder PPP. Even though several precompetitive PPPs have been established to identify and develop repurposing opportunities for shelved experimental assets, interviewees were of the opinion that this model would not be viable to fully fund clinical research to repurpose off-patent, generic or biosimilar medicines due to a lack of financial incentives for private stakeholders. Finally, the pay-for-success or Social Impact Bond (SIB) model was explored, which leverages private investments to develop public health services or interventions. Only few interviewees had prior knowledge of SIBs but they considered it a model with great potential that warrants further exploration. Overall, new funding mechanisms require initial public or philanthropic investments to cover the implementation and transaction costs and are typically associated with some risks. While those challenges should definitely be considered, interviewees were of the opinion that it should not prevent new funding mechanisms from being tested to fund independent clinical research. Finally, this study also emphasized the need to improve collaboration and centralisation at a European or supranational level to make clinical research more efficient and to maximize the value of the limited public funding.

The **second objective** was to portray the regulatory framework relevant for making repurposed medicines available to patients in Europe and to explore solutions that have been proposed to overcome regulatory and financial barriers for clinical adoption of repurposed medicines. This objective was addressed in **Part 3** of this dissertation in Chapters 5, 6 and 7.

In **Chapter 5**, we explored two routes relevant to the clinical adoption of a repurposed medicine in Europe. First, a new indication can be approved, and thus brought "on-label", via various legal bases established in the European and national legislation. A marketing authorisation application for a new therapeutic indication initiates an independent assessment of the benefits and risks of a medicinal product in that specific indication and is typically a prerequisite for the reimbursement and the adoption of the treatment in clinical practice guidelines. This study outlined available regulatory incentives to promote marketing authorisation of new indications (*e.g.*, one additional year of marketing protection or data exclusivity, incentives for orphan and paediatric medicines). However, where these incentives do not apply, pharmaceutical companies typically choose not to invest in new therapeutic indications for medicines that are out of basic patent and regulatory protection, because this entails a high administrative burden and significant costs while the return on investment is expected to be low or absent. A second route is off-label prescribing of a medicine for the new indication, which is managed at the national level in Europe. While off-label use could provide timely access to treatments for patients with urgent medical needs, it also entails important ethical, legal and financial concerns for patients, physicians and society at large. Finally, to overcome the current regulatory barriers and bring new uses "on-label", Chapter 5 introduces a number of proposed solutions, which were elaborated upon in Chapter 6 and 7.

Chapter 6 focuses on one specific solution, namely the repurposing framework proposed by the European Expert Group STAMP. This framework is based on scientific and regulatory advice to support a champion who has evidence and scientific rationale for a new indication and wants the indication to be brought "on label". In preparation of a pilot to test the proposed framework, we collected information for nine promising repurposing candidates in oncology with varying characteristics in terms of available evidence, development stage and combinations with other medicines. We also developed a template to guide evidence generation for the repurposing candidates. One or more of the proposed candidates in this study could be submitted for inclusion in the repurposing pilot, but the pilot will also be open to submissions from other champions in all disease areas.

In **Chapter 7**, we investigated cancer patient and HCP perspectives on specific aspects of the clinical implementation of repurposed medicines for anticancer treatment in Belgium via semi-structured interviews. Interviewees agreed that the ultimate goal of each repurposing project should be to obtain regulatory approval for the new indication as this offers a number of advantages over off-label prescribing. Nonetheless, given the current regulatory and financial barriers in off-patent drug repurposing, off-label use might be the only route to deliver repurposed medicines to patients with urgent medical needs in a timely manner. To overcome the barriers that hinder the development and clinical implementation of repurposed medicines, we explored the feasibility of several pragmatic solutions by organising two focus group discussions with cancer patients and HCPs who are primarily specialized in oncology.

Part 4, Chapter 8 focuses on the **third and final objective**, which was to integrate the knowledge obtained from all previous studies and to propose pragmatic policy recommendations for addressing the current challenges in the clinical research and implementation of repurposed medicines, taking into account different stakeholder perspectives. These proposed recommendations aim to capitalize on the economic and societal benefits of drug repurposing, as this treatment development strategy holds the promise of contributing to more sustainable health care systems in the long term.

SAMENVATTING

Kanker is een ziekte die veel mensen treft. Er is daarom dan ook een dringende medische behoefte aan translationeel onderzoek naar veilige, effectieve en betaalbare behandelingen voor kankerpatiënten. **Het heroriënteren of herbestemmen van bestaande medicijnen voor nieuwe oncologische indicaties** werd naar voren geschoven als een innovatieve maar grotendeels onbenutte oplossing om aan de huidige medische behoeften tegemoet te komen. Het heroriënteren van geneesmiddelen is een strategie met als doel bestaande geneesmiddelen te gebruiken voor nieuwe medische indicaties in plaats van *de novo* moleculen te ontwikkelen.

Deel 1 van dit proefschrift bestaat uit twee hoofdstukken. **Hoofdstuk 1** geeft een algemene introductie tot het onderzoekdomein van het heroriënteren van geneesmiddelen en verduidelijkt de definities, de terminologie, de voordelen, de opportuniteiten en de huidige onderzoeksactiviteiten in oncologie. Bovendien introduceert dit hoofdstuk belangrijke regulatoire en financiële barrières met betrekking tot het klinisch onderzoek en de klinische adoptie van geheroriënteerde geneesmiddelen waarvoor een vergunning voor het in de handel brengen is verleend en waarvoor het basisoctrooi en de wettelijke beschermingstermijn reeds verstreken zijn.

Hoofdstuk 2 beschrijft de scope, de doelstellingen en de onderzoeksopzet van dit project. Het **algemene doel van dit doctoraatsproject** was het onderzoeken van de regulatoire en financiële aspecten die het klinische onderzoek en de implementatie van geheroriënteerde geneesmiddelen belemmeren en het verkennen van mogelijke oplossingen om het volledige potentieel van deze strategie te benutten. Dit vooropgestelde doel werd vertaald naar drie afzonderlijke doelstellingen.

De **eerste doelstelling** was het onderzoeken van initiatieven voor gegevensuitwisseling, samenwerkingen nieuwe financieringsmechanismen die het onderzoek naar en de ontwikkeling van geheroriënteerde geneesmiddelen zouden kunnen vergemakkelijken. Deze doelstelling wordt behandeld in **deel 2** van dit proefschrift, meer specifiek in de hoofdstukken 3 en 4.

Hoofdstuk 3 richt zich op een van de belangrijkste voordelen van het heroriënteren van geneesmiddelen ten opzichte van *de novo* ontwikkeling, namelijk de beschikbaarheid van niet-klinische en klinische gegevens voor de bestaande geneesmiddelen. Via een literatuuroverzicht en semigestructureerde interviews onderzochten we hoe de grote hoeveelheid beschikbare gegevens kan worden gebruikt om het onderzoek naar en de ontwikkeling van geheroriënteerde geneesmiddelen te vergemakkelijken. Deze studie heeft aangetoond dat bestaande niet-klinische, klinische en “real-world” gegevens kunnen worden toegepast in elke fase van het heroriënteringsproces, namelijk voor de identificatie en prioritering van kandidaten, de validatie en selectie van de beste kandidaten, de vertaling van de hypothese naar klinisch onderzoek en tenslotte voor de klinische adoptie van een succesvol geheroriënteerd geneesmiddel. Het louter bestaan van deze gegevens is echter niet voldoende, de gegevens moeten ook beschikbaar, toegankelijk en van voldoende kwaliteit zijn. Daarom hebben we een reeks interviews afgenomen over het delen van gegevens via open access databanken en publiek-private samenwerkingen (PPPs). Hoewel geneesmiddel-, ziekte- of target-gerelateerde gegevens die relevant zijn voor het heroriënteren van geneesmiddelen al worden gedeeld via een aantal web-gebaseerde databanken, benadrukten geïnterviewden dat het delen van klinische proef- en patiëntgegevens gevoeliger ligt, voornamelijk

vanwege de bezorgdheid over de privacy en vanwege commerciële overwegingen. De geïnterviewden gaven aan dat zij de voorkeur geven aan het delen van gegevens in controlled access modellen, in plaats van het verstrekken van gegevens via open access modellen. De geïnterviewden waren positief over PPPs voor het delen van gegevens, middelen en expertise, hoewel werd opgemerkt dat er over het algemeen een positieve business case nodig is om private partners bij een PPP te betrekken, wat vaak niet het geval is voor het heroriënteren van geneesmiddelen die niet langer beschermd worden door het basisoctrooi, noch door data- en marktbescherming.

Hoofdstuk 4 focust op een van de meest belangrijke financiële belemmeringen voor het heroriënteren van geneesmiddelen, namelijk het gebrek aan financiering en economische prikkels om de veiligheid en werkzaamheid van geheroriënteerde geneesmiddelen te testen in fase III gerandomiseerde klinische studies (RCTs). In deze studie, bestudeerden we verschillende financieringsmechanismen voor niet-commerciële klinische studies en onderzochten we de standpunten van belanghebbenden over de toepasbaarheid van deze mechanismen in Europa via semigestructureerde interviews. Het meest eenvoudige en gebruikelijke mechanisme is de financiering van onderzoek via onderzoekbeurzen of subsidies die doorgaans worden verstrekt door overheidsinstanties of filantropische organisaties en soms door farmaceutische bedrijven. Daarnaast werd crowdfunding besproken als een alternatieve manier om fondsen te werven. Geïnterviewden gaven echter aan dat crowdfunding niet duurzaam zou zijn om grote RCTs te ondersteunen omdat het benodigde bedrag de betalingsbereidheid van "the crowd" overtreft en omdat crowdfunding aanleiding geeft tot verschillende ethische en praktische vragen. Een ander model dat succesvol is geweest op verschillende gebieden van geneesmiddelenontwikkeling, is de multi-stakeholder PPP. Hoewel er verschillende pre-competitieve PPPs zijn opgericht om mogelijkheden voor de heroriëntering van experimentele geneesmiddelen te identificeren en te ontwikkelen, waren de geïnterviewden van mening dat dit model niet toepasbaar is voor het volledig financieren van klinisch onderzoek naar geneesmiddelen waarop niet langer een basisoctrooi rust (inclusief generieke of biosimilaire geneesmiddelen) omdat er in dit geval geen financiële stimulansen zijn voor private partners. Ten slotte werd het "pay-for-success"- of "Social Impact Bond"-model (SIB) onderzocht. Dit is een model dat privé- investeringen gebruikt om een maatschappelijk probleem aan te pakken, zoals het ontwikkelen van geneesmiddelen voor patiënten met medische noden. Slechts enkele geïnterviewden hadden voorkennis van SIBs, maar zij beschouwden het als een model met veel potentieel dat verder onderzoek vereist. Belangrijk om weten is dat er steeds publieke of filantropische investeringen nodig zijn om de implementatie- en transactiekosten van nieuwe financieringsmechanismen te dekken. Dit soort mechanismen gaan doorgaans ook gepaard met enkele risico's. Hoewel deze uitdagingen zeker moeten worden erkend, waren de geïnterviewden van mening dat dit niet mag verhinderen dat nieuwe financieringsmechanismen worden getest om niet-commercieel klinisch onderzoek te financieren. Ten slotte benadrukte deze studie ook de noodzaak om de samenwerking en centralisatie op Europees of supranationaal niveau te verbeteren om klinisch onderzoek efficiënter te maken en om de waarde van de beperkte publieke financiering te maximaliseren.

De **tweede doelstelling** van dit doctoraatsproject was om het regelgevend kader te schetsen dat relevant is voor het beschikbaar stellen van geheroriënteerde geneesmiddelen aan patiënten in Europa en om te zoeken naar oplossingen voor de regulatoire en financiële belemmeringen die de klinische toepassing van

geheroriënteerde geneesmiddelen verhinderen. Deze doelstelling werd in **deel 3** van dit proefschrift behandeld, meer specifiek in de hoofdstukken 5, 6 en 7.

In **Hoofdstuk 5** onderzochten we twee routes die relevant zijn voor de klinische adoptie van een geheroriënteerd geneesmiddel in Europa. Ten eerste kan een nieuwe indicatie worden goedgekeurd, en dus "on-label" worden gebracht, via verschillende wettelijke basissen zoals vastgelegd in de Europese en nationale wetgeving. Een vergunningsaanvraag voor het in de handel brengen van een bestaand geneesmiddel voor een nieuwe therapeutische indicatie geeft aanleiding tot een onafhankelijke beoordeling van de voordelen en risico's van een geneesmiddel in die specifieke indicatie en is doorgaans een voorwaarde voor terugbetaling en voor opname van de behandeling in klinische richtlijnen. Daarnaast bracht deze studie ook de beschikbare regulatoire exclusiviteitsmechanismen om vergunningen voor het in de handel brengen van nieuwe indicaties te bevorderen in kaart (bijv. één extra jaar marktbescherming of dataexclusiviteit voor een nieuw indicatie of de specifieke stimulansen die beschikbaar zijn voor weesgeneesmiddelen en pediatrische geneesmiddelen). Wanneer deze stimulansen echter niet van toepassing zijn, kiezen farmaceutische bedrijven er doorgaans voor om niet te investeren in nieuwe therapeutische indicaties voor geneesmiddelen die niet langer beschermd worden door het basisoctrooi noch door data- en marktexclusiviteit aangezien dit een hoge administratieve last en aanzienlijke kosten met zich meebrengt terwijl het rendement op de investering naar verwachting laag of afwezig zal zijn. Een tweede route voor de klinische adoptie is het off-label voorschrijven van een geneesmiddel voor de nieuwe indicatie. Dit wordt in Europa op nationaal niveau geregeld. Hoewel off-label gebruik patiënten met dringende medische behoeften tijdig toegang geeft tot behandelingen, brengt het ook belangrijke ethische, juridische en financiële uitdagingen met zich mee voor patiënten, artsen en de samenleving als geheel. Hoofdstuk 5 introduceert dan ook een aantal potentiële oplossingen om de huidige belemmeringen in de regelgeving te overwinnen. Deze oplossingen werden verder uitgewerkt in de hoofdstukken 6 en 7.

Hoofdstuk 6 concentreert zich op één specifieke oplossing, namelijk het kader voor het heroriënteren van geneesmiddelen dat werd ontwikkeld door de Europese experten groep "Safe and Timely Access to Medicines for patients (STAMP)". Dit kader is gebaseerd op wetenschappelijk, technisch en regulatoir advies ter ondersteuning van een "champion" die evidentie en wetenschappelijke rationale heeft voor een nieuwe indicatie en die wil dat de indicatie "on-label" wordt gebracht. Ter voorbereiding van een pilootproject om het voorgestelde kader te testen, verzamelden we in deze studie informatie voor negen veelbelovende kandidaat-geneesmiddelen die geheroriënteerd zouden kunnen worden in de oncologie. Deze geneesmiddelen beschikken over uiteenlopende kenmerken wat betreft de beschikbare evidentie, de ontwikkelingsfase en de combinaties met andere geneesmiddelen. We hebben ook een template ontwikkeld om het genereren van evidentie voor kandidaat-geneesmiddelen te vereenvoudigen. Een of meer van de voorgestelde kandidaat-geneesmiddelen in deze studie kan worden ingediend voor het pilootproject, maar dit project zal ook open zijn voor inzendingen van andere "champions" in alle ziektegebieden.

In **Hoofdstuk 7** onderzochten we de perspectieven van kankerpatiënten en zorgverleners op specifieke aspecten met betrekking tot de klinische implementatie van geheroriënteerde geneesmiddelen voor de behandeling van kanker in België via semigestructureerde interviews. De geïnterviewden waren het

erover eens dat het uiteindelijke doel van elk heroriënteringsproject het verkrijgen van een vergunning voor het in de handel brengen van een geneesmiddel voor een nieuwe therapeutische indicatie moet zijn, aangezien dit een aantal belangrijke voordelen biedt ten opzichte van het off-label voorschrijven. Gezien de huidige regulatoire en financiële belemmeringen voor het heroriënteren van geneesmiddelen, is off-label voorschrijven vaak de enige manier om patiënten met dringende medische behoeften tijdig te behandelen. Om de toepasbaarheid van verschillende pragmatische oplossingen te bespreken organiseerden we vervolgens ook twee focusgroepgesprekken met kankerpatiënten en zorgverleners die de barrières in de ontwikkeling en klinische implementatie van geheroriënteerde geneesmiddelen zouden kunnen aanpakken. Deze oplossingen werden verder uitgewerkt in Hoofdstuk 8 in de vorm van pragmatische beleidsaanbevelingen.

Deel 4, Hoofdstuk 8 richt zich op de **derde en laatste doelstelling**, namelijk het integreren van de kennis verkregen uit alle voorgaande studies en het voorstellen van pragmatische beleidsaanbevelingen voor het aanpakken van de huidige uitdagingen in het klinisch onderzoek en de klinische implementatie van geheroriënteerde geneesmiddelen, rekening houdend met de perspectieven van verschillende belanghebbenden. De voorgestelde aanbevelingen zijn bedoeld om de economische en maatschappelijke voordelen van het heroriënteren van geneesmiddelen optimaal te benutten, aangezien deze behandelingsstrategie potentieel kan bijdragen aan een duurzamer gezondheidszorgsysteem op de lange termijn.

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Chapter 1 & 2
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Chapter 3
We thank all interview participants for sharing their knowledge, expertise and opinions about data, data sharing and partnership initiatives in drug repurposing. We also thank Anke Pieters, Dorien Voorter and Renée Devos for helping to conduct and transcribe the interviews as part of their master thesis in pharmaceutical care under supervision of the PhD applicant. In addition, Isabelle Huys, Ilse Rooman and Greet Musch contributed to proofreading of the final text.

Chapter 4
We thank the interview participants for sharing their knowledge, expertise and opinions about funding models to support independent clinical research. We thank Camille Deltomme and Camille Lapère for helping to conduct and transcribe the interviews as part of their master thesis in pharmaceutical care under supervision of the PhD applicant. In addition, Isabelle Huys, Ilse Rooman and Greet Musch contributed to proofreading of the final text.

Chapter 5
We thank Dr. Daniel O'Connor from the Medicines and Healthcare products Regulatory Agency in the UK (MHRA), Dr. Greet Musch and Dr. Wim Penninckx from the Federal Agency for Medicines and Health Products in Belgium (FAMHP) and Dr. Pan Pantziarka from the Anticancer Fund for sharing their expertise and for providing constructive feedback on the manuscript. In addition, Isabelle Huys, Ilse Rooman and Lydie Meheus contributed to proofreading of the final text.

Chapter 6
We thank all members of the STAMP group, in particular the members of the STAMP working group on drug repurposing, and the EMA representatives for sharing their insights on the selected case studies and on the proposed template. We also thank Lydie Meheus, Gauthier Bouche and Pan Pantziarka from the Anticancer Fund for helping to identify the pilot cases. In addition, Isabelle Huys, Ilse Rooman, and Greet Musch contributed to proofreading of the final text.

Chapter 7
We thank all interview participants for sharing their perspectives about various aspects of drug repurposing. We also thank Kelly Saviolo and Sanne van Rijn for helping to conduct and transcribe the interviews and focus group discussions as part of their master thesis in pharmaceutical care under supervision of the PhD applicant. In addition, Isabelle Huys and Ilse Rooman contributed to proofreading of the final text.

PERSONAL CONTRIBUTION

Chapter 1 & 2

Ciska Verbaanderd wrote the chapters and co-authored the publications used in the general introduction of this thesis.

Chapter 3

Ciska Verbaanderd initiated the research, designed the study and developed the research methods, performed the literature study, conducted the interviews and supervised Anke Pieters, Dorien Voorter and Renée Devos in conducting interviews. She coded the interview transcripts, analysed the data and wrote the chapter.

Chapter 4

Ciska Verbaanderd initiated the research, designed the study and developed the research methods, performed the literature study, conducted the interviews and supervised Camille Deltomme and Camille Lapère in conducting interviews. She coded the interview transcripts, analysed the data and wrote the chapter.

Chapter 5

Ciska Verbaanderd initiated the research, designed the study and developed the research methods and reviewed the legislation, guidance documents and literature. She analysed the data and wrote the chapter.

Chapter 6

This research was initiated following the discussions related to drug repurposing in the STAMP Expert Group. Ciska Verbaanderd selected the candidates in consultation with colleagues at the Anticancer Fund. She searched the literature and created a standardized template with input from members of the STAMP working group. She collected and analysed the data and wrote the chapter.

Chapter 7

Ciska Verbaanderd initiated the research, designed the study and developed the research methods, conducted interviews and supervised Kelly Saviolo and Sanne van Rijn in conducting interviews. She led the focus group discussions, coded the interview and focus group discussion transcripts, analysed the data and wrote the chapter.

CONFLICT OF INTEREST STATEMENT

PhD candidate

Ciska Verbaanderd's work as a PhD researcher at the KU Leuven was supported by a grant from the Anticancer Fund. The Anticancer Fund is a Belgian Foundation of Public Utility that depends fully on donations and private funding with no commercial shareholders or interference from special interest groups or pharma companies.

Supervisors

Isabelle Huys, PhD, is full professor at the Department of Pharmaceutical and Pharmacological Sciences, Clinical Pharmacology and Pharmacotherapy of the KU Leuven. Ilse Rooman, PhD, is professor at the Oncology Research Centre of the Vrije Universiteit Brussel and Programme Director Pancreatic Cancer at the Anticancer Fund. Greet Musch, PhD, is General-Director at the Federal Agency for Medicines and Health Products (FAMHP).

Other co-authors

Lydie Meheus, PhD, is managing director at the Anticancer Fund. Pan Pantziarka, PhD, is Programme Director Drug Repurposing at the Anticancer Fund. Gauthier Bouche, MD, is Director Clinical Research at the Anticancer Fund.

PROFESSIONAL CAREER

EDUCATION

2016 - 2020	PhD in Pharmaceutical Sciences, Faculty of Pharmaceutical Sciences, KU Leuven
2014 - 2016	Master of Biomedical Sciences, Faculty of Medicine, KU Leuven, *Magna cum laude*
2011 - 2014	Bachelor of Biomedical Sciences, Faculty of Medicine, KU Leuven, *Magna cum laude*
2005 - 2011	Latin and Modern Languages, Jan-van-Ruusbroeckollege, Brussels

TRAINING COURSES

2017	Interdisciplinary Program in Translational Medicine, I3h Institute & ULB
2020	Strategic Management in the Pharmaceutical Sector, KU Leuven

PROFESSIONAL EXPERIENCE

2016 - 2020	Policy and regulatory science activities at the Anticancer Fund, Brussels
2017 - 2020	Active participation in *ad hoc* stakeholder meetings and working group on drug repurposing of the European Commission expert group on Safe and Timely Access to Medicines for Patients (STAMP) and the European Repurposing Observatory Group

PEER-REVIEWED PUBLICATIONS IN INTERNATIONAL JOURNALS

Pantziarka P, **Verbaanderd C**, Huys I, Bouche G, Meheus L. Repurposing Drugs in Oncology: From candidate selection to clinical adoption. Seminars in Cancer Biology. 2020 [In Press].

Broes S, **Verbaanderd C**, Casteels M, Lacombe D, Huys I. Sharing of clinical trial data and samples: The cancer patient perspective. Frontiers in Medicine. 2020;7:33.

Verbaanderd C, Rooman I, Meheus L, Huys I. On-label or off-label? Overcoming regulatory and financial barriers to bring repurposed medicines to cancer patients. Frontiers in Pharmacology. 2020;10:1664.

Pantziarka P, **Verbaanderd C**, Meheus L. Biased by design? Clinical trials and patient benefit in oncology. Future Oncology. 2020;16(3):4419-4423.

Pantziarka P, **Verbaanderd C**, Sukhatme V, Capistrano RI, Crispino S, Gyawali B, Rooman I, Van Nuffel AMT, Meheus L, Sukhatme VP, Bouche G. ReDO_DB: the repurposing drugs in oncology database. Ecancermedicalscience. 2018;12:886.

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Repurposing Drugs in Oncology (ReDO) — Chloroquine and Hydroxychloroquine as anti-cancer agents. Ecancermedicalscience. 2017:781.

Verbaanderd C, Meheus L, Huys I, Pantziarka P. Repurposing Drugs in Oncology: Next Steps. Trends in Cancer. 2017;3(8):543-546.

Agbaje JO, Van de Casteele E, Hiel M, **Verbaanderd C**, Lambrichts I, Politis C. Neuropathy of Trigeminal Nerve Branches After Oral and Maxillofacial Treatment. Journal of maxillofacial and oral surgery. 2016;15(3):321-32

ARTICLES IN PREPARATION

Verbaanderd C, Rooman I, Huys I. New mechanisms to fund independent clinical trials for repurposing off-patent or generic medicines. Preprint available. DOI: 10.21203/rs.3.rs-26065/v1

Verbaanderd C, Rooman I, Huys I. Data-driven decision-making in drug repurposing: Tapping into the potential of data sharing and partnership initiatives.

Verbaanderd C, Rooman I, Huys I. Patient and healthcare professional perspectives on clinical adoption of repurposed medicines.

PRESENTATIONS AT CONFERENCES AND MEETINGS

Poster	Jul 2020	Online	DIA Europe 2020
Oral	Feb 2020	Brussels	29th EURORDIS Round Table of Companies Workshop
Oral	Nov 2019	New Delhi	2019 World Conference on Access to Medical Products Achieving the SDGs 2030
Session chair	Apr 2019	Leuven	Symposium 'Towards more sustainable access to medicines in Belgium'
Poster	Nov 2018	Barcelona	ISPOR Europe 2018
Oral	Oct 2018	Zaventem	BRAS Annual symposium
Poster	Sep 2018	Antwerp	European Biobank Week
Oral	Jul 2018	Toulouse	EuroScience Open Forum
Poster & Oral	Apr 2018	Berlin	ENLIGHT-TEN summer school - "Translational Research and Medicine Development"
Oral	Nov 2017	Amsterdam	Autumn meeting Vereniging Farma & Recht