Article title: Using Interventional Pharmacoeconomic Clinical Trials and Outcomes-Based Contracts to Repurpose Generic Drugs with Cost-Savings
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Journal: DrugRxiv
Review statement: The manuscript is currently under review and should be treated with discretion.
Manuscript submission date: 27 March 2024
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

THE 2ND INTERNATIONAL CONFERENCE ON
SYSTEMS MEDICINE, AI & DRUG REPURPOSING

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

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Abstract

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.[1] And so despite their great medical and cost-saving potential, repurposed generic drugs are referred to as “financial orphans” [2], “highly non-excludable therapies” [3], or “unmonopolisable therapies” [4], 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.[5] 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 health insurers. 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.[6] 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 (PFS) contracts, Advance Market Commitments (AMC) [7], or Social Impact Bonds (SIBs).[8] Such “prize-like” incentives have been used to accelerate the development of Covid vaccines [9] and antibiotics [10], but not yet for repurposing generic drugs.

The IVPE concept has been called a ‘revolving research fund’ in Europe, where the cost-savings of clinical trials are used to fund additional research.[11] Similar cost-saving trials are also being funded by a consortium of health insurers in the Netherlands on a case-by-case basis.[12] It is hereby proposed that establishment of an IVPE + AMC fund by private or public health insurers can develop repurposed generic drugs, which can address the “financial toxicity” of new patented drugs while improving patient outcomes.[13] There are many known IVPE opportunities, for example, comparing repurposed generic IV ketamine to patented esketamine for treatment resistant depression [14] or off-label bevacizumab (Avastin) to ranibizumab (Lucentis) for macular degeneration.[15] There is an opportunity to discover and medically de-risk additional IVPE repurposing candidates for self-funding trials by conducting retrospective studies and meta-analyses of medical records and clinical data.

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

A New Financial Model for Developing Affordable Therapies

New patented drugs are prohibitively expensive with a median cost of approximately US$200,000 per annum [16]. Even in wealthy countries such as the United States, an estimated 42% of newly-diagnosed cancer patients will deplete all of their assets within two years due to the 'financial toxicity' of these drugs [17]. Notwithstanding the far worse situation for patients in LMICs, even relatively wealthy countries such as UK, Netherlands, Germany, France, Sweden, Canada, Australia and New Zealand may not reimburse new drugs due to excessive cost, which results in many patients not getting access to treatment or paying out-of-pocket. New drugs are also estimated to cost over US$1 billion and take over 10-15 years for pharmaceutical companies to develop [18], unlike repurposing generic drugs which could be developed at a fraction of the time and cost [19].

There is an opportunity for health insurers and government agencies responsible for reimbursement of new drugs (referred to as 'payers') to support a new financial model for generic drug repurposing that can address these issues, namely, IVPE and prize-like contracts such as AMCs. This turns the 'flaw' of low-cost generic drugs, which disincentivises private investment into clinical trials, into a 'feature' that leverages the potential of multi-billion dollar cost-savings for payers to help fund their development [20]. In essence, IVPE allows a payer 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 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 payers 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 not 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 payers 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) which should be far less than the billions of dollars that would usually be spent by payers on a new patented drug [21].

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 [22]. Immunotherapies such as pembrolizumab or nivolumab currently generate approximately US $30 billion in annual

sales [23], but could be effective at less than 10% of the dose [24] or discontinued early after a complete response [25]. Conducting such de-escalation or 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 or discontinuation is that the pharmaceutical manufacturer could increase the cost of the drug [26]. 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 payers, although such agreements may ironically disincentivise payers 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 4 steps:

1. A researcher designs a treatment protocol to compare a repurposed generic (e.g. IV ketamine for depression & suicidality at US$1,000 p/a) to an expensive patented drug (e.g. esketamine at US$30,000 p/a). Ideally, the trial 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 racemic ketamine which is likely more effective and bioavailable than esketamine [27], which is a more patentable intranasal formulation.

2. The researcher submits the treatment protocol to a payer along with an economic analysis showing the projected cost-savings during the IVPE trial itself (US$29,000 per patient if observational or US$14,500 if randomised) if patients are recruited from the payer’s insured population. There should also be an estimate of the number of patients that could be treated with the repurposed generic drug rather than the patented drug, if supported by clinical data from the IVPE trial. The payer agrees to transfer a percentage of its cost-savings from its patients enrolled in the trial.

3. The researchers obtain ethics approval and sponsors the trial. The payer reimburses the sponsor for each patient from their insured population that participates in the trial, which is less than the payer’s overall cost-savings (e.g. $10-20,000 per patient). Preferably, if the trial is successful, the same IVPE process is used to fund a larger trial (e.g. Phase 3) that will trigger an AMC mechanism where payer(s) would guarantee a minimum purchase of the repurposed generic at a subsidised price. This would incentivise 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. The AMC would also not be triggered, so there would be no additional cost to the payer and the IVPE design means the researcher / sponsor has not taken on any financial risk.

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. The only criteria are that 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. There are many medically de-risked IVPE examples and many more are waiting to be discovered. In the author's view, the main barrier to adoption of this new financial model by payers would be opening a dialogue between researchers with IVPE candidates and payers so the latter can transfer cost-savings to fund IVPE trials, appropriately managing any medical risk, and overcoming any commercial or political leverage applied by large pharmaceutical companies on payers.

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