DISCUSSION

Using Interventional Pharmacoeconomic Clinical Trials and Outcomes-Based Contracts to Repurpose Generic Drugs with Cost-Savings

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ABSTRACT
The inability to enforce a monopoly price over low-cost therapies, such as repurposed generic drugs by using patents for new medical uses, means that pharmaceutical companies are not interested to develop these potentially lifesaving therapies, even if clinical trials would be significantly cheaper. With the cost of new drugs increasing unsustainably, new financial models are needed that can incentivize the development of such low-cost therapies, by leveraging the cost-savings they generate for payors. For example, by conducting a trial comparing a low-cost generic drug to an expensive patented drug, the cost-savings from patients taking a low-cost therapy rather than an expensive drug during the trial itself can exceed the cost of running the clinical trial, which means it is “self-funding,” while also potentially improving patient outcomes due to better safety, efficacy, convenience, or accessibility. This is referred to as “interventional pharmacoeconomics” or a “revolving research fund” and allows the sponsorship of clinical trials that can be entirely funded by payors. “Prize-like” outcomes-based contracts or advance market commitments can also be combined with such self-funding trials to incentivize obtaining regulatory approval and solve the “last-mile” problem. Self-funding trials can provide significant cost-savings for payors without financial risk. This article illustrates a four-step process for conducting such self-funding trials and other ethical, commercial, political, and legal barriers that need to be overcome in order to scale this novel and practically unlimited source of funding for the development of low-cost therapies.

KEYWORDS
interventional pharmacoeconomics; outcomes-based contracts; pay-for-success contracts; advance market commitments; self-sustaining fund; generic drug repurposing; generic drug repositioning; social impact bonds; financial innovation; financial toxicity.

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INTRODUCTION

One of the greatest barriers to the repurposing of generic drugs is the lack of a financial model to recover the costs of clinical trials. Academics have acknowledged this “problem of new uses” for many years. So despite their great medical and cost-saving potential, repurposed generic drugs are referred to as “financial orphans,” “highly non-excludable therapies,” or “unmonopolizable therapies” that are extremely unlikely to receive the funding needed for regulatory approval. One proposed solution to the problem of new uses is to restrict off-label use and allow reimbursement of the repurposed generic at a higher price for the new indication. Another option is the increased public funding of clinical trials. However, this has been politically, legally, and practically difficult to achieve.

A financially innovative solution to the problem of new uses is to leverage the immediate and future cost-savings of payors. In particular, the novel discipline of interventional pharmacoeconomics (IVPE) allows for self-funding clinical trials by comparing a low-cost intervention (such as a repurposed generic) to expensive standard of care. The cost-savings from patients taking the low-cost intervention in one arm can exceed the cost of the trial itself, even if it fails, which means there is no financial risk. However, an IVPE trial requires the substitution of the low-cost intervention for expensive standard of care, and may not be appropriate for all repurposing opportunities, especially where no expensive comparator intervention is available. For this latter situation, it is possible to use outcomes-based incentives similar to prizes called pay-for-success contracts, advance market commitments (AMC), or social impact bonds. Such “prize-like” incentives have been used to accelerate the development of Covid vaccines (in the United States, see https://en.wikipedia.org/wiki/Operation_Warp_Speed. The EU has entered into similar advance purchase agreements the IVPE + AMC fund by private investment into clinical trials, into a “feature” that leverages the potentially unlimited cost-savings of payors during IVPE trials to help fund their development. In essence, IVPE allows a payor to fund development of new affordable therapies while also reducing expenditure from their existing pharmaceutical budget i.e., unlocking a “free” and novel source of funding. The only requirement for this funding to exist is that the difference in price between the low-cost intervention(s) being compared to the expensive intervention would exceed the cost of running the IVPE trial. This means that if payors agree to transfer a fraction of their cost-savings to cover the sponsor’s costs, there is no financial risk to either party. Although there is a medical risk of failed trials, this is no different from any kind of drug development, with such risk being managed with ethically approved trial design and informed consent. In fact, generic drugs can be expected to be safer than testing novel molecules, and clinical trial emulation from analysis of existing off-label use in electronic medical records can further de-risk the trials. The cost-savings generated for payors during the IVPE trial also provide a first-mover advantage. If label expansion or regulatory approval is not the goal, the sponsor can fund academic trials to determine the optimal treatment protocol for the repurposed generic(s), which can then be prescribed off-label. AMCs can also be used to provide the financial incentive to obtain regulatory approval (e.g., US$250m in guaranteed payments over 10 years) which should
be far less than the billions of dollars that would usually be spent by payors on a new patented drug.\(^\text{26}\)

Cost-savings from IVPE trials for other therapies can also be used to unlock funding for generic drug repurposing, either as adjunct therapies or for unmet medical needs. For example, the earliest use cases for IVPE trials were to research whether a lower dose or shorter duration of treatment would be as effective with fewer side effects.\(^\text{7}\) Immunotherapies such as pembrolizumab and nivolumab currently generate approximately US$30 billion in annual sales,\(^\text{24}\) but could be effective at less than 10% of the dose\(^\text{25}\) and/or discontinued after 6–12 months with close monitoring of residual disease.\(^\text{26}\) Conducting such de-escalation and/or early-discontinuation trials can unlock billions of dollars in savings from pharmaceutical budgets to fund generic drug repurposing and also improve access to these essential medicines globally. However, the major issue with de-escalation and early discontinuation is that the pharmaceutical manufacturer could increase the cost of the drug.\(^\text{27}\) Notably, this is not an issue with generic drug repurposing, where the drug is off-patent and available from many generic manufacturers. It is also likely that any increase in cost of a patented drug would be delayed due to pricing agreements with payors, although such agreements may ironically disincentivize payors to support the IVPE + AMC mechanism because of contractual obligations to purchase a minimum amount to obtain a rebate or discounted price.

The IVPE + AMC mechanism for funding generic drug repurposing can be illustrated in four steps:

1. A researcher designs a study protocol to compare a repurposed generic (e.g., IV or IM ketamine for depression and suicidality at US$1,000 p/a) to an expensive patented drug (e.g., esketamine at US$30,000 p/a). Ideally, the study protocol design should aim to show the repurposed generic is superior to the patented drug so that it has a chance of being widely adopted as “best-in-class.” For example, this is likely the case with IV or IM racemic ketamine that clinical evidence suggests is more effective and bioavailable than esketamine,\(^\text{17}\) which is a more patentable intranasal formulation.

2. The researcher submits the study protocol to a payor along with an economic analysis showing the projected cost-savings during the IVPE trial itself (e.g., US$29,000 p/a per patient if they receive ketamine rather than esketamine in a single arm trial or US$14,500 p/a per patient if they are randomized to receive either ketamine or esketamine), assuming patients can be recruited from the payor’s insured population. This economic analysis could also include a retrospective study/randomized controlled trial (RCT) emulation to medically de-risk the prospective IVPE trial. The payor can also calculate cost-savings from patients enrolled in the trial and treated with the repurposed generic drug rather than the patented drug, and future cost-savings if the IVPE trial is successful and the repurposed generic is superior or non-inferior. The payor agrees to transfer a percentage of its cost-savings from its patients enrolled in the trial, which is guaranteed, irrespective of clinical outcome.

3. The researchers obtain ethics approval and sponsor the trial. The payor reimburses the sponsor for each patient from their insured population that participates in the trial, which is less than the payor’s overall cost-savings (e.g., $20,000 per patient p/a if a single arm trial or $12,000 p/a per patient if an RCT). Preferably, if the trial is successful, the same IVPE process is used to fund a larger trial (e.g., phase III) that will trigger an AMC mechanism where payor(s) would guarantee a minimum purchase of the repurposed generic at a subsidized price. This would incentivize a sponsor to obtain regulatory approval and be responsible for pharmacovigilance.

4. If the IVPE trial does not achieve the expected clinical outcome, the researcher can go back to step 1 and design another suitable IVPE trial study protocol. The AMC would also not be triggered, so there would be no additional cost to the payor and the IVPE design means the sponsor has not taken on any financial risk.

As noted under step 1, to address ethical concerns with moving patients off an approved, albeit expensive drug, under IVPE trials, it is important that generic repurposing candidates are chosen which are the most likely to achieve superior clinical outcomes. This can be achieved by conducting literature reviews in consultation with medical experts but also leveraging retrospective analysis and RCT emulation of real-world data including electronic medical records.\(^\text{28}\) Stratification of patients according to biomarkers can also predict better outcomes for the repurposed generic compared to expensive standard of care. Notably, informed consent should also be freely given without undue pressure on patients, such as payors refusing to reimburse an expensive patented drug unless a patient enrolls in an IVPE trial. Arguably, however, there is a greater ethical concern with not implementing IVPE trials, namely, that payors and patients will not be able to afford treatments at all. If pharmaceutical companies pursued a low-cost high-volume strategy, this could also maximize the number of patients that benefit while still allowing for relatively high profits.

There may also be various other commercial, political, and legal barriers to the implementation of IVPE trials. In particular, co-ordination between multiple parties will be needed, including ethics committees, hospitals, researchers, and the various entities responsible for pharmaceutical reimbursement. This could be facilitated by a contract research organization paid by the sponsor, which is normally responsible for such project management, including co-ordination of the clinical trial in compliance with applicable regulation, and obtaining the necessary consents from patients and regulatory bodies. Political barriers and legal barriers may also exist where payors are not permitted to fund clinical trials, because taxpayer funds cannot be put “at risk” of failed clinical trials under applicable law. However, it is arguable that IVPE trials do not result in any financial risk, because the
cost-savings they generate exceed the cost of the trial. It may be that the main political and legal barriers are likely due to the leverage of pharmaceutical companies on payors under confidential rebate agreements which provide discounts for minimum sales of expensive patented drugs or other commercial agreements. Overcoming such barriers would require grassroots support as well as political will.

CONCLUSION

The IVPE + AMC mechanism described in this review can fund the development of any protocol or therapy, not just repurposing generic drugs, including non-pharmaceutical interventions, open-source drugs, nutraceuticals, plant medicines, lifestyle interventions, or even patented new drugs, subject to contractually binding commitments of affordable access. If the low-cost intervention can substitute or reduce reliance on the more expensive intervention, and the cost difference is more than the cost of running the trial, this effectively provides unlimited funding. There are many medically de-risked IVPE examples and many more are waiting to be discovered in the medical records or literature. In the author’s view, the main barriers to adoption of this new financial model by payors would be (i) opening a dialogue between sponsors of generic drug repurposing research and payors so the latter can agree to transfer cost-savings to fund IVPE trials; (ii) appropriately managing any medical risk during ethics approval and informed consent processes; and (iii) overcoming any commercial, legal, or political barriers to reimbursement.

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REFERENCES


