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Authors: Teebah Abu-Zahra[1,2], Sabine Grimm[1,2], Mirre Scholte[1,2], Adam Raymakers[3], Aaron Kesselheim[3], Manuela Joore[1,2]
Affiliations: department of clinical epidemiology & medical technology assessment (kemta), maastricht university medical centre, maastricht, the netherlands[1], care and public health research institute (caphri), maastricht university, maastricht, the netherlands [2], program on regulation, therapeutics, and law, division of pharmacoepidemiology and pharmacoeconomics, department of medicine, brigham and women's hospital and harvard medical school, boston, ma, usa[3]
Orcid ids: 0000-0002-1090-1721[1,2]
Contact e-mail: teebah.abu-zahra@mumc.nl
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How Can Health Technology Assessment Help in Addressing Challenges in Drug Repurposing: A Conceptual Framework

Authors: Teebah Abu-Zahra[a,b], Sabine E Grimm [a,b] , Mirre Scholte [a,b], Adam J N Raymakers[c], Aaron S Kesselheim[c], Manuela Joore [a,b]

[a]Department of Clinical Epidemiology & Medical Technology Assessment (KEMTA), Maastricht University Medical Centre, Maastricht, The Netherlands

[b]Care and Public Health Research Institute (CAPHRI), Maastricht University, Maastricht, The Netherlands

[c]Program On Regulation, Therapeutics, And Law, Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA

Abstract

Drug repurposing faces various challenges that impede its success. We developed a framework outlining key challenges in drug repurposing to explore when and how health technology assessment (HTA) methods can address them. Based on 73 articles, an expert meeting, and seven semi-structured interviews, we identified 20 challenges across the categories of data access, research and development, collaboration, business case, regulatory, and legal challenges. Early incorporation of HTA methods including literature review, empirical research, stakeholder consultation, health economic evaluation, and uncertainty assessment can help address these challenges. HTA methods can assess the value proposition of repurposed drugs, inform further research, and ultimately help bring cost-effective repurposed drugs to patients.

Keywords: Drug Repurposing, Health Technology Assessment (HTA), Challenges in Drug Repurposing, HTA methods.

Introduction

By finding new clinical indications for already existing drugs, drug repurposing can reduce development time and costs by identifying effective treatments for new groups of patients. This proposition has led to increased research into drug repurposing; approximately 30% of annually approved drugs are repurposed drugs [1], and the index rate of publications on drug repurposing has steadily risen in the past decade [2]. Baricitinib, a rheumatoid arthritis treatment, is a recent example of a repurposed drug that became the first FDA-approved immunomodulatory treatment for COVID-19 [2]. Various initiatives, involving experts from around the world, are actively working towards advancing the practice of drug repurposing. For example, the REPO4EU consortium [3], launched in September 2022, aims to create an EU-level online platform for mechanism-based drug repurposing that provides key information, training, and collaboration opportunities globally. Target mechanism-based drug-repurposing integrates information from signalling pathways, treatment omics data, and protein interaction networks to uncover novel mechanisms of action for drugs [4]. Other initiatives for drug repurposing include REMEDi4ALL in the EU region [5], the Medicines Repurposing programme in the UK [6], and Drug Repurposing at the National Centre

for Advancing Translational Sciences (NCATS) in the US [7], among others. As most of the repurposing candidates have already gone through the investigational stages of safety, toxicology, and pharmacokinetic profiles, repurposing can shorten the development time and save substantial costs at the pre-clinical phases [8]. The failure risk from a safety point of view is also thought to be lower in later stages [9].

Despite the advantages, drug repurposing faces challenges that impede its success and may discourage researchers from pursuing repurposing projects. These are widely discussed in several articles [1,8-11], including the systematic review by Krishnamurthy et al [12]. Potential drug repurposing candidates include shelved drugs that failed phase II trials (due to lack of efficacy), off-patent drugs, generics, and drugs with limited patent life [1,10,11]. If these drug candidates are not repurposed by the original manufacturer or patent holder, accessing data and obtaining additional patents may be challenging.

Furthermore, many academic investigators and non-profit organizations conduct drug repurposing research [13]. Van Den Berg et al [14] found that twelve out of sixteen of rare disease drug repurposing cases originated in academia. In the Repurposing Drugs in Oncology (ReDO) project, 4% of 190 trials associated with one of the 72 project-linked drugs were sponsored by pharmaceutical companies, 67% by universities or hospitals, 28% by research centres or non-profits, and 2% by government agencies [15] [16]. However, academic investigators and non-profits typically lack the expertise and resources for navigating regulatory procedures and commercialising repurposed drugs.

Many challenges described in the literature are related to identifying the potential value of drug repurposing candidates during their different development stages. Thus, health technology assessment (HTA) can be a useful approach for addressing some drug repurposing challenges. HTA is a multidisciplinary field of research that evaluates the value of health technology at different points in its lifecycle [17]. Early HTA or development-focused HTA (DF-HTA) [18] refers to the use of HTA methods during the early stages of health technology development, with the aim of informing evidence generation on the technology's potential value, while quantifying and managing uncertainties around return on investment and societal impact. Early HTA [19] methods focus on finding the evidence gap at initial stages of the development cycle, and facilitating early discussions among developers, regulators, and reimbursement agencies [18]. HTA also considers the assessment of different markets and reimbursement criteria, and prioritisation of research efforts and expenditures.

To our knowledge, the role of HTA in supporting drug repurposing has not been explored. Therefore, our aim was to develop a framework of drug repurposing challenges, and based on this, explore how and when HTA can support drug repurposing.

Methods

We identified challenges in drug repurposing, as well as methods, which can address these challenges through a literature review, focus group discussions, and semi-structured interviews.

Literature review

First, we sought to identify English peer-reviewed scientific articles mentioning challenges of drug repurposing. Recently, Krishnamurthy et al. published a systematic literature review on root causes, barriers, and facilitators of drug repurposing [12]. We used the articles citing drug repurposing challenges and other relevant articles in the reference list from this review as a starting point.

Next, we updated the search strategy by Krishnamurthy et al [12] (originally until April 16, 2020) was updated to April 20, 2023. We only updated the search of Ovid Embase and PubMed as 35 of the 47 articles that cited drug repurposing challenges the original review were found in these two databases. The updated search is detailed in Appendix A. Search results were exported to an Excel sheet, and abstracts and titles were screened for eligibility by one author (TA). English language full-text articles were reviewed against the inclusion criteria that the articles related to drug repurposing and challenges mentioned.

From the included articles, challenges in drug repurposing were extracted by TA and subsequently categorised by TA and SG. Any disagreements in categorisation were resolved in a discussion among TA, SG and MJ. Our categorisation of the challenges was informed by categorisations found in the included articles

Expert meeting

A 60-minute online expert meeting was conducted to assess two primary outcomes: the completeness and appropriateness of the categorization of the list of challenges. Twenty participants with different professions and expertise related to drug repurposing within the REPO4EU consortium were invited via email.

Before the meeting, the participants received the list of categorised drug repurposing challenges based on the literature review, an agenda, and a set of open-ended questions (Appendix B) to guide the discussion. The meeting was recorded with participants' consent. The video recording was transcribed, summarised, and sent back to all participants. Any feedback was included for accuracy in the final summary. Information related to the primary outcomes of the meeting were analysed by TA, SG, and MJ, and incorporated into the final list of challenges.

Interviews

Semi-structured in-depth interviews were conducted by TA and MS following the expert meeting to further validate the completeness of our findings [20]. A convenience sampling approach was followed by selecting experts from the 8 different work streams within the REPO4EU consortium. Interviewees are listed in Appendix B. Informed consent was obtained from all participants.

All interviewees were provided with a list of categorised challenges and a set of open-ended questions relating to the appropriateness of the challenges and their categorisations (Appendix B). A pilot interview was conducted to solicit feedback on the interviewing method. Interviews lasted between 30 to 60 minutes and were recorded with participants' permission. The video recordings were transcribed using Microsoft Teams and summarised manually (TA). Participants reviewed and provided feedback on the

summarised interview transcripts. This approach follows the guidelines of the Consolidated Criteria for Reporting Qualitative Research [21].

Transcripts were analysed using deductive thematic analysis. Predetermined categories of the challenges guided the coding and themes identification process. TA identified emergent and anticipated themes, which were then reviewed by SG. Disagreements in coding were resolved through consensus with MJ. Finally, the anticipated and emergent themes were analysed and incorporated into the list of challenges. Microsoft Excel was used for thematic analysis, following the guidelines of Braun and Clarke (2006).

Developing the framework

The challenges that were identified through the literature review, focus group and interviews were summarised in the form of a conceptual framework of all drug repurposing challenges. Challenges extracted from the literature are cited, while those without references were identified in the expert meeting or interviews.

HTA methods

Drug repurposing challenges within our framework were matched with HTA methods that might help address them. HTA methods were retrieved from two recent publications that reviewed and categorised early HTA methods [22,23]. We supplemented this with HTA methods regarding clinical effectiveness, ethical analysis, legal aspects and safety based on the HTA core model, a methodological framework for generating and sharing HTA information that includes HTA questions, and guidance on answering these questions and reporting results [24]. TA matched the HTA methods with the challenges based on the methods' objectives. Next SG and MJ reviewed the matches, with any discrepancies resolved among the three researchers through consensus.

Results

Of the 47 articles discussing challenges in drug repurposing in Krishnamurthy et al. [12], 43 were included in our review. Three articles were excluded after detailed review as there we no challenges for drug repurposing, and one article was no longer available (Appendix C). Seven additional articles were included from Krishnamurthy et al. 's reference list and the manual search of the reference lists of included articles. Updating strategy, we added 22 additional articles discussing drug repurposing challenges. Altogether, our review included 73 articles that discussed challenges in drug repurposing (Figure 1).

Out of the 73 articles, seven provided a categorization of the challenges as summarized in Appendix D. We consolidated all the relevant categorizations into a list of six main categories (Table 1). Appendix C includes all articles in this study.

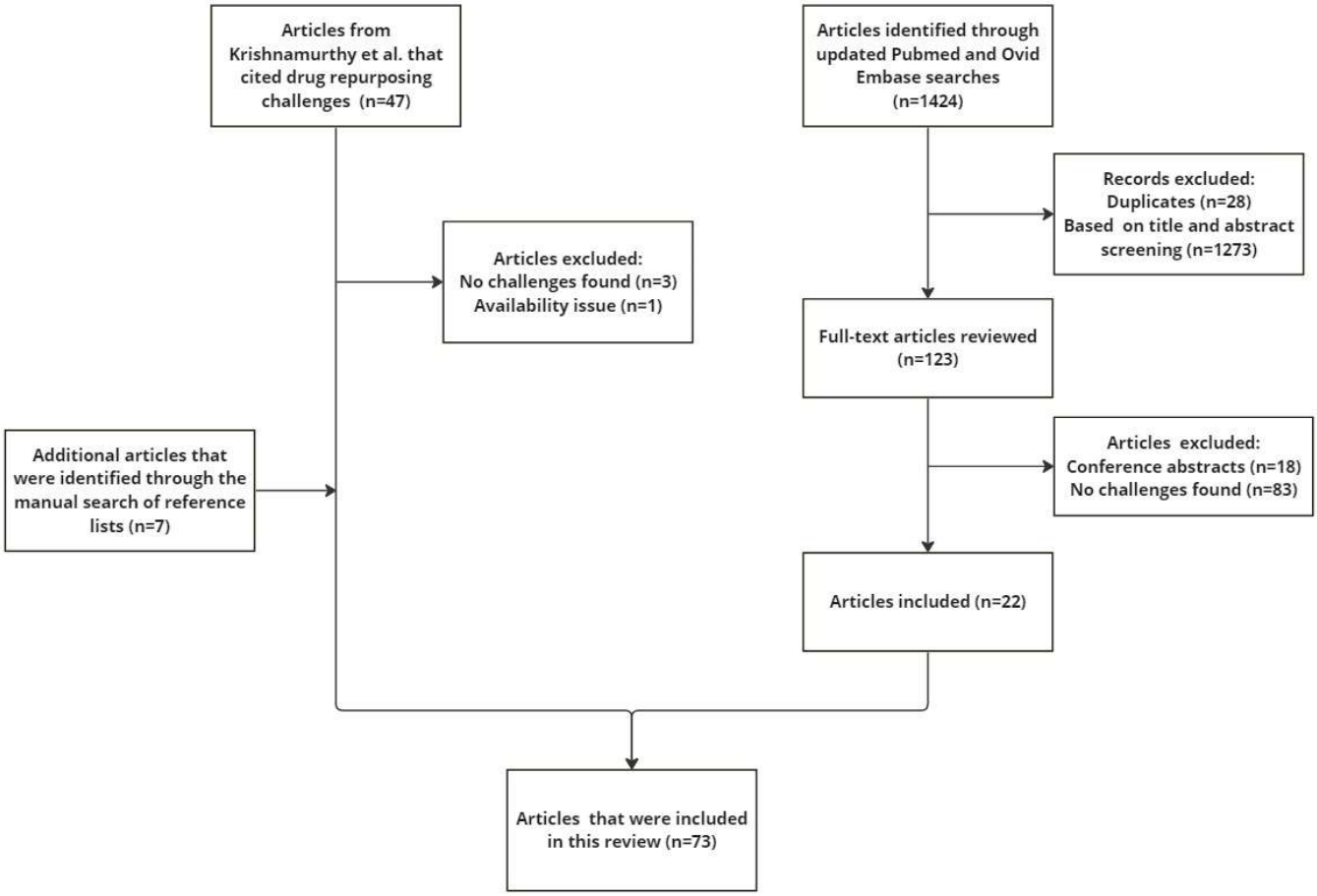

Figure (1): Literature search results

Expert meeting

Five participants joined the expert meeting on February 27, 2023. The participants had backgrounds in biochemistry and drug development (n=1), business development and legal services (n=1), network medicine (n=1), and pharmacoepidemiology (n=2). Themes that emerged from the meeting were incorporated in the list of challenges. More details are documented in Appendix E.

Interviews

Seven interviews were conducted online between March 14 and March 31, 2023, covering 14 participants. The participants had a background in biomarkers, *in vitro* and *in vivo* diagnostics and translational research (n=1), development and commercialisation of repurposed drugs for untreatable diseases (n=2), drug development (n=4), medical ethics (n=1), open access publishing and topical collections (n=1), precision medicine, systems biology and AI-driven identification of relevant patient subgroups (n=2), and precision diagnosis and mechanism-based drug repurposing (n=3).

Themes that emerged from the interviews were incorporated in the list of challenges. More details are documented in Appendix E.

Framework of drug repurposing challenges

The final framework consists of 20 challenges in drug repurposing, categorised into six main categories as summarised in Figure 2 and Appendix F.

(i) Data access challenges

Compound databases: There is currently no established framework for independent and academic investigators to access compound databases to identify new indications. Pharmaceutical companies have substantial advantages in accessing their compounds, leaving many of the promising repurposing candidates as shelved drugs or those still under patents inaccessible to unaffiliated researchers [1,10,25]. Pharmaceutical companies hesitate to out-licence their shelved compounds due to concerns of losing a competitive advantage in case the drug would turn out to be a blockbuster in what is referred to as the "not sold here" syndrome [8,26].

*Clinical data***:** Accessing clinical data related to drug repurposing candidates is challenging due to scattered resources and limited public access, especially for compounds in development and in repurposing projects that do not involve partnerships with the original manufacturer [27-30]. This can lead to incompleteness and inaccurate data. In rare diseases, the lack of consensus on a definition for the disease leads to difficulties in identifying the disease-related data. Industry investigators, particularly in small- and medium-sized enterprises, face challenges in obtaining data such as health records, which are often owned by clinical centres. Regulations and privacy concerns restrict access to these data.

(ii) Research and development challenges

Prioritisation: Although there are many methods for prioritising existing compounds reported in the literature [31], there is a lack of consensus regarding which prioritisation method or combination of methods is preferred. Drug repurposing often rely on prior knowledge and available information from studies to select appropriate prioritisation methods, however, this can be challenging especially in rare diseases [31]. Furthermore, *in vitro* efficacy might not translate to clinical efficacy and better approaches are needed to evaluate *in vitro* data when prioritising drugs candidates [32]. The effectiveness of these methods also varies depending on the identified compound candidates, the intended indication, and the targeted population.

Pre-clinical development: In drug repurposing, pre-clinical evidence is crucial to support research decisions and regulatory approval. When a new indication requires a new formulation or dosage, the usability of existing pre-clinical safety data will be limited. In other cases, such as in rare diseases, pre-clinical data could be outdated or limited [30,31].

Clinical development: When drug repurposing involves different routes of administration, different formulations, or a combination of multiple drugs (e.g., cancer therapies), proving sufficient safety and efficacy may still require a full development program [1,4]. Previous data might not predict adverse effects from the repurposed drug interaction with the new indication. Furthermore, gaining access to licensed molecules or those still under development for repurposing can be challenging without manufacturer authorization. In cases in which the molecule is discontinued, restarting the manufacturing process becomes necessary, adding hurdles to development stages [30].

Ethical considerations: Phase I trials with healthy volunteers can be bypassed in cases where the same formulation is used for which safety data already exist. However, ethics committees may still require phase I trials and the same scrutiny of evidence as in a new drug.

(iii) Collaboration challenges

Identifying collaborators: Identifying potential collaborators with complementary interests among academic researchers and pharmaceutical companies for advancing drug repurposing research requires resources and awareness [33,34].

Incentives: Collaboration between academia and pharmaceutical companies can help in advancing the registration and commercialisation of repurposed drugs [27]. However, collaboration is hampered by the varying incentives and reward systems. For example, academic investigators prioritise publications that could hamper 'Intellectual property protection, while pharmaceutical companies prioritise that protection. Pharmaceutical companies may be reluctant to test already-approved drug for secondary indication as it could uncover new adverse events [35].

*Attitudes and beliefs***:** When repurposing shelved compounds, academic investigators fear the risk of adverse selection in which pharmaceutical companies may want to keep the best compounds and out-licence less valuable ones [26]. Within an organization, repurposing their own shelved compounds may face opposition from the original development team due to safety concerns and allocating resources to a once abandoned compound [8]. Furthermore, an organization may hesitate to consider repurposing compounds from other organizations, a phenomenon referred to as the "not invented here" syndrome [8,26].

(iv) Business case challenges

Development costs: Although drug repurposing is cheaper than *de novo* drug development, it can still be costly, especially when new formulations, dosages, diagnostics, or routes of administration are involved [1,10,36].

Funding: Financial incentives and private funding for drug repurposing research are limited as the patent status and prevalent off-label use of repurposing candidates lead to uncertainty around return on investment, and regulatory and reimbursement outcomes [9,14,37].

Pricing: Although drug repurposing can be less costly than *de novo* drug development, high research and development costs, more limited prospects for market exclusivity, and risk of failure may mean that repurposed drugs are made available at high prices, leading to reimbursement uncertainty [14,29].

Commercialisation: An increasing number of academic investigators and small biotech companies are working on drug repurposing projects [13,27]. However, they often lack the expertise and resources to commercialise repurposed drugs themselves [27,38]. Commercialising the repurposing drug can also be hampered if the candidate is still under patent or widely used off-label [37,39].

Expertise: Limited resources and expertise pose a fundamental challenge for drug repurposing. When the new indication falls outside a drug manufacturer's core areas of expertise, there may be a lack of understanding of the disease pathophysiology [8,29,34,40,41]. If drug repurposing is carried out in an academic institution, there may be a lack of knowledge regarding the necessary evidence and timelines to submit for registering and marketing of the repurposed drug [14].

Benefit-risk ratio: Uncertainty regarding the benefit-risk ratio of a drug poses a business risk. In case of repurposing a drug with a known safety profile, this uncertainty may be reduced. However, the benefit-risk ratio must be carefully considered when repurposing drugs, as acceptable side effects for one indication might not be acceptable for another [36,42].

(v) Regulatory challenges

*Fragmented regulations***:** The regulations for gaining marketing authorization differs across jurisdictions, for example between the EU and US, posing a challenge for registering and marketing repurposed drugs. Fetro et al. observed a longer and varying time-to-market for repurposed drugs compared to *de novo* drugs in certain EU countries (979 days vs. 462 days in Italy, 502 days vs. 350 days in France, and 624 days vs. 378 days in Spain) [36]. Small biotech companies might have difficulty in navigate these fragmented regulations for getting their drug to the market.

Regulatory pathways: Current regulations are not fully adapted for drug repurposing in terms of process and evidence requirements, as they are primarily designed for *de novo* drugs [14,37]. Navigating these regulations becomes more challenging when the new indication employs a new formulation or technique (e.g., it uses two active substances) that is different from the formulation and techniques of the original indication.

Scientific advice: The knowledge gap and lack of alignment in timely interactions and necessary information for regulatory bodies further complicates the repurposing process [14]. Obtaining scientific advice may also incur costs. For example, although small and medium enterprises are eligible for fee reductions, the regular costs range between €51,800 to €103,800 for European Medicines Agency (EMA) scientific advice in human medicine [43].

(vi) Legal challenges

Patents: If repurposing involves off-patent drugs for which cheap generics exist, or investigational drugs with limited remaining patent life, obtaining composition of matter patents can be difficult [36]. The new indication might also be documented in medical literature or widely used “off-label” in clinical practice, which limits its patentability. In such cases, enforcing a patent and preventing off-label use can be challenging, thereby impacting the profitability of the repurposed drug [9,29,36,37].

Contracting: Drafting and negotiating Material Transfer Agreements for compounds can be challenging and time-consuming for all parties involved. The out-licensing process can be challenging when it comes to negotiations around limiting the use of the compound to non-commercial research, protecting, and defining confidential information, intellectual property provisions, and limiting the company's liability [33,44].

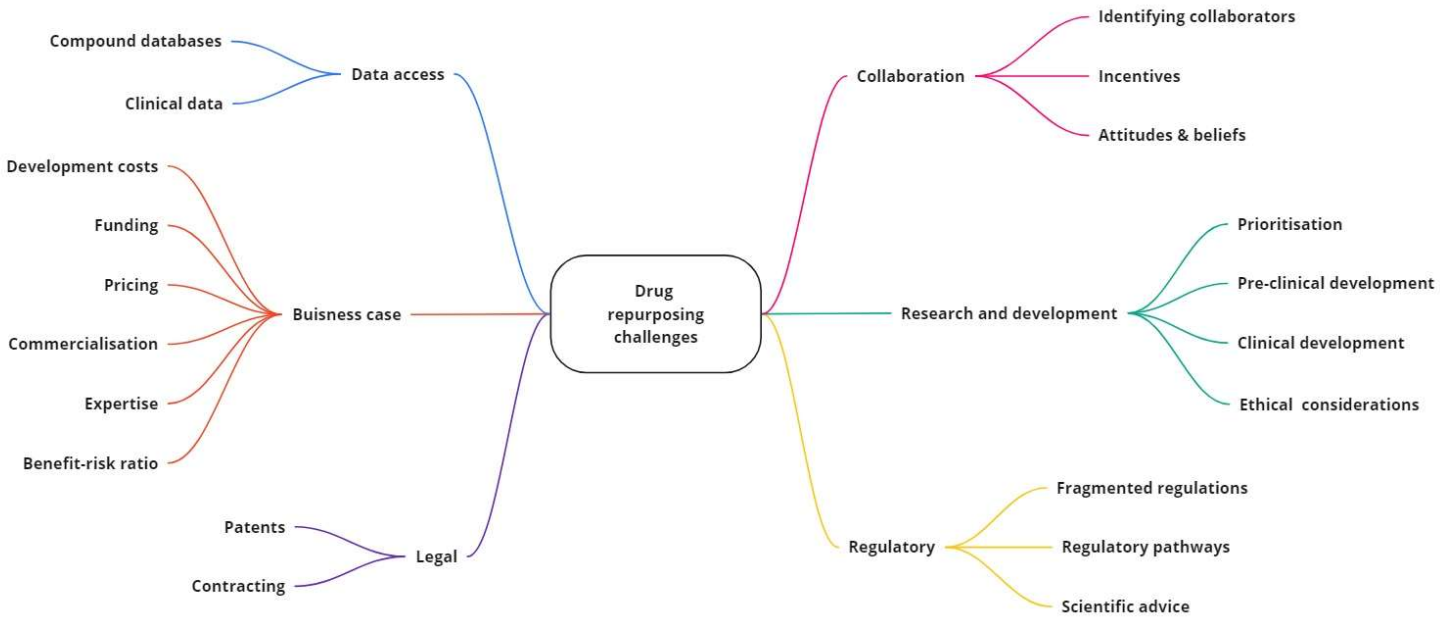

Figure 2: Framework of drug repurposing challenges

How can HTA help in addressing drug repurposing challenges?

HTA methods include literature review, stakeholder consultation, empirical (effectiveness) research, health economic evaluation and uncertainty assessment. HTA methods can be implemented on an iterative basis, starting from early stages (research, development, and design of the new technology) and extending to later stages in the technology's life cycle (pre-market, during market approval, and post-market phases). These methods can be initially simple and exploratory, and become more complex with more evidence [18,19]. Some HTA methods help address the repurposing challenges described above, while others help deal with the consequences of the challenges. Table 1 summarises HTA methods that were matched with drug repurposing challenges according to their objectives.

(i) Data access: HTA methods can help mitigate the consequences of a lack of data access. Literature review, stakeholder consultation methods (collecting views), structured expert elicitation, and iterative Bayesian economic evaluation can help fill evidence gaps. Literature review methods (systematic reviews and evidence synthesis) help in gathering evidence from publicly available data on the new indication, the targeted population, and the existing care pathways. Stakeholder consultation methods (collecting views) can help in guiding and supplementing the literature review process and explore evidence gaps. Structured expert elicitation collects the knowledge and beliefs of stakeholders [45]. In health economic analysis, iterative Bayesian economic evaluation can help in synthesising relevant data by combining prior and more recent data based on various sources and time points in the repurposed drug life cycle [46].

(ii) Research and Development: All HTA methods can help overcome research and development challenges. Literature review is useful in collecting already available pre-clinical and clinical data on the

repurposed indication, for example those available in clinical guidelines, previous HTA reviews and regulatory reviews. Stakeholder consultation methods (collecting views, visual methods, multicriteria methods, preference elicitation and consensus building) can assess unmet medical needs and thus help prioritise drug repurposing candidates. They can also be used to articulate the value proposition of the repurposed drug, and inform changes in the development, as well as inform trial designs. For example, patient engagement can inform chosen endpoints. Empirical (effectiveness) research methods (patient reported outcomes, pre-clinical and clinical research, structured expert elicitation and) help in designing and optimising (pre)-clinical trials, including well-defined endpoints and understanding the impact of the repurposed drug on the patient's quality of life.

Health economic analysis (economic evaluation, health economic modelling, budget impact analysis, headroom analysis, return of investment, and iterative Bayesian economic evaluation) can generate evidence about the expected value of the repurposed drug at different points in the development pathway and inform where and when further research is needed [47]. Uncertainty assessment methods are useful for exploring the value of the repurposed drug under different conditions. For example, scenario analysis and sensitivity analysis identify parameters that contribute significantly to uncertainty about the drug's cost-effectiveness [48]. Value of information analyses and real options analyses assess the need for further research and can guide clinical research design, while payback from research reframes research as an investment opportunity and identifies key areas for further research [49,50].

(iii) Collaboration: Stakeholder consultation methods for collecting views, multicriteria decisions and consensus building can help overcome some challenges in collaboration by facilitating early conversations among different stakeholders and aligning the different perspectives and expectations from the repurposed drug. Collecting view methods (interviews, focus groups, surveys, online discussion groups, brainstorming sessions, informal discussions, user perspective methods, expert opinions, and stakeholder analysis) help in gathering and understanding stakeholder perspectives and expectation on the repurposed drug's value. Multicriteria methods (multicriteria decision analysis, qualitative weighing of relevant factors, and analytic hierarchical process) can help in obtaining and quantifying the different preferences of relevant stakeholders. Consensus building methods (Delphi panels and patient engagement forums) help in aligning the various perspectives and preferences on the expected value of the repurposed drug and allow including the patient perspective in the process [24,51].

(iv) Business case: Literature review, stakeholder consultation, empirical research, health economic evaluation and uncertainty assessment can help address the business case challenges. Reviewing published literature helps in gathering information about the current care pathways, comparators, and estimates of costs and clinical effectiveness the help inform decisions in the business case. Stakeholder consultation methods such as collecting views, preference elicitation and consensus building facilitate the early interaction with relevant stakeholders who can articulate the value proposition of the repurposed drug and give an early indication of its potential societal value. A clear value proposition early in the drug repurposing cycle can help inform the development, financing, and marketing of the repurposed drug as well as identify strategies to recoup investments. The early collection of patient-reported outcomes, in

which patients directly express their own health status and quality of life when receiving a treatment, can provide insights on the benefit-risk ratio of the repurposed drug [52].

Health economic analyses, including iterative Bayesian economic evaluation, generate evidence-based information that supports decision-making regarding the business case for repurposed drugs. Economic evaluation methods assess the (potential) cost-effectiveness of the repurposed drug in terms of costs and consequences compared to current care pathways, at different development stages. This helps HTA and reimbursement agencies inform decision-making about efficient allocation of resources. For developers, the use of these methods facilitates the anticipation of considerations on the part of HTA and reimbursement agencies, which in turn can inform their pricing strategies. This can contribute to greater certainty about the return on investment [47]. Budget impact analysis can assess the impact of the repurposed drug on health care service budgets at the total population level, which is an important criterion for reimbursement decisions in some jurisdictions [53]. Potential years of life lost can indicate the potential value of the drug by identifying the health gap in the current care pathways [54]. Headroom analyses also provide an early indication of the price at which the repurposed drug would be considered cost-effective [48]. Finally, return-on-investment analyses can direct research and development spending by estimating potential returns in terms of health gains, costs savings, and commercial returns [55].

Uncertainty assessment methods, such as scenario analysis and sensitivity analysis are useful in exploring uncertainties surrounding the societal value of repurposed drugs and can "stress test" economic models or identify evidence gaps. Value of information, real options, and payback analyses can direct research and development efforts and inform return-on-investment analyses [48-50].

(v) Regulatory: Literature review and stakeholder consultation can help mitigate regulatory challenges. Review of relevant existing regulations and directives regarding drug products can help guide the collection of evidence ultimately useful in registering the repurposed drug. Electronic libraries, databases and scientific journals can also be searched to gather relevant information. Collecting stakeholder views and building consensus methods facilitate the early engagement with regulatory bodies, which can help in aligning the investigators and regulators on what is needed to evaluate the repurposed drug. These methods can also include the early involvement of HTA bodies for harmonising evidence and regulatory requirements across jurisdictions.

(vi) Legal and Intellectual property: Reviewing of national and international laws, legislation in development, and court judgement can guide investigators in identifying the legal and intellectual property questions they need to consider when repurposing drugs. This gathering of information can be guided by the set of questions provided in the legal domain in the HTA core model [24] and collecting stakeholders' views on relevant laws and directives that need to be reviewed. However, this cannot replace the professional legal advice if needed.

Table 1: HTA methods and Related Challenges in Drug Repurposing

HTA methods category	Methods	DR challenges					
		Data access	Research and development	Collaboration	Business case	Regulatory	Legal
Literature review	Systematic reviews, evidence synthesis	o	X		X	o	o

Stakeholder consultation	Collecting views: interviews, focus groups, surveys, online discussions, brainstorming sessions, informal discussions, UPM, EO, SA	○	X	X	X	○	○
	Visual methods: multipath mapping, road mapping		X				
	Multicriteria methods: MCDA, QWRF, AHP		X	X			
	Preference elicitation method: discrete choice experiments, choice-based conjoint analysis		X		X		
	Consensus building methods: Delphi panels, patient forums		X	X	X		
Empirical research	Patient reported outcomes		X		X		
	Clinical studies		X				
	Pre-clinical studies		X				
	Structured expert elicitation	○	X				
Health economic analysis	Economic evaluation: CUA, CCA, CBA, CMA, CEA		X		X		
	Health economic modelling: DTA, DS, STM, DES, CTS		X		X		
	Budget impact analysis		X		X		
	Potential years of life lost		X		X		
	Headroom analysis		X		X		
	Return-on-investment analysis		X		X		
	Iterative Bayesian economic evaluation	○	X		X		
Uncertainty assessment methods	Impact of uncertainty: sensitivity analysis, scenario analysis		X		X		
	Value of research: value of Information analysis, real options analysis, payback from research		X		X		

X: for HTA methods that can address the challenges
○: for HTA methods that can deal with the consequences of the challenge

Abbreviations: UPM indicates user perspective methods; EO, expert opinions; SA, stakeholder; MCDA, multicriteria decision analysis; QWRF, qualitative weighing of relevant factors; AHP, analytic hierarchical process; CUA, cost–utility analysis; CCA, cost–consequence analysis; CBA, cost–benefit analysis; CMA, cost–minimization analysis; CEA, cost-effectiveness analysis, DTA, decision tree analysis; DS, dynamic/systems simulation; STM, state transition model; DES, discrete-event simulation; CTS, clinical trial simulation

Discussion

In this study, we identified 20 challenges that investigators face in drug repurposing and identified HTA methods designed to address these challenges. Among the six categories of challenges—data access, research and development, collaboration, business case, regulatory, and legal and intellectual property—are topics that also challenge *de novo* drug development but are more acute in drug repurposing because repurposing is often done by sponsors other than the originators that are academic or not-for-profit organizations. These challenges are highly interconnected, that some recommendations for resolving a particular challenge may thus impact other challenges.

All HTA methods we have included can help address challenges in research and development. Stakeholder consultations, health economic analysis, and uncertainty assessment methods support pricing and reimbursement decisions in the business case. Data access challenges cannot be solved by HTA methods, but systematic review, expert elicitation and iterative Bayesian economic evaluation can deal with the gap of knowledge that results from this. Stakeholder consultation methods can be useful to deal with challenges related to collaboration. Systematic review and stakeholder consultation can be valuable to help overcome regulatory challenges and legal and intellectual property challenges. To our knowledge, this review is the first to propose HTA methods for addressing challenges in drug repurposing. Krishnamurthy et al. (2022) provided a valuable systematic review on reasons why drugs are abandoned and barriers to drug repurposing. Our research went beyond this by using a literature review, an expert meeting, and semi-structured interviews for developing a comprehensive categorization of identified challenges and exploring HTA methods that may address them.

Some study limitations should be noted. Our search strategy for literature on drug repurposing challenges, based on Krishnamurthy et al. (2022), was updated only in Ovid Embase and PubMed after April 2020, and pre-April 2020 literature was sourced from the reference list. This approach may have missed additional literature that may have been relevant, although we consider it unlikely that any major repurposing challenges were missed. Our expert interviews also support the completeness of our framework.

Given the many worldwide initiatives for facilitating drug repurposing research, we recommend revisiting the completeness of this framework over time and monitoring what policy measures are made to support the progress in drug repurposing. Further research should involve a broad range of stakeholders to develop targeted measures to address drug repurposing challenges. Implementing HTA methods on a flexible and iterative basis along the very early stages of drug repurposing research can help in addressing its challenges and ensure the cost-effectiveness of the repurposed drug, while taking any evidence limitation into account. Engagement with a wide spectrum of stakeholders, including regulators and HTA bodies, is crucial for identifying challenges early in the project. Selecting HTA methods that are tailored to each project's needs is essential for prioritising drug candidates and ensuring the cost-effectiveness of the repurposed drug. We recognise that HTA expertise is not available to all drug repurposing projects, therefore, we recommend the development of a HTA toolbox that includes templates, guidance, and resources that facilitate the use of HTA methods in drug repurposing research.

Conclusion

We have developed a framework for challenges in drug repurposing, which can help investigators in anticipating challenges during drug repurposing projects. The framework highlights the potential value of HTA methods to help address them. The next step is incorporating HTA methods at early stages in drug repurposing research.

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Declaration of interest

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