From Survival to Significance: Evolving Endpoints Beyond Mortality and Related "Hard" Outcomes Across Clinical Research

FROM INSIGHT TO ACTION

On October 8-9, 2025, the Duke Clinical Research Institute (DCRI) convened cross-disciplinary experts from across the clinical research ecosystem to critically examine current approaches to clinical trial endpoints, with particular focus on considerations for leveraging surrogate and alternative endpoints in regulatory-enabling clinical trials. The Think Tank explored fundamental challenges in how surrogate endpoints are selected, validated, and interpreted across the clinical trial continuum, from early-phase trials through post-market surveillance. Discussions highlighted the need to balance scientific rigor with pragmatic considerations of cost, time, and stakeholder value while ensuring that endpoints meaningfully capture patient experience and clinical benefit for the targeted population.

KEY TAKEAWAYS AND THEMES:

- **The surrogate endpoint validation continuum remains uncertain for sponsors and regulators.** While the FDA framework distinguishes between candidate surrogates that are "reasonably likely" and "validated" surrogates, the pathway for progression along this continuum lacks clarity. For example, treatment effects on decline in eGFR have very strong associations with treatment effects on the established clinical endpoint for CKD progression (kidney failure or doubling of serum creatinine) and is consistent across populations and interventions. Yet FDA has approved its use in select studies or settings. On the other hand, well-established surrogates like progression-free survival in oncology are often widely used despite a lack of strong associations to overall survival. It remains difficult to determine whether these differences in the validation and utilization of surrogate endpoints in trials represents a challenge in providing an established evidence base for the surrogate endpoint or a clear, well-defined path for approval of surrogate endpoint use in clinical trials. This uncertainty may contribute to the lack of progress in surrogates across the medical spectrum.

- **Misalignment between different stakeholder goals, timeframes, and incentives creates tensions in endpoint selection and value assessment.** Regulators, payers, clinicians and patients may all have differing goals, timelines and incentive structures, leading to the potential for misalignment among stakeholders in the use of surrogate endpoints. Surpassing regulatory hurdles comes first in clinical development therefore driving initial endpoint selection while payers and patients may be more concerned about the balance between benefit or harms over the longer-term horizon.

- **Extended trials for traditional endpoints are not feasible for evaluation of many preventative therapies or treatment in low-risk populations.** Prevention trials face an inherent feasibility challenge. Demonstrating clinical benefit requires potentially decades of follow-up, which would require enormous upfront investment to support long, costly trials with delayed time-to-market to recognize revenue. Validated surrogate endpoints that demonstrate early disease modification is one approach but requires extension of the evidence base for populations with disease to populations without disease, who are the target for prevention.

- **Traditional composite endpoints fail to capture the variability and cumulative nature of patient experience.** Traditional composite endpoints such as major adverse cardiovascular events (MACE) treat all components equally (death, stroke, myocardial infarction), losing critical information about disease burden, event severity, and cumulative effects. Novel analytical frameworks offer potential solutions, such as the Desirability of Outcome Ranking (DOOR) which determines weight based on ordinal categories ranked by stakeholder input. Innovative approaches to composite endpoints allow incorporation of surrogate endpoints or patient related outcomes together with clinical endpoints and may enable a more holistic assessment of clinical benefit. Both require new statistical methods and regulatory acceptance of more complex analytical frameworks. These novel frameworks have the capacity to capture both treatment efficacy and adverse events, leading to a single estimate of net benefit but also requires in depth considerations.

- **Real-world data represents an underutilized opportunity to refine understanding of benefits and harms of treatments.** Post-marketing surveillance represents a critical but underutilized opportunity to evaluate surrogate endpoints retrospectively where robust real-world evidence collection could justify earlier approvals based on "reasonably likely" surrogates with the understanding that confirmatory data would follow. However, implementation faces significant infrastructure barriers such as fragmented healthcare systems, inconsistent EHR platforms, and the absence of centralized databases making comprehensive outcome tracking very difficult.

ACTIONABLE ITEMS

Develop Infrastructure to Inform Best Practices and Formal Grading System for Surrogate Endpoints
- Create a multidimensional framework that grades surrogate endpoints that considers a range of issues such as biological plausibility of the endpoint, nature of the disease, class of evidence (individual vs trial level) supporting the surrogate endpoint, and magnitude of the association
- Clarify the paths of evaluation of a surrogate from "exploratory" through "reasonably likely" to "validated" status and develop disease-specific considerations while maintaining general principles applicable across therapeutic areas

Create Stakeholder Education and Resources to Advance Surrogate Endpoint Development
- Provide education on development and implementation of successes and failures of surrogate endpoints
- Using these examples, discuss utility, appropriate use cases, and standardized approaches for use of surrogate endpoints
- Provide support to disease groups who wish to generate evidence for new surrogate endpoints
- Reinforce the current data sharing expectations, while many journals require data sharing from author groups, sponsors have increased restrictions on sharing

Support Strategic Planning for Surrogate Endpoint Use and Evaluation Across Short- and Long-Term Horizons
- Involve payers or health technology assessors, or health economists in the planning for surrogate endpoint evaluation
- Increase discussions with payers so that there can be a programmatic approach for the range of studies required for both assessment of benefit for regulatory approval and potentially longer-term studies that may be more relevant for time horizons for patients and payers

Enable Feasible Prevention Trials and Low-Risk Treatment Trials through Development Strategies for Surrogate Endpoints that Represent Early Disease Progression
- Provide education and facilitate dialogue among stakeholders to clarify evidentiary thresholds and appropriate use of surrogate endpoints in low-risk populations and prevention studies
- Encourage collaboration and data sharing to align on best practices for identifying, refining, and validating surrogate endpoints that reflect early disease modification
- Support development of guidance materials and case examples illustrating successful use of surrogate endpoints in early disease and low-risk populations

Advance Investigation of Novel Approaches to Composite Endpoints that Allows Incorporation of Surrogate Endpoints, Patient Related Outcomes and Clinical Endpoints
- Encourage research groups to advance the science of construction and validation of alternative methods for composite endpoints such as hierarchical or ordinal composite endpoints, including the DOOR and similar methods for treatment benefit and net clinical benefit
- Advance these endpoints to also include patient related outcomes as well as benefits and harms for assessment of net clinical benefit
- Provide education to stakeholders on the design, interpretation, and practical implementation of these novel endpoints
- Encourage collaboration across industry, academia, and regulators to identify case examples and best practices for use of these novel composite endpoints

Build Infrastructure for Comprehensive Post-Market Evidence Generation
- Invest in tokenization and data standardization to enable efficient multi-stakeholder data sharing
- Establish best practices for integrating continuous monitoring and real-world data into surrogate endpoint assessment
- Develop methods for long-term surveillance systems which have the potential to further refine surrogate endpoint development

For more information, please visit https://dcri.org/insights-and-news/insights/dcri-think-tanks.