Duke | MARGOLIS CENTER for Health Policy

Translational Science in Drug Development: Surrogate Endpoints, Biomarkers, and More

Virtual Public Workshop • Zoom
May 24 & 25, 2021

Discussion Guide

As the biological mechanisms of diseases and pharmacological activities of therapeutics are better understood, this information provides opportunities to improve clinical trial efficiency. One such opportunity includes identification and use of surrogate endpoints that indicate disease progression or clinical response in clinical trials. In instances where disease progression or clinical response is slow, surrogate endpoints may provide a measurable prediction of the outcomes for clinical trials in a shorter and more feasible timeframe.[a] Development and validation of such surrogate endpoints, however, often requires sustained efforts and dedication from multiple stakeholders.

Surrogate endpoints represent only one opportunity where translational science can be leveraged to support clinical development of medical products. Understanding the causal pathways of a disease can assist with identification of prognostic or predictive biomarkers. Animal models of disease can provide supportive evidence for candidate therapeutics when the pathophysiology of disease is well understood and the animal model recapitulates important aspects of the human disease. When developing these types of mechanistic evidence to support a clinical development program, early discussions with regulators on the type(s) of evidence and how the evidence would be used can be beneficial.

The Robert J. Margolis, MD, Center for Health Policy at Duke University, under a cooperative agreement with the US Food & Drug Administration, is hosting a workshop to discuss best practices and provide use cases for successfully bringing forward evidence generated through translational science for regulatory submissions. Participants will discuss how collaboration between academic researchers, industry, clinicians, patient organizations, and regulators can drive innovation and facilitate the use of translational science during clinical development.[b] Stakeholders will also discuss potential barriers to using translational science to support therapeutic development and strategies to overcome those barriers. This workshop will include the following:

- Presentations of efforts from FDA, NIH, academia, patient groups, and industry to support surrogate endpoint and other biomarker identification and development for use in therapeutic development and regulatory submissions.
- Successful examples of using translational science in the development of therapeutics.
- Identification of current challenges and opportunities in developing innovative drug development tools and applying them in therapeutic development.
- Interaction and discussion among the stakeholders who are developing these tools and implementing them in therapeutic development programs.

[a] Mack, A., et al., Perspectives on biomarker and surrogate endpoint evaluation : discussion forum summary. 2011, Washington, D.C: The National Academies Press.
[b] Luke, D.A., et al., The Translational Science Benefits Model: A New Framework for Assessing the Health and Societal Benefits of Clinical and Translational Sciences. Clin Transl Sci, 2018. 11(1): p. 77-84.

Session 1: Enhancing Clinical Development Programs by Leveraging Translational Science Throughout the Drug Development Lifecycle

The incorporation of biomarkers, surrogate endpoints, and other translational approaches can enhance the ability of a clinical development program to achieve its objectives. They can improve clinical trial efficiency, help achieve optimal dosing, and render studies feasible when clinical endpoints would require long, expensive trials. In this session, speakers from academia, industry, and regulatory sectors will present their views on the incorporation of translational evidence into clinical development programs. Speakers will discuss the benefits and challenges of using biomarkers as surrogate endpoints relative to the direct measurement of a clinical endpoint to demonstrate efficacy in clinical development.

Discussion Questions:

1. What are key decision points and challenges of incorporating biomarkers in clinical development programs?
2. How can the incorporation of biomarkers and other translational approaches help promote trial efficiency?
3. How do developers identify internal or external candidate biomarkers for inclusion in clinical trials? What are the risks when including candidate biomarkers and how are they mitigated?
4. What more can be done to promote the use of translational science in drug development programs?

Session 2: Identification and Development of Novel Surrogate Endpoints for Use in Clinical Development Programs

In this session, the presenters and panelists will discuss the identification and development of biomarkers as novel surrogate endpoints that could be used in clinical development programs. The discussion will highlight common challenges during development, strategies for overcoming those challenges, and opportunities to streamline the process. Speakers will highlight recent advancements in a variety of biomarker and translational research programs, including:

- Inborn errors of metabolism - methylmalonic acidemias and propionic acidemias
- Imaging biomarker for cavernous angioma
- Proteomic surrogate endpoint for cardiovascular outcomes
- Neurofilament light chain as a biomarker in neurological disorders

Discussion Questions:

1. What are key success factors in developing novel surrogate endpoint?
2. What are some of the challenges that biomarker developers face in developing surrogate endpoints?
3. What are the key opportunities and challenges for establishing disease mechanisms and causal chains with novel surrogate endpoints?
4. What are the best methods of assessing the limitation of a novel surrogate endpoint in relation to established clinical endpoints?
5. How do cross-sector partnerships play a role in identification of novel surrogate endpoints? How can cross-sector partnerships lead to innovation in this space?

Session 3: Clinical Validation and Regulatory Acceptance of Biomarkers as Surrogate Endpoints

The process to validate surrogate endpoints for regulatory acceptability in prospective clinical trials is rigorous. As a result, developers may face challenges in achieving validation for a candidate surrogate endpoint due to lack of resources, samples, or sufficient data.

In this session, presenters and panelists will discuss the process of validating a novel surrogate endpoint for accelerated approval and traditional approval, including common challenges during validation and solutions for overcoming them. Speakers will highlight examples of successful translation of biomarkers from academic discovery to regulatory acceptance, as well as examples of fields that have faced significant challenges. Topics will include:

- Use of surrogate endpoints in oncology
- Development and validation of cerebral spinal fluid biomarkers for use in blood-based assays in neurodegenerative diseases
- Use of imported clinical assessment tools in rare disease
- GFR decline as a surrogate endpoint

Discussion Questions:

1. What are the challenges associated with validating biomarkers, and what approaches may support efficient biomarker validation?
2. What characteristics and processes are shared by programs with a strong track record in evaluating candidate surrogates?
3. What more can be done to assist developers in validating candidate surrogates?
4. How can early involvement and communication with regulatory agencies support biomarker validation?

Session 4: Beyond Surrogate Endpoints: Other Ways Translational Science Can Support Drug Development

The primary use of biomarkers in drug development is to serve as surrogate endpoints, which has been appealing due to the potential for demonstrating efficacy in shorter, smaller clinical trials. However, there are many other ways that biomarkers and other translational approaches can make clinical development programs more efficient, including the development of evidence to support a causal relationship between the biomarker and the condition and providing confirmatory evidence for clinical development programs in rare and common diseases that rely on a single adequate and well-controlled trial for approval.

In this session, presenters and panelists will present use cases beyond use of surrogate endpoints. Discussions will highlight how translational research guided the design of shorter, smaller, more efficient clinical trials and helped minimize risks to meeting efficacy and safety standards. Speakers will discuss topics including:

- Model-informed drug development
- Pediatric extrapolation for Pulmonary Arterial Hypertension using a physiologic biomarker of pulmonary artery pressures
- Research understanding Lamin A in Progeria – from benchtop to clinical trials to acceptance

Discussion Questions:

1. What translational approaches assist in drug development programs beyond use of surrogate endpoints?
2. What benefits and challenges exist in using these translational approaches to support drug development?
3. How can translational science approaches other than surrogate endpoints support regulatory submissions for accelerated approval or traditional approval?
4. Is there more that can be done to encourage use of these approaches?

Session 5: Opportunities and Challenges for Incorporation of Translational Science in Clinical Development Programs

In this closing session, panelists will discuss opportunities to increase the use of translational research studies to support clinical development that achieve regulatory acceptance. Panelists will discuss how programs may be able to learn from the successes and failures in other therapeutic areas, and how to best facilitate collaboration to achieve the goals of drug development programs.

Discussion Questions:

1. Reflecting on the meeting, what are key strategies for optimizing the use of surrogate endpoints and other translational approaches for drug development?
2. What are the challenges to taking a biomarker from discovery to validation?
3. Is there more that can be done to facilitate the process? What mechanisms might be able to increase the use of translational research studies?
4. What are key strategies for facilitating collaboration between stakeholders, with the overall goal of improving therapeutic development and approval?
5. What are current challenges facing and the use and acceptability of these approaches? What steps can be taken to advance future translational science studies?

This publication was supported by the Food and Drug Administration (FDA) of the U.S. Department of Health and Human Services (HHS) as part of a financial assistance award (U19FD006602) totaling $3,344,533 with 100 percent funded by FDA/HHS. The contents are those of the author(s) and do not necessarily represent the official views of, nor an endorsement, by FDA/HHS, or the U.S. Government.