



The triple win – implementation science benefits patients, healthcare systems and industry alike

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“The incorporation of implementation science into clinical development programs is not a ‘box-ticking’ exercise; it represents a change in mindset and a departure from the traditional models of drug development.”

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Innovation translation – what is the issue?

Historically, randomized controlled trials (RCTs) have been considered the ‘gold standard’ data source for regulatory approval. However, RCTs traditionally do not provide pragmatic evidence for how innovations are used or implemented in real-world clinical practice. This means that there is often a gulf of up to 17 years between the publication of evidence and its application in routine clinical settings [1]. Even then, only about 14% of clinical innovations are estimated to enter routine practice [2,3].

The impact of this is often shouldered by those we aim to serve – the patients. Even in developed nations such as the USA, patients may be receiving as little as half the recommended care for their condition [4]. A new approach is urgently needed to bridge this translational gap – one that addresses implementation early to ensure the timely access and uptake of new interventions.

‘The valley of death’

A 2019 Swiss Academy of Medical Science bulletin addressed the enormous rift between the discovery and approval of innovative medical therapies and their widespread adoption into clinical practice. The report termed this gap ‘the valley of death’ [5]. Even well-conducted studies of proven therapies need to cross the wasteland between clinical trials and real-world settings to guarantee successful implementation.

One example is the heart failure (HF) drug sacubitril/valsartan (Entresto). The PARADIGM-HF trial was the largest HF study ever conducted and was lauded as an exemplary RCT. Sacubitril/valsartan treatment showed a clear benefit over standard therapy in reducing the risk of cardiovascular death and hospitalization. Additionally, US clinical guidelines released by the American College of Cardiology recommended sacubitril/valsartan as standard of care for HF with reduced ejection fraction as an alternative to angiotensin-converting enzyme inhibitors or angiotensin receptor blockers [6]. Nevertheless, its clinical adoption was much slower than predicted, which highlighted the fact that RCTs with definitive clinical evidence resulting in marketing authorization do not provide sufficient evidence for rapid and broad implementation into healthcare systems.

Introducing a new therapy into clinical practice is challenging, even for experienced clinicians. Many will not prescribe new products unless they see the research as relevant and within the context of their practice. In the case of sacubitril/valsartan, several clinical and nonclinical barriers hampered uptake. Barriers to implementation included the lack of awareness amongst clinicians around the use of this novel product, a reluctance to switch the

treatment of patients who were stable on older therapies and concerns regarding potential long-term side-effects. These issues were compounded by delays in payer-reimbursement deals [7].

How can implementation science bridge the gap?

Implementation science is “*the scientific study of methods to promote the systematic uptake of research findings and other evidence-based practices into routine practice, and, to therefore improve the quality and effectiveness of health services and care*” [8]. Implementation science is distinct from real-world evidence or pragmatic trial models.

The COVID-19 pandemic has provided a reminder of the importance of implementation science. Clinical trials of vaccine candidates progressed with historic speed and efficiency but considerations about implementation did not keep pace, leading to rollouts that were fractured along socioeconomic and demographic lines. The Pfizer-BioNTech COVID-19 vaccine was the first to be approved, but the requirement for ultra-cold (-70°C) storage made distribution complex. Research related to the associated costs, feasibility and adoption of ultra-cold storage was not performed, missing an opportunity to investigate solutions for implementation. Data were subsequently released showing that the undiluted COVID-19 vaccine could be stored at standard freezer temperatures (-20°C) for up to 2 weeks [9].

Pragmatic trials, which undertake scientific evaluation of the effectiveness, acceptability, appropriateness, fidelity, cost or coverage of an intervention in a real-world setting, have gained traction in recent years. Implementation science goes one step further, revisiting these metrics to evaluate how and why an intervention succeeds or fails in a specific context and identifying optimal approaches for particular healthcare systems. Research questions should be framed based on needs identified by stakeholders within healthcare systems (e.g. payers, policymakers and clinicians) in collaboration with industry.

Implementation science was born out of the demand for more evidence-based knowledge on how implementation is achieved in healthcare systems. In its early forms it was empirically driven, but over the past decade an increasing number of implementation science theories, models and frameworks have been developed with three overarching aims [10]:

- To describe and/or guide the translation of research findings into routine clinical practice.
- To understand and/or explain factors that exert a positive or negative effect on implementation outcomes.
- To evaluate implementation studies, to include levels of uptake, integration and sustainability.

Implementation science has since gained traction worldwide as a valuable scientific approach; however, it has not yet been broadly adopted by industry. Early incorporation of implementation science into a development program has the potential to reduce the time from launch of a drug and initial patient access to its widespread use. Without implementation science, we are likely to encounter reduced access to and slow uptake of healthcare innovations, as was seen with sacubitril/valsartan. Today's healthcare systems, clinicians and patients deserve earlier and more active work in this area.

Why should the pharmaceutical industry embrace implementation science?

Investing in implementation science can address practical questions for healthcare system stakeholders, lead to improvements in policy design, health management and service delivery and empower communities and beneficiaries [11]. If we truly wish to serve patient needs, it is the optimal course of action.

Drug development is hugely expensive, costing approximately US\$1 billion per approved drug [12]. Although implementation is as relevant to healthcare delivery as safety and efficacy, it is typically addressed by investigator-initiated trials and real-world evidence studies in the 5 years after regulatory approval and access authorization, resulting in delayed answers to key questions by healthcare system stakeholders and challenges to patient access. Applying implementation science early in the pipeline can increase cost-effectiveness by both reducing the time from drug discovery to routine clinical use and allowing us to understand and address barriers to adoption early. This demonstrates the cost to the system of one implementation strategy over another, highlighting that the value of a new medical innovation goes beyond clinical benefit.

Why should governments/healthcare systems embrace implementation science & partner with industry?

These cost savings would be a boon to healthcare systems that, regardless of the payer model, are under rising pressure to increase efficiency and return on investment [13]. Designing studies and testing implementation strategies

to overcome translational barriers will improve the uptake of a product. This, in turn, will maximize value for patients, healthcare systems and regulatory bodies.

For example, Novartis has partnered with the UK National Health Service to accelerate the uptake of a new therapy, inclisiran (Leqvio) and reduce the health and economic burden of atherosclerotic cardiovascular disease. Through the evaluation of implementation strategies, this partnership aims to improve the scale and efficiency of manufacturing and establish an efficient clinical trial platform for a widespread disease [14]. If this is successful, it could pave the way for improved early collaboration between industry and healthcare systems.

Recommendations & insights

Several recommendations for the adoption of implementation science by industry have been made [3,15].

- Implementation science has great potential for improving patient care and must be treated as an integral component of the development process.
- Industry needs to be adept at changing and embracing new skills, knowledge and capabilities. The ideal research team is multidisciplinary, aligning the skills of implementation scientists with those of other stakeholders, including policy- and decision-makers.
- Implementation scientists should feed into study design early in Phase II and Phase III clinical research to ensure that implementation outcomes are incorporated and that implementation evidence is available for launch.
- Different methodologies need to be embraced to test, document and analyze medical innovations and implementation strategies in local contexts. These should consider the balance of rigor versus usefulness of the research, context-specific problem-solving versus generalizable knowledge and the right incentives for those responsible for implementing healthcare.
- An improved understanding of the complexity of healthcare systems and the formation of solid partnerships with stakeholders is also required to facilitate shared decision-making.
- Reliable and sustainable funding mechanisms must be established for implementation science projects, and routine economic evaluation of related strategies should be undertaken.

Conclusion

The incorporation of implementation science into clinical development programs is not a ‘box-ticking’ exercise; it represents a change in mindset and a departure from the traditional models of drug development.

Industry needs to embed implementation science into clinical development teams and create a distinct discipline that crosses clinical, market access, medical affairs and commercial functions and interacts directly with healthcare systems and their decision-makers. Different functions within industry typically work in siloes; although efforts are being made across the leading organizations to improve synergies between these groups, more effort is needed to ensure collaborative implementation science.

There may be concerns about investment in this unknown territory. However, these concerns are far outweighed by the potential benefits that implementation science can confer, including the sustained uptake of new interventions. There are several benefits to collaborations between industry and healthcare systems. The primary aim of these partnerships is to improve patient access to novel therapies, ultimately leading to improved patient outcomes.

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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