Commentary: Femida Gwadry-Sridhar

Natural history studies underpin clinical research

Historians writing about the origin of clinical research often cite studies conducted in the UK as setting some of the fundamental standards in this field. The Medical Research Council conducted a trial of patulin for the common cold in 1943 which was the first double-blind controlled trial. Three years later it carried out a study to evaluate streptomycin in pulmonary tuberculosis – the first randomised controlled trial. Decades later, with more research taking place to treat rare diseases, clinical trials have evolved further to take into account patient data outside the clinical setting such as data from patient registries and health insurance claims.

This information has become known as real world data – or data from sources other than a clinical trial. The analysis of this raw data is called real world evidence. In addition, natural history studies, which collect information about the natural history of a disease, are part of the modern arsenal. These in turn have led to the creation of external control arms where data in certain populations is collected to supplement an existing randomly allocated control arm of a trial.

The last decade has seen a considerable shift in the acceptability of real word data by both the US Food and Drug Administration and the European Medicines Agency. Both agencies have issued guidance clarifying when this data may be used when a traditional randomised control trial may not be feasible. In 2019, Pfizer Inc used real world data to gain FDA approval of a new indication for Ibrance (palbociclib), a breast cancer drug. The indication was for use of the drug in men, a small patient population unable to support a traditional trial.

Other drugs that have been evaluated using real world data include Elevidys (delandistrogene moxeparvovec) for Duchenne muscular dystrophy, approved by the FDA in 2023, and Zolgensma (onasemnogene abeparvovec), approved for spinal muscular atrophy in 2019. Of particular interest is the use of real world data for external control arms where data in certain populations may not be available for randomisation. Here, the design of a natural history study can be important.

Natural history studies and external control arms are becoming more relevant as regulatory agencies, companies and payers seek faster, more cost effective ways to evaluate new therapies without compromising scientific rigour. The quality of the underlying natural history data often determines whether an external control arm can withstand regulatory and payer scrutiny. To achieve quality, some biotech investors are even insisting that a natural history study is initiated prior to Phase 1.

Patient deaths and serious adverse events that led to clinical holds and drug failures in 2024 and 2025 have generated support for the use of real world data in the context of natural history studies. These studies have become the scaffolding on which external control arms stand. When executed well, these arms align with the inclusion criteria, endpoints, and follow-up cadence of an interventional trial, while capturing the full arc of disease progression in the absence of treatment.

Rare diseases, oncology, and other high-unmet-need areas are leading this shift. Testing drugs for these diseases in traditional randomised trials is often neither feasible nor ethical. Instead, robust natural history studies using external control arms can achieve scientifically credible, clinically meaningful comparisons acceptable to regulators.

Patients with severe and rapidly progressive rare diseases, such as those with a lysosomal storage disease (LSD), often oppose placebo-controlled trials because receiving no active treatment can mean irreversible decline or death within a short period of time. In these small populations, retention in placebo arms is also a major challenge where even a few patient dropouts can drastically undermine statistical power and risk trial failure. As the UK advocacy group for LSD called the Cure & Action for Tay-Sachs Foundation has regularly stated, "there is nothing worse than a trial failing, not because the drug didn't work, but because the trial design was so bad." This highlights the need to use real world data or natural history cohorts as comparator arms to address these ethical and practical challenges, enabling every participant to access treatment while still providing credible, comparative evidence of efficacy.

Natural history studies, when designed prospectively and to regulatory standards, capture the patient journey before any therapeutic intervention. They document disease trajectory, progression variability, and presentation heterogeneity. Without this foundation, an external control arm risks being little more than retrospective data stitched together, risking inconsistent measures, missing outcomes and unmeasured confounders.

Recently, regulators have clarified what they expect. The FDA's draft guidance on externally controlled trials underscores several minimum requirements, including patient-level data, pre-specified analytic plans, clearly defined eligibility and outcome criteria, bias mitigation strategies, and contractual data access provisions[1]. More recently, on 25 July, the EMA issued a scientific guideline on the use of evidence generation in regulatory decision-making[2].

Retrospective analyses show that about 34 FDA and 41 EMA applications relied on external control arms between 2005 and 2017 of which 98% received an FDA approval and 79% an EMA positive opinion. In the period from 2016 to 2021 external control arms were used in 20% of oncology approvals in the EU and 82% of approvals for drugs for rare diseases.

References: 1. FDA, *Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products*, February 2023. 2. EMA, *Development of a reflection paper on the use of external controls for evidence generation in regulatory decision-making* – Scientific guideline, 25 July 2025.

This article was written by Femida Gwadry-Sridhar, PhD, CEO and Founder of Pulse Infoframe Inc.