

# New Mechanisms to Fund Independent Clinical Trials for Repurposing Off-Patent or Generic Medicines

Ciska Verbaanderd (✉ [ciska.verbaanderd@kuleuven.be](mailto:ciska.verbaanderd@kuleuven.be))

Katholieke Universiteit Leuven <https://orcid.org/0000-0003-3850-5613>

Ilse Rومان

Vrije Universiteit Brussel & Anticancer Fund

Isabelle Huys

Katholieke Universiteit Leuven

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## Research

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## 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 in pilot projects.

## Background

Drug repurposing means finding new therapeutic indications for existing medicines and essentially covers four different scenarios (1,2). 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 (3,4). Second, pharmaceutical developers continuously monitor and investigate potential new uses for their approved medicines that are still under patent or regulatory protection. Developing new uses for innovator products may expand the patient population while delaying generic competition, and falls within a company's drug life cycle management programs (5,6). 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 (7–9). A fourth and final 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 generic or off-patent drug repurposing (10). A major benefit is that the pharmacokinetic, pharmacodynamic and toxicity profiles of approved medicines are well-known, so the new use can more easily be translated into Phase II/III clinical trials (11–14). Off-patent and generic 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 (15–17). However, return on investment (ROI) is expected to be low or absent in this last scenario due to a lack of economic incentives (5,6). 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' (18,19).

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 (20). 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 (21,22). Synonyms include academic, non-commercial, physician-led, investigator-driven, investigator-initiated, investigator-sponsored or publicly funded clinical trials (23). 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 (24). 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 (25–27). 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) (27,28). 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 (29), investments would still need to be substantial (30). Therefore, additional financial support is needed to conduct robust, phase III clinical trials that address the translational gap in off-patent drug repurposing (13,31).

In this study, we searched 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 (Supplementary material S1). 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.

Semi-structured interviews were conducted with a selected number of stakeholders to identify new funding models and explore their application potential in Europe. Study participants were identified and selected through purposive sampling based on their knowledge and expertise related to clinical research, funding mechanisms and/or drug repurposing. 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 (Supplementary material S2). 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 finally v) the current and 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 female interviewers (with a background in pharmaceutical and/or biomedical sciences) to optimize the interview guide and to standardize the interview approach. Next, the other 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 by the first author of this study using the NVivo qualitative data analysis software (32,33). Some quotes used in this manuscript were translated from Dutch to English as accurately as possible to represent participants' views. Participant recruitment ceased once data saturation was established.

The results of the literature review and the stakeholder interviews are collectively summarized in the results section below.

## Results

Based on the literature review, four potential mechanisms for funding clinical research with off-patent or generic repurposed medicines were identified and are summarized in (Figure 1). 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 organisations (N = 5), academia (N = 3), university hospitals (N = 2), pharmaceutical industry (N = 2), a health research funding organisation (N = 1), a private bank (N = 1), a consultancy company (N = 1) and a health technology assessment body (N = 1) (Table 1. Characteristics of interview participants).

**TABLE 1. CHARACTERISTICS OF INTERVIEW PARTICIPANTS**

INTERVIEW	STAKEHOLDER GROUP	COUNTRY
A	Academia	Ireland
B	University hospital	Belgium
C	Not-for-profit research organisation	The Netherlands
D1	Consultancy	Belgium
D2	Private bank	Belgium
E	Not-for-profit organisation	UK
F	Not-for-profit organisation	Belgium
G	Health technology assessment body	Belgium
H	Not-for-profit research organisation	Belgium
I	University hospital	Belgium
J	Health research funding organisation	The Netherlands
K	Academia	Belgium
L	Not-for-profit research organisation	Belgium
M	Academia	Belgium
N1	Pharmaceutical industry	Belgium
N2	Pharmaceutical industry	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 (34). 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 (35): *“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 (36–40) (Table 2). 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 (41). 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 (42,43). 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 (44–46). Some pharmaceutical companies also provide grants to support investigator-initiated clinical research with their approved medicines (47–51). Bayer even ran a specific ‘Grants4Indications’ program that provided grants and further financial support to explore new therapeutic indications for their own compounds (52).

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 2. 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
Not-for-profit organisations	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
	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 1, Figure 1). 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 (53). Additionally, crowdfunding enables patient and public engagement in prioritizing clinical research goals and increases public awareness of research needs (54,55).

Crowdfunding can be particularly interesting for early-career investigators, who generally have a lower chance of success in competitive grant programs (56,57).

#### BOX 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 (62). 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 (56). High overhead and administrative costs, including transaction costs of platforms, can make crowdfunding efforts less efficient (58). 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 (59,60). An inconclusive or negative trial outcome, which is relatively common in clinical research, could also erode public trust (61).

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 (57,62). 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 (59,60,62).

“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 (63). 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 (54,56,58,61).

## 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 (64,65). 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 1). 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 (30). Consequently, PPPs have been proposed as a potential model to facilitate and fund drug repurposing research (66,67).

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 (4,68). 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 (69). Moreover, the UK-based aPODD foundation is open to supporting partnerships in drug repurposing projects for paediatric oncology indications (70) 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 (39).

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) (11). 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 (30,71,72).

## **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 2, Figure 1). So far, SIBs have predominantly been applied to fund preventive health measures that could result in significant long-term health care savings (73,74). 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 (37,39,74–76). 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 (16). Recently, the US-based think tank Helena and its partners proposed a similar financial model to fund generic drug repurposing for Alzheimer's disease (77).

A SIB concept is a win-win-win model that, if successful, improves health outcomes, reduces healthcare spending and realizes economic return (78). 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 (73). 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 (75). 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 (79), 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 (79). 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)

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 (16,80). 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)

## BOX 2 | IMPACT INVESTING: BASIC PRINCIPLES

Currently, about 441 million dollars have been raised for 138 Social Impact Bonds (SIBs) worldwide (108). 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 (109). 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 1) (110). 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 (39). 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 (111). 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 (112).

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.

FIGURE 1. OVERVIEW OF MECHANISMS TO FUND CLINICAL DRUG REPURPOSING RESEARCH

Abbreviations: Social Impact Bond (SIB); Return-On-Investment (ROI)

## 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 (38,81). 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 overseeing 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 (82). 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 multi-arm/multi-stage or platform trials (83–85), registry-based RCTs (86,87), N-of-1 trials for rare diseases (88), and crowdsourcing studies of real-world patient data (15,89).

“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 (12,90). 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 (17). As a result, pharmaceutical companies rarely pursue new indications after expiry of basic patent and/or regulatory protection, especially for inexpensive small-molecule medicines (5).

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 (24). 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 (36). With investments of more than US\$40 billion a year, the US NIH is the largest public funder of biomedical research in the world (91). 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) (92). 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 (93)), the Dutch ZonMw, the German Research Foundation, the French INSERM, the Innovation Fund Denmark, and many more. However, all these programs are extremely competitive and have relatively low acceptance rates (26). 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 and creative way to raise funds for early-phase clinical studies, but it is unlikely to be sustainable to support large and expensive RCTs (57,62). It was also argued that research funding should be based on a project's scientific merit rather than on its potential to attract emotional donations (54,58,61,94). It is therefore recommended to have all crowdfunding campaigns for clinical research reviewed by an independent ethics committee and a scientific advisory board (56,94).

Third, multi-stakeholder PPPs have proven to be extremely valuable in facilitating drug development over the years (64,65), 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 (4,68), this model would not be sustainable for repurposing off-patent or generic medicines due to the lack of monetary 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 (30,95).

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 (74). Moreover, governments, payers, private insurance companies and social security organisations could actually save money on 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 (96,97). 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, especially SIBs, from being tested 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 (98–101). 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 (102). Inadequate funding mechanisms, like national grants with geographic restrictions, and mismatches in international clinical regulations and guidelines may stifle multinational independent research (25,26). 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 (103). 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 (104). Moreover, European countries could join forces in transnational research and innovation projects via a European Research Area Network (ERA-Net) co-fund scheme (26,105). 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 (83–85).

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 (106)), 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 (17,107), but will likely not be sustainable on the long term.

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 profound 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, such as SIBs, in one or more pilot projects. 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.

## Declarations

## Ethics approval and consent to participate

This study protocol was approved by the Ethics Committee of UZ Leuven, Belgium on 28 August 2018. All interview participants gave written informed consent in accordance with the Declaration of Helsinki.

## Consent for publication

By signing the informed consent form, interview participants gave consent to use their data anonymously and publish the results of this study.

## Availability of data and materials

The raw data supporting the conclusions of the current study can be made available by the corresponding author to any qualified researcher on reasonable request.

## Competing Interests

The authors declare that they have no competing interests.

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## Authors' contributions

IH, IR and CV participated in the design of the study. CV (MSc) conducted the research, interpreted the data and drafted the initial version of the manuscript. IR and IH revised the manuscript critically and contributed to the interpretation of the data. All authors read and approved the final manuscript.

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## Figures

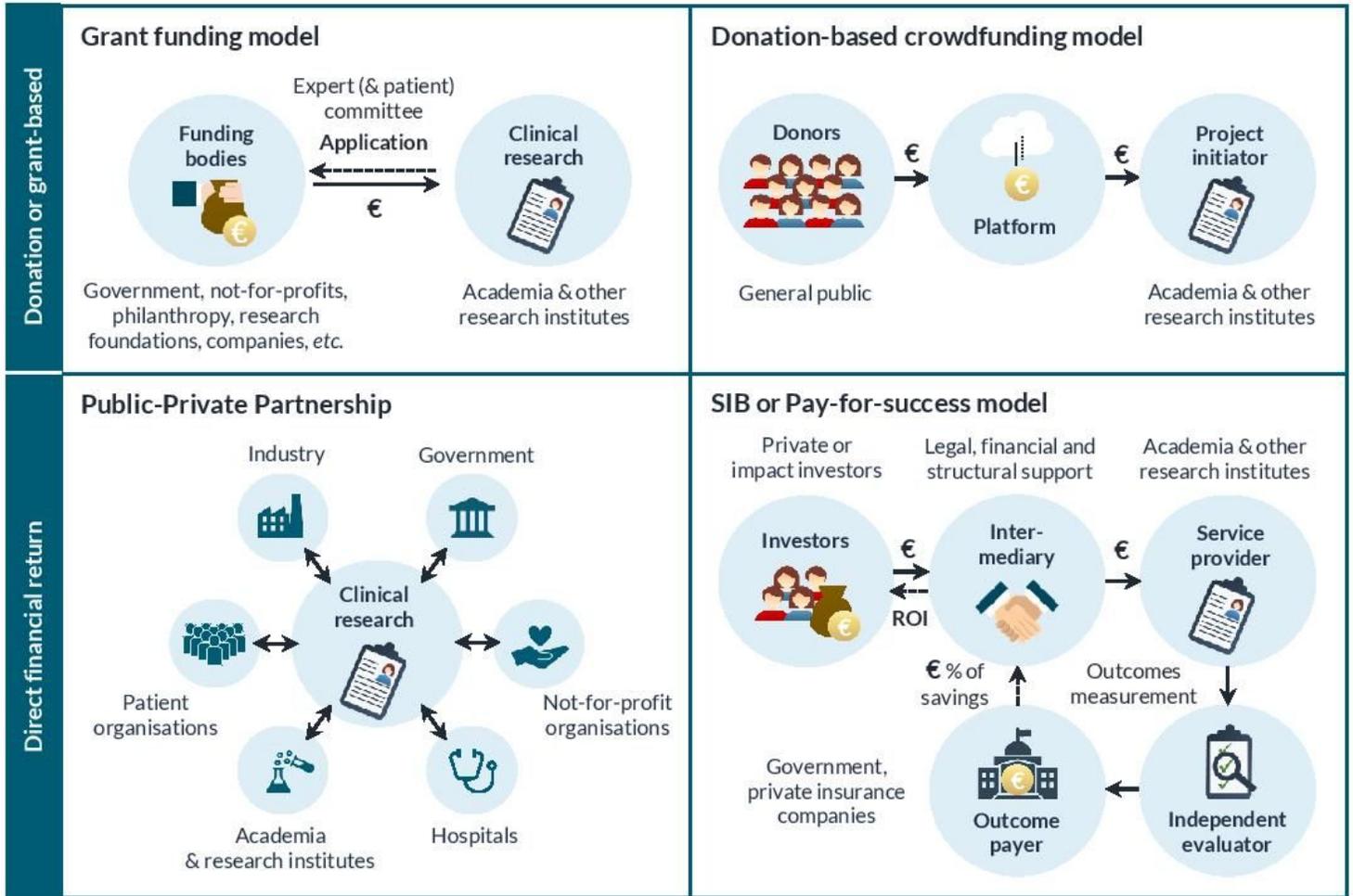


Figure 1

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

## Supplementary Files

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