“THE EVER-PROMISING BUT ELUSIVE SURROGATE ENDPOINT: WHAT WILL IT TAKE?”

WORKSHOP AGENDA

DECEMBER 1, 2014 (DAY 1)
MEETING ROOM – BALLROOM

MEETING CO-CHAIRS:  
Anna D. Barker, Ph.D., NBDA and Arizona State University  
George Poste, D.V.M., Ph.D., NBDA and Arizona State University  
Carolyn Compton, M.D., Ph.D., NBDA and Arizona State University  
Federico Goodsaid, Ph.D., Vertex Pharmaceuticals

FACILITATION:  
Robert Mittman, MS, MPP  
Director, Biomedical Strategy and Knowledge Development,  
Complex Adaptive Systems; Professor of Practice,  
Ira A. Fulton Schools of Engineering, Arizona State University

8:00 a.m. – 8:50 a.m.  
Breakfast - Salon

9:00 a.m. – 9:10 a.m.  
Workshop Background – Why Rethink Surrogate Endpoints? Why Now?  
Anna D. Barker, Ph.D.  
President and Director, National Biomarker Development Alliance  
Director, Transformative Healthcare Knowledge Networks  
Co-Director, Complex Adaptive Systems  
Professor, School of Life Sciences, Arizona State University

9:10 a.m. – 9:25 a.m.  
Workshop Process and Outcomes  
Robert Mittman, MS, MPP

Brief summary of the process for the next two days: this workshop will initially focus on a dialogue on surrogate endpoints – what has changed and likely to change further? What does evidentiary standards for surrogate endpoints mean in today’s environment? Is it time to rethink the concept through the lens of 21st Century biomedical science? However, as is the case with all of the NBDA workshops, the operative word is “working”; so all that we do to explore the problems and potential solutions will be employed by our Action Groups that will meet tomorrow to deliberate and make recommendations for action.
9:25a.m. – 9:30a.m.  Introduction of Workshop Keynote Presentation
Anna D. Barker, Ph.D.

9:30a.m. – 10:00a.m.  Expect the Unexpected: The Problematic Nature of Surrogate Endpoints
Janet Woodcock, M.D.
Director, Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Surrogate biomarkers (surrogate endpoints) are the "holy grail" of biomarkers. FDA has created a number of innovative approaches to use surrogate endpoints (SE) in trials; but the reality is that there are numerous reasons that SEs to fail to prove to predict a specific clinical outcome. This is likely to get worse as we intensify our focus on creating new molecularly-based interventions for complex diseases - such as cancer, Alzheimer’s disease, diabetes, cardiovascular and psychiatric diseases. Given the complexity of these and many other diseases, and the emerging "tsunami" of "omics" data, will it be more (or less) difficult to achieve the original vision for surrogate endpoints in phase III trials? Creating the evidentiary standards today for SEs is a major hurdle. Is it the job of the affected communities to address this challenge? Are there new, innovative high-value SE options for the future?

10:00a.m. – 10:20a.m.  Questions/Discussion

10:20a.m. – 10:40a.m.  Break

10:40a.m. – 11:10a.m.  Small Group Discussion: Identifying the Major Barriers in the Discovery and Development of Surrogate Endpoints?

Clinical endpoints (often survival for complex diseases such as cancer and the cardiovascular diseases) mean long duration (and expensive) trials. The Surrogate biomarker (surrogate endpoint) is an exciting concept that portends shorter (hopefully less expensive) clinical trials for new clinical interventions (e.g. new drugs, vaccines, diagnostics) – i.e., faster delivery of safe and efficacious drugs to patients. Although we have achieved some successes in a few diseases (e.g., cardiovascular diseases), overall achieving successful robust surrogate endpoints that can correctly predict a specific clinical outcome remains a very high bar - thus true SEs are still relatively rare.

Overall the expectation that SEs would greatly speed up the clinical trials process for interventions where the real clinical endpoint is survival (or the data needed cannot be collected) has rarely been realized. Are there real barriers to creating the evidence needed for regulatory review of a clinical trial that employs a SE? Work together to identify the real barriers in the field?

11:10a.m. – 11:40a.m.  Capturing the Current Status of Surrogate Biomarkers
Facilitated Group Discussion
Robert Mittman MS, MPP
11:40a.m. – 12:00a.m. Reflections on the Future of SEs from a FED Who Decamped to the Private Sector
Federico Goodsaid, Ph.D.
Vice President for Strategic Regulatory Intelligence, Vertex Pharmaceuticals
SEs are a great idea - with potential to save real time and ultimately reduce the cost of clinical trials. The FDA recognized this concept a number of years ago and has created a number of approval pathways that are enabled by SEs. However, a number of challenges remain for all concerned - most notably in processes to reach consensus on required types and levels of evidence. How do we work together to address these challenges now and in the future?

12:00p.m. – 1:00p.m. LUNCH - Salon

1:00p.m. – 1:30p.m. The Surrogate Endpoint: Past - Present - Future
Robert J. Temple, M.D.
Deputy Center Director for Clinical Science,
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
The use of surrogate endpoints to enable the evaluation of interventions in clinical trials dates from the mid-1990s. From a regulatory standpoint the SE is viewed as a marker (laboratory measurement or a physical sign) that can substitute for the real clinical endpoint (how a patient feels, functions or survives). A correlate is not a surrogate - which continues to present significant challenges to both those who design and implement clinical trials and for the regulatory agencies. Where are we in the quest for evidentiary standards for SEs and where might the science take us in the future?

1:30p.m. – 1:45p.m. Questions/Discussion

1:45p.m. – 3:00p.m. Panel Discussion: Where Have All the Surrogate Biomarkers Gone?
Some biomarkers have been successfully developed to the point of approval as a surrogate endpoint. Many others have failed. And still others are a work in progress (some could represent new thinking or new direction for the field). This panel will make brief comments on their "case", discuss the underlying reasons for success or failure, the type and level of evidence needed for approval and/or why it failed. The panel will engage in a conversation with the other panelists and audience on "lessons learned": Two success stories; a work in progress and a cautionary tale.

PCR - A (SE) High-Value Outcome from the ISPY-2 Trial
Laura van’t Veer, Ph.D.
Professor, Helen Diller Family Comprehensive Cancer Center
Angela and Shu Kai Chan Endowed Chair in Cancer Research;
University of California, San Francisco
KIM-1- A "Qualified Biomarker" for Kidney Injury - Is it a Potential SE
Joseph V. Bonventre, M.D., Ph.D.
Director, Chief, Renal Division;
Harvard Medical School
Samuel A. Levine Professor of Medicine, Brigham and Women’s Hospital

SE Successes for Prostate Cancer
Howard Scher, M.D.
Chief, Genitourinary Oncology Service
Memorial Sloan Kettering Cancer Center

SE Lessons Learned from Cardiovascular Disease and Other Diseases
Anna D. Barker, Ph.D.
Co-Director, Complex Adaptive Systems
President and Director, National Biomarker Development Alliance
Professor, School of Life Sciences, Arizona State University

3:00p.m. – 3:15p.m.  Break

3:15p.m. – 3:45p.m.  Re-Looking and Prioritizing Current Barriers to Achieving Successful SEs - Explore Potential Solution(s)
Small Group Discussion

3:45p.m. – 4:15p.m.  Converging on the Barriers – “Rethinking the Possible” for SEs
Large Group Discussion

4:15p.m. – 4:35p.m.  Systems Approaches to Rethinking SEs - Through the Lens of Angiogenesis
William Li, M.D.
President, Medical Director, and Co-Founder
Angiogenesis Foundation

A change in the state of angiogenesis is one of the "hallmarks" of cancer, and indeed alteration(s) in this very basic physiologic system impacts across a number of disease types. Has biomedical science evolved to a point that it is possible to employ systems thinking as a lens to view future SEs? Blue sky - could such thinking produce SEs that more appropriately and accurately reflect real clinical endpoints?

4:35p.m. – 4:45p.m.  Questions/Discussion

4:45p.m. – 5:00p.m.  Summing Up Today, Plans for Tomorrow

6:00p.m.  Reception – Salon

6:30p.m.  Dinner – Capital Room
THE NATIONAL BIOMARKER DEVELOPMENT ALLIANCE (NBDA)
WORKSHOP VI
DECEMBER 1-2, 2014

“THE EVER-PROMISING BUT ELUSIVE SURROGATE ENDPOINT: WHAT WILL IT TAKE?”*

WORKSHOP AGENDA

December 2, 2014  (Day 2)
Meeting Room – Ballroom

7:30a.m. – 8:20a.m.  Breakfast - Salon

8:30a.m. - 8:45a.m.  Recap from Day 1 - Plan for Today
Robert Mittman, MS, MPP

8:45a.m. – 9:15a.m.  “Let’s Revisit and Perhaps Reinvent the Surrogate Endpoint”
Donald Berry, Ph.D.
Berry Consultants, LLC, Professor, Department of Biostatistics
MD Anderson Cancer Center

With some exceptions, given the rapidly changing landscape of biomarker science and the difficulties associated with the development of biomarkers per se, is the SE likely to remain elusive or is this an era for real change? In that regard, how good are our REAL surrogate endpoints today in complex diseases like cancer? If SEs are the key to achieving precision (personalized) medicine, what might such biomarkers look like in the future and how/when might you prove that you have such a prize? How might this new generation of SEs change clinical trials?

9:15a.m. – 9:30a.m.  Discussion

9:30a.m. – 9:45a.m.  Break

9:45a.m. - 11:00a.m.  Panel Discussion: Predictions are Hard - Especially About the Future:
What Changes/Actions/Discoveries could be Transformative in Discovering and Developing Robust SEs (Perspectives from the FDA, Private and Academic Sectors)

The world needs great ideas to better deal with the SE issues and problems. Each of these experts thinks a great deal about the challenges that surround SEs. What ideas (or your favorite/best idea) could have a major impact in identifying, measuring and developing new approaches to achieve accurate SEs.
Are there combinations that could capture sufficient numbers of “casual” pathways? Are there technologies on the horizon that could directly tie biomarkers to real clinical endpoints? Bring your ideas!

Peter Kuhn, Ph.D.
Professor, Biological Sciences
Southern California Physics Oncology Center
University of Southern California

Elizabeth Mansfield, Ph.D.
Deputy Office Director for Personalized Medicine
U.S. Food and Drug Administration

John Quackenbush, Ph.D.
Professor of Biostatistics, Computational and Cancer Biology
Dana-Farber Cancer Institute (DFCI)
Harvard Medical School

Patrick C. Roche, Ph.D.
Senior Vice President, Research and Development
HTG Molecular Diagnostics

11:00 a.m. - 12:00 p.m. A Trans-Sector Roundtable Discussion: The Future of SEs: What Changes Would Most Benefit Your Respective Sector/Community?

For example, would we derive greater benefit from a trans-sector effort today to develop/better define the type and level of evidence really needed for SEs (by disease class and context of use for the marker); or would we be better served to turn our attention to rethinking the whole concept in the light of advances in the molecular sciences and advanced technologies? Or both? (All ideas thinking/rethinking welcome)

Carl Barrett, Ph.D.
V.P. of Translational Science in Oncology
AstraZeneca

Jimmy Lin, M.D., Ph.D.
Founder & President
Rare Genomics Institute

Lynn M. Matrisian, Ph.D., MBA
Vice President of Scientific & Medical Affairs
Pancreatic Cancer Action Network

Kenneth D. Noonan, Ph.D.
Venture Partner, Advanced Technology Ventures
Senior Advisor, L.E.K. Consulting LLP
European Biopharmaceuticals & Life Sciences Practice
LUNCH - Salon  

Work Groups I and II Deliberate, Decide and Declare  

We will pursue our earlier discussions through two NBDA Action Groups. The focus for the Action Groups (AGs) will be:

AG – 1 – This group will begin with the assumption that the current regulatory definition for SEs (and guidance documents) will continue without change. Given this assumption, using the NBDA’s big six strategic elements to guide biomarker discovery and development (the right clinical question – context of use, a robust experimental design, appropriate numbers of high quality samples, robust technology standards, high quality data and appropriate analytics), and in view of the state of biomarkers science today, define the type and level of evidence needed for regulatory approval (generally within the context of a clinical trial). We will embellish this change at the meeting!

AG – 2 – This group will focus on identifying and exploring new ideas and approaches to the discovery and development of surrogate endpoints. Your group can either assume the current FDA definition and respective FDA guidance for an SE or redefine the surrogate concept. Capture the results of your brainstorming and offer recommendations that the NBDA can act on.

Work Group Reports and Assembly of Recommendations  

NBDA Plans for Implementation of Workgroup Recommendations  

Closing Comments – Meeting Ends