# The Rise of Registries


Identifying risk has consistently remained a top priority in clinical trials – especially in transformative therapies. With changes to study development, safety, value and innovation, the widespread utilisation of registries could mean a transformational shift across the whole trial landscape

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A range of novel scientific approaches to address various disease targets have characteristics associated with 'transformative therapies' – namely therapeutic interventions, which shift the objective of care from management of symptoms to control of disease through a modification of disease processes. Broad catagories of scientific platforms exist under this umbrella, such as cell therapy (induced pluripotent stem cells, direct reprogramming of differentiated cells), a variety of small molecules within different chemical classes, antisense RNA interference therapy, monoclonal antibodies and gene therapy.

## Transformative Therapies

Although a variety of clinical development programmes can be characterised by investigational compounds meeting transformative definitions, the higher number of potentially breakthrough products in cancer reflects the growing understanding of disease processes at the molecular level. This includes insights gained through compounds investigated for multiple cancers that have similar underlying molecular mechanisms, but which may affect different organ systems.

Correspondingly, immunological conditions also share common pathophysiological touch points in spite of discrepancies in clinical expression, so potential therapeutic agents may be effective across multiple indications. As an example, there are more than 20 therapeutic monoclonal antibodies – either approved or in various stages of clinical development – that target molecular components of the cytokine cascades mediating inflammation (1). These diverse agents may interrupt pathways essential to the pathobiology of allergic asthma, inflammatory bowel disease (2), Crohn's disease (transmural inflammation) and ulcerative colitis (mucosal inflammation).

## Implications for Clinical Development

The translation of molecular discoveries in the laboratory into novel clinical research and healthcare delivery mechanisms drives the development of clinical trial methodology. Innovative study designs adaptively evaluate unique product attributes, while accommodating patient subtypes and simultaneously building a longitudinal model of the disease process, which has clinical care implications (3). For instance, agents that affect nodal points in pathophysiology may be targeted across clinical conditions, which have different clinical expressions in an early clinical development strategy exploiting 'therapeutic adjacencies'.

In this stratagem – which continues discovery into development – an evaluation of pharmacological properties is pursued, using a common, existing target across multiple indications before committing to a clinical indication. Clinical research activity is predicated under an assumption that successful target engagement in one disease state may be transferable into another. However, as these agents can also have a locus of action upstream from the ultimate clinical presentation, there is a potential for introducing unanticipated adverse effects detected only with longer-term therapy in a more heterogeneous population. Given this potential, the contribution of registries to clarify treatment effects in representative populations – in the hands of representative physicians and over longer durations of exposures – is key.

## Long-Term Safety

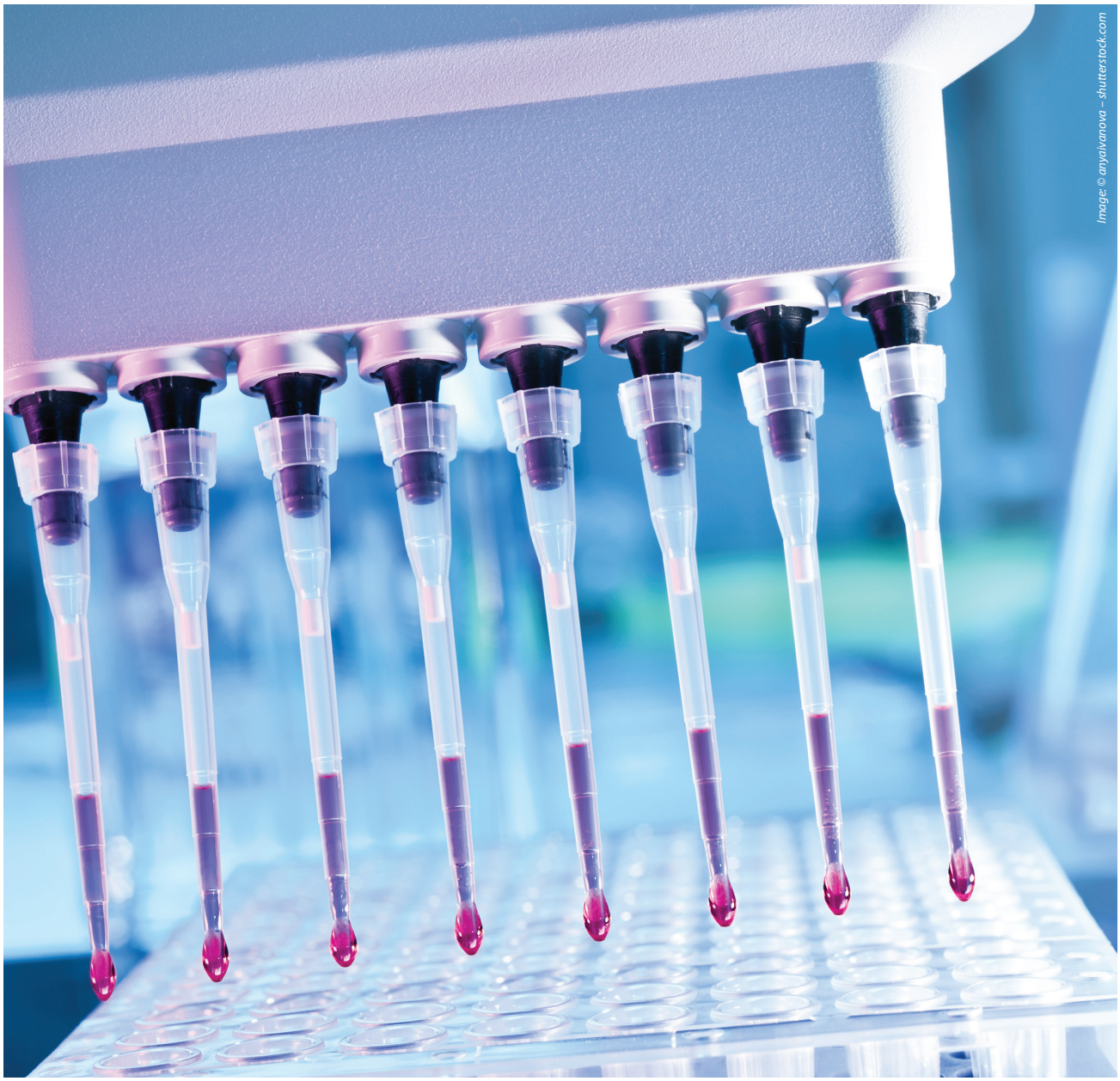
With transformative therapies, there is a need for long-term follow-up to identify risk, as well as value and benefits. These benefits can be seen as increased quality of life, prolongation of life (compatible with reasonable quality of life), and cost benefits based upon overall reductions in healthcare utilisation. This last attribute allows healthcare providers to facilitate access to expensive therapies without reducing provision for other healthcare needs, and to decrease the burden of illness from both a patient and social level.

Historically, registries have been associated with risk identification methods in relevant clinical settings.

According to the *Guidance for Industry: Good pharmacovigilance practices and pharmacoepidemiologic assessment of 2005*, a registry is defined as "an organised system for the collection, storage, retrieval, analysis and dissemination of information on individual persons exposed to specific medical intervention who have either a particular disease, a condition (e.g., a risk factor) that predisposes [them] to the occurrence of a health-related event, or prior exposure to substances (or circumstances) known or suspected to cause adverse health events" (4). However, potential contributions now extend far beyond this initial pharmacovigilance theme to address the data demands of diverse stakeholders during pre-market evaluation, as well as after the registration stage.

Registries tend to be initiated and driven by requirements for data from multiple sources. This has led to disjointed approaches, inconsistent processes and data silos, where information is not shared and analysed in the wider scientific community. Interactions and collaboration between stakeholders prompt the need for harmonisation of workflows and transparency. For example, the EMA set-up initiative 2014 is aimed towards facilitating information sharing, while introducing standards for high-quality registries (5). With transformative interventions, new guidance will need to be developed to allow these standards – originally created based upon the mechanism of action of today's therapies – to also address new interventions that offer the latest mode of actions on a cellular and/or genetic level, for instance. Additionally, given the unique pharmacological properties, organisations would be able to track how novel treatments interact with established pharmacotherapy in a more ecologically relevant environment.



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## Adding Value

Long-term health benefits – such as, a return to full or near-to-full activities or health – and treatable/manageable adverse reactions of a new innovative therapy will be the most critical factors to the majority of patients. Also of equal importance is the cost of the therapy as it influences access, due to the price of insurance and co-payment arrangements and methods of reimbursement by national healthcare systems (such as the NHS in the UK), other governments (Centers for Medicare and Medicaid Services) or commercial plans within the US.

With regards to government payers, the review will take place against a context in which a cost/benefits ratio assessment of a new therapy will be completed before the new medicine can be added to the standard treatment protocol. From multiple perspectives, and in the majority of cases, costs will be the most significant consideration and will be calibrated against long-term benefits, including a reduction in future healthcare expenses with superior health gains.

## Trial Innovation

Transformative therapies have a direct impact on study design and conduct for subsequent interventions within the same diagnostic category. Because of the highly personalised approach to therapy exhibited by many of these agents, and the presumptive modification of the disease process, a subset of patients within a diagnostic category are removed from consideration for future comparative trials – particularly against placebo or standard of care, once these agents are approved for commercialisation. Nowhere would this be more problematic than under the umbrella of orphan disease indications: fewer patients remain treatment-naïve for evaluation of innovative therapy, accommodating disease heterogeneity in clinical trial design becomes more difficult,


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and traditional experimental designs do not provide solutions for product evaluations (6).

In this environment, innovation in study design in the context of a regulatory review process that demonstrates flexible standards offers an opportunity for research, in which patient data from an orphan disease registry augment inferences obtained from a concurrent control group (7). In essence, the control is partially contained within the registry, rather than only concurrent in the interventional trial. Recognised limitations in attempts to employ a case-control matching paradigm using the small datasets within a registry have been noted, but the potential for innovative study methodology appears plausible based upon access to registries (8).

### A Strategic Imperative

Pharmaceutical companies and governments have a compelling interest to provide safe and beneficial therapies that have proven their long-term value, judging by accrued benefits and risks. Concurrent observational research directed towards the use of registry data for evaluation of safety is well-recognised, as well as the emerging importance of registries in establishing product value through data to educate patients, demonstrate transitions in healthcare utilisation, and facilitate reimbursement decisions for healthcare payers and providers.

Although not yet fully articulated, the possibility of using registries to support the registration process – particularly within the orphan disease space – when randomisation to concurrent controls proves to be difficult or untenable, has merit as a topic for exploration and biostatistical research. Developing registries of patients with the index condition as early as Phase 1, and extending the registry platform through Phase 3 and beyond, becomes a strategic imperative in an era of innovative therapy.

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