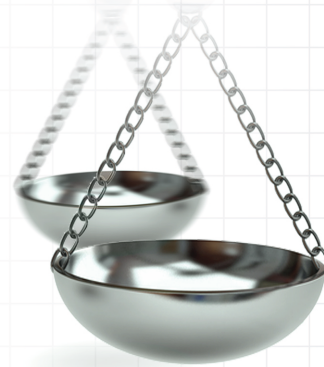




How pharma can amplify product value with implementation science

Melvin (Skip) Olson^{*,1} , Leah L Zullig²  & Sabina De Geest^{3,4} 

¹Olson Strategies GmbH, Allschwil, 4123, Switzerland

²Center for Innovation to Accelerate Discovery & Practice Transformation (ADAPT), Durham Veterans Affairs Health Care & System, & Department of Population Health Sciences, School of Medicine, Duke University, Durham, NC 27701, USA

³Institute of Nursing Science, Department of Public Health, University of Basel, Basel, 4056, Switzerland

⁴Academic Center for Nursing & Midwifery, Department of Public Health & Primary Care, KU Leuven, Leuven, 3000, Belgium

*Author for correspondence: skipinbasel@gmail.com

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Achieving blockbuster status requires more than clinical trial success. Crucial barriers often include real-world factors like patient acceptance, prescriber behavior and timely and full reimbursement. Implementation science can be used to identify such barriers, develop strategies to overcome them, as well as test their effect. Used correctly and at the right time, implementation science can amplify product value and lead to a triple win for patients, healthcare systems and pharma. Three easy steps that focus on context, strategies and outcomes, can be followed by pharma to bring implementation thinking and research into their processes. A ‘what if’ case study is shared to give an indication of how this might work and the impact it might have.

Shareable abstract: Achieving blockbuster status requires going beyond clinical trial success. Real-world factors like patient acceptance, prescriber behavior and integration in healthcare systems are crucial. Implementation science can help identify and overcome these barriers, boosting product value.

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Blockbuster status is now the prerequisite for pharma consideration & planning

Products not poised to reach this status are jettisoned. However, a sole focus on blockbuster status contributes to inflated forecasts, often disregarding realistic sales targets, that ignore barriers that aren't aligned with the standard drug development pathway. The irony in ignoring these barriers is that achieving blockbuster status requires more than clinical trial success. The crucial barriers in question include real-world factors like patient acceptance, prescriber behavior and timely and full reimbursement. Overlooking these barriers can delay a product's blockbuster potential or prohibit it from being achieved.

Implementation science is critical to the pharma industry

Implementation science (IS) focuses on addressing practical challenges in applying innovations, such as considering real-world factors and barriers, gaining global traction to expedite their real-world effectiveness. Vital for the pharma industry, IS facilitates the ‘triple win’ [1] for patients, healthcare systems and pharma. Without IS, research often remains trapped in the ‘valleys of death’ [2], leading to missed opportunities for improving healthcare, including terminated studies and problems with patient understanding, physician prescribing, integration with clinical workflows and healthcare system support.

Specific IS structures and roles are essential for addressing implementation issues in drug development [3]. Multiple stakeholders, including pharma, healthcare systems, organizations and patients, can contribute. Pharma, with its potential gains from integrating IS, could lead the way in adopting these structures and roles but will they?



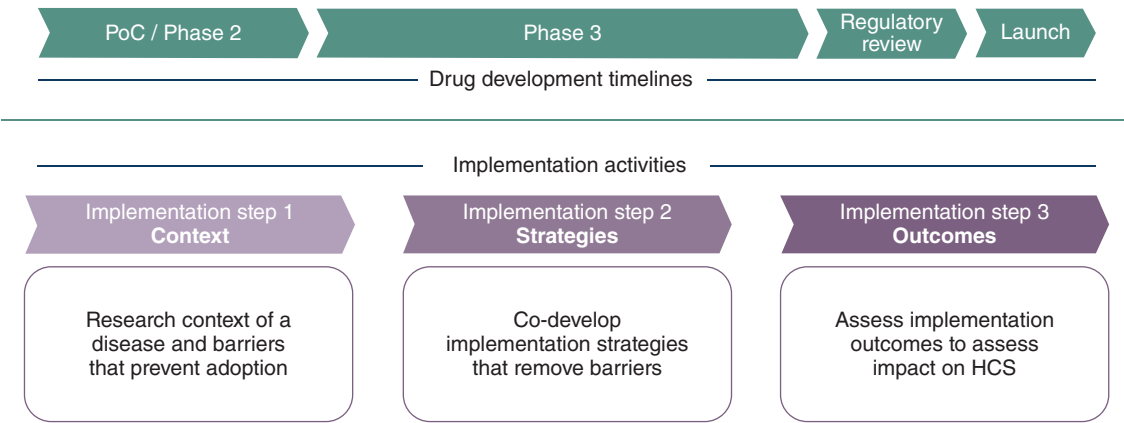


Figure 1. Three steps of implementation science with corresponding drug development timelines.
HCS: Healthcare system.
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Internal structure & competing interests hinder pharma from embracing IS

Simply put, pharma’s current focus is first on registration and then on reimbursement, both of which are addressed in silos. In addition, funding for ‘expensive’ activities for reimbursement is often delayed until registration is assured. This sequential process results in a delayed availability of evidence, that leads to a projected uptake of a product that is difficult to modify because the proverbial train has left the station. Consequently, financial returns are average, and only a modest number of patients benefit, with implementation problems addressed reactively rather than proactively due to the absence of a dedicated function for implementation within pharma companies. The relatively new push for integrated evidence planning within pharma presents an opportunity to identify, organize and execute implementation programs more effectively through cross-functional teams, once awareness of implementation issues and their impact is established.

We propose three steps of incorporating IS into the pharma model

With such an established focus on registration and reimbursement in a not-so-agile industry, how do you introduce change, even if it is a ‘triple win’ [1]? We propose that a workable strategy is to introduce a process that makes only minor modifications to existing processes. A simplified version of IS for pharma consists of 3 steps: contextual analysis, strategies and outcomes (CSO; Figure 1).

Step 1: starts with a slight adaptation to the standard process by adding a new section to the initial situation analysis (typically in an early value dossier), focusing on identifying implementation barriers within healthcare systems and, thus, defining the context in which the innovation needs to succeed in the real world. This entails examining prevailing clinical care processes, infrastructure deficits, negative attitudes, conflicting preferences and resource limitations that may impede the adoption of an innovation in routine clinical practice. Identifying these barriers early in the drug development process offers a significant opportunity to address them effectively later on. If the simplified analysis reveals significant implementation gaps, the next action involves establishing a network of stakeholders dedicated to implementation. Furthermore, as contextual analysis is an ongoing process, it must be regularly updated throughout the drug development cycle and before advancing further with implementation efforts.

Step 2: involves developing strategies to tackle the barriers identified in step 1. These strategies aim to improve implementation outcomes, as opposed to clinical outcomes, such as the adoption, reach, sustainability and scalability of interventions. If the potential impact from step 1 is deemed significant, experts and stakeholders are enlisted to co-develop the implementation strategy in this step.

Step 3: is designed to assess the implementation outcomes and their potential impact on the healthcare system and is only conducted conditionally on having developed an effective implementation strategy in step 2, ideally by involving experts.

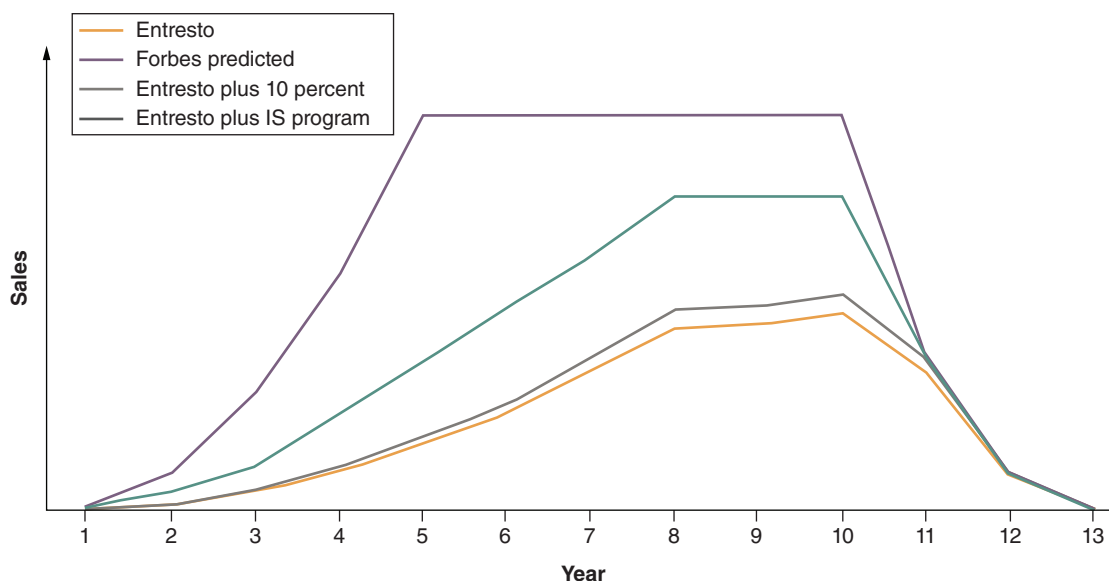


Figure 2. Case study of Entresto with sales curves showing hypothetical gains had implementation science been implemented during drug development program.

IS: Implementation science.

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This method requires minimal additional resources to expand existing processes for all compounds. Additional resources are only needed if the initial assessment indicates significant implementation gaps in treating the disease. Specialized expertise can be sourced from academic and research institutions rather than built in-house, if preferred.

Implementation steps spread across the drug development phases to minimize risk & costs while amplifying benefit

To infuse implementation thinking into drug development, weighing risks and costs is crucial. Initiating implementation steps early on, we suggest factoring in phase transition probabilities [4] to prioritize higher-cost actions during phases with high transition likelihoods.

Given the low probability (0.29) of transitioning from phase II to phase III, it is most cost-effective to prioritize contextual analysis in proof of concept (PoC) and in phase II. Implementation strategies should follow in phase III, with implementation outcomes assessment starting later in phase III or during regulatory review. By structuring implementation programs in this way, higher costs of implementation steps 2 and 3 are incurred only after significant progress in step 1 and the continuation of the program through the development lifecycle. For instance, assuming a conservative 10% increase in sales for a blockbuster compound due to a comprehensive implementation program, with costs of \$0.75 million for step 1, \$2 million for step 2 and \$50 million for step 3, the ROI easily exceeds 2000%.

Case study: what this could have looked like for Entresto

In understanding the importance of integrating IS into the pharmaceutical workflow, let's examine the case of Entresto. Introduced in 2015 for heart failure treatment, Forbes forecasted its peak sales at \$10 billion [5]. A hypothetical sales curve based on the Forbes prediction is shown in Figure 2. However, actual sales (based on Novartis annual reports through 2023 and suitable extrapolation beyond), influenced by factors like resistance from insurers and doctors, deviated significantly from this prediction (Figure 2). A Harvard Business Review article [5] said that “Resistance from insurance companies and cardiologists to a new and expensive treatment” and that the “route to market strategy hasn't changed in decades, even though the reality of the market has”. It is noteworthy that the Forbes predicted curve would have resulted in more than double the cumulative sales than what was achieved. An IS approach with only a modest impact of only 10% could have increased accumulated sales by more than \$3 billion (Figure 2, orange curve). A more comprehensive IS program following the 3-step, CSO approach, starting early and focusing on behavioral, organizational and health system barriers to innovation adoption, could have potentially

increased adoption to the level shown in Figure 2 (gray curve). The result is a cumulative sales increase of about 55%, or about \$17 billion. The net gain would be a win for pharma, fewer lives lost is a win for patients, and a more efficient system with better outcomes is a win for providers/payers.

A more comprehensive IS program would have started with a contextual analysis and an assessment of potential collaborators prior to phase II. The contextual analysis would have revealed, already at that early time point, that major barriers include: payers would not be fully convinced by the phase III end points [6] and cardiologists feel that the current drugs are sufficient [7], their practices/clinical processes are not set up to incorporate new drugs and their associated prescription/reimbursement/follow-up [7] and medical questions would remain beyond the phase III end points [6,8]. All of these barriers could then have been addressed during the drug development process using the CSO-IS framework in a continuous process.

Recommendations & insights

Step 1 of the CSO steps of IS is to be done early, at risk, at a low cost using an existing process. Step 2 is to be done if step 1 is 'promising' using external experts and the interested stakeholders to design. The 'promise' from step 1 can be quantified in terms of incremental NPV/eNPV or ROI if needed. Similarly, step 3 can be done with the use of external experts if steps 1 and 2 have been promising. Following these 3 easy steps, at the right time, can reduce the time to adoption, increase the number of patients reached, and fill the 'valleys of death' while providing a win-win-win solution for patients, pharma, and providers/payers. It is not necessarily up to pharma to take the first step in the transformation of incorporating implementation issues into their focus, but here is an easy way for them to do so, if they are really living a motto around 'everything we do is for the patient' and to achieve the triple win.

Author contributions

All authors have fulfilled the authorship criteria and accept accountability for all content. Each author has significantly contributed to, reviewed and approved the editorial.

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M Olson is an employee of Olson Strategies GmbH and consults on this subject matter with RTI Health Solutions and Boehringer Ingelheim GmbH. L Zullig and S De Geest are employees of Duke University and the University of Basel, respectively. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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The authors have no competing interests or relevant affiliations with any organization or entity with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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No writing assistance was utilized in the production of this manuscript. The text was written fully by the authors without artificial intelligence (AI) support. AI was used to shorten the text to meet word count restrictions.

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