COALITION AGAINST MAJOR DISEASES (CAMD)
2016 ANNUAL REGULATORY SCIENCE WORKSHOP
OCTOBER 19, 2016

ATTENDEES

Name	Company
Andrea Kho	AbbVie
Dora Donaldson	Alzheimer's Association
James Hendrix	Alzheimer's Association
Monica Moreno	Alzheimer's Association
Brian Van Buren	Alzheimer's Association
Penny Dacks	Alzheimer's Drug Discovery Foundation
Nick Brandon	AstraZeneca
Jesse Cedarbaum	Biogen
Alvydas Mikulskis	Biogen
Jennifer Patrillo	Biogen
Jane Rhodes	Biogen
Bjoern Sperling	Biogen
Nancy Myers	Catalyst Healthcare Consulting, Inc.
Sam Hume	CDISC
Cheryl Fitzer-Attas	CHDI Foundation
Stephen Arnerić	Critical Path Institute
Steven Broadbent	Critical Path Institute
Martha Brumfield	Critical Path Institute
Daniela Conrado	Critical Path Institute
Jennifer Ashley Ferstl	Critical Path Institute
Volker Kern	Critical Path Institute
Klaus Romero	Critical Path Institute
Diane Stephenson	Critical Path Institute
Jennifer Goldsack	CTTI
Johan Luthman	Eisai
Jeffrey Dage	Eli Lilly and Company
Janice Hitchcock	Eli Lilly and Company
Albert Lo	Eli Lilly and Company
Debra Lappin	FaegreBD Consulting
Shashi Amur	Food and Drug Administration (FDA)
Eric Bastings	Food and Drug Administration (FDA)

ShaAvhrée Buckman-Garner	Food and Drug Administration (FDA)
Teresa Buracchio	Food and Drug Administration (FDA)
Billy Dunn	Food and Drug Administration (FDA)
Cheryl Grandinetti	Food and Drug Administration (FDA)
Nick Kozauer	Food and Drug Administration (FDA)
Sean Khozin	Food and Drug Administration (FDA)
Tim Marjenin	Food and Drug Administration (FDA)
Ameeta Parekh	Food and Drug Administration (FDA)
Gerald Poldskalny	Food and Drug Administration (FDA)
Ameeta Parekh	Food and Drug Administration (FDA)
Kaveeta Vasisht	Food and Drug Administration (FDA)
Derek Hill	IXICO
Michael Ropacki	Loma Linda University SOM
Lisa Gold	Merck and Company
Mary Savage	Merck and Company
Robert Umek	Meso Scale Diagnostics
Lauren Bataille	Michael J. Fox Foundation (MJFF)
Richard Meibach	Novartis Pharmaceuticals
Jeffrey Kaye	Oregon Health and Science University
Jill Gallagher	Parkinson's UK
Brian Corrigan	Pfizer, Inc.
Daniel Karlin	Pfizer, Inc.
Timothy Nicholas	Pfizer, Inc.
Zhiyong Xie	Pfizer, Inc.
Yoshiko Komuro	Pharmaceuticals and Medical Devices Agency (PMDA)
Ken Sakushima	Pharmaceuticals and Medical Devices Agency (PMDA)
Chris Edgar	Roche
Megan Zoschg-Canniere	Roche
Rita Balice-Gordon	Sanofi
Paula Hines	Teva Pharmaceuticals
Spyros Papapetropoulos	Teva Pharmaceuticals
John Gallacher	University of Oxford
Jason Hassenstab	Washington University in St. Louis

AGENDA HIGHLIGHTS AND SUMMARY

Introduction, Martha Brumfield and Stephen Arnerić

[Presentation LINK]

Martha Brumfield, PhD, Critical Path Institute, welcomed all attendees to the meeting on behalf of Critical Path Institute's Coalition Against Major Diseases (CAMD). She noted the power of collaboration and importance of partnerships for scientific advancement. She described how public-private partnerships and the idea of pre-competitive space have changed in the last ten years and the incredible advancements that have been made in data sharing. She reminded the group that CAMD accomplished one of the first

public clinical data sharing efforts (C-Path Online Data Repository; CODR; LINK) and Clinical Trials Simulations tools [LINK] to advance the Alzheimer's disease field. CAMD has enabled other groups to share data and assisted in new biomarker approvals through the FDA and EMA regulatory submission process. Dr. Brumfield expressed her excitement about the forward-path of CAMD, and shared her pride in the accomplishments of the consortium.

Stephen Arnerić, PhD, Critical Path Institute, reflected on CAMD's achievements over the past year, including the *Role of Pharmacometrics in Regulatory Science* workshop held in Australia in August 2016. He reinforced how CAMD is an integral member of a global community coming together to attack Alzheimer's disease and related disorders. The main focus of CAMD is to progress drug development tools to advance innovative medicines. Dr. Arnerić reflected on the future of CAMD's various teams, including the foundational work of the modeling and simulation team for data usability, Biometric Monitoring Devices (BMDs) to enable a better understanding of disease progression and potentially treatment outcomes, and the importance of biomarker qualification to increase clinical trial efficiencies. The CODR database has grown considerably in the last four months with data contributions provided by academia and industry.

The Voice of the Alzheimer's Disease Patient - Brian Van Buren

Brian Van Buren, Alzheimer's Association National Early-Stage Advisory Group, provided his personal perspective as a 65 year old black, gay man diagnosed with Alzheimer's disease. Brian is the third generation of his family to be diagnosed He explained the various effects of the disease including memory loss, anxiety, and the impact the disease has had on his career. He also reinforced the expectation that patients with dementia have in wanting their data and samples to be used to find a cure.

Informed Consent – Making Patient Data Count! - Penny Dacks and Monica Moreno

[Presentation LINK]

Theme: CAMD's successful completion of the revised Informed Consent Form (ICF) for multiple disease-states, receiving endorsement from patients, caregivers, and membership.

Penny Dacks, PhD, Alzheimer's Drug Discovery Foundation, described the importance of sharing clinical trial data and the difficulties surrounding current Informed Consent documents. Presently, the documents are excessively long (15-40 pages) and overly complex. She provided an overview of the team's objectives and progress, including a walk-through of the completed U.S. Informed Consent document of only 1.5 pages in length.

Monica Moreno, Alzheimer's Association, described the patient perspective of the Informed Consent Form (ICF). She explained that the Alzheimer's Association provided the CAMD-created document to a National Early-Stage Advisory Group and Caregivers Group for comment. Responses included:

- "To me this is a no-brainer. I am just learning now that this data was tossed out the window. I am shocked."
- "I am getting emotional. It makes me angry to think that they could be using this [data] to find a cure."

The advisory members agreed that the future sharing of critical patient-level information and samples far outweighs any potential risks. She ended with the importance of engaging with patients and caregivers living with the disease.

The ICF has been endorsed by CAMD's Coordinating Committee to be shared with other Patient-Advocacy groups, and for integration into future clinical trials by the end of 2016. To aid in this process, the team will be submitting an editorial to New England Journal of Medicine to facilitate use of the team's accomplishment.

FDA Priorities and Initiatives - ShaAvhrée Buckman-Garner

[Presentation LINK]

Theme: The U.S. Food and Drug Administration (FDA) encourages community collaboration amongst the entire research community, the utilization of qualification and Fit-for-Purpose tools, and the incorporation of the patient's voice into clinical trials.

ShaAvhrée Buckman-Garner, MD, PhD, Director of Translational Sciences at the U.S. Food and Drug Administration (FDA), described the innovative discussions that began in 2004 to improve efficiency and create better tools for medical technologies, with the creation of the Critical Path Initiative. Consortia have filled the need to assist in the development of medical products. CAMD has utilized the opportunity to engage with the FDA to help develop tools and methodologies utilizing the Letter of Support initiative, and Drug Development Tools (DDTs) qualification programs (biomarkers, clinical outcome assessments). She discussed the impact modeling and simulation have on the landscape, building efficiency and increasing the probability of success and regulatory certainty. The FDA encourages community collaborations and the incorporation of the patient's voice.

Dr. Buckman-Garner noted FDA's strategic priorities: improve predictability, consistency, transparency and efficiency.

The proposed draft PDUFA VI Commitment Letter [LINK] concentrates on incorporating the patient's voice, the utilization of Fit-for-Purpose tools [LINK] to collect patient input, the enhancement of benefit-risk and understanding, and the increased capacity to review complex innovative designs. The future depends on data. "Data is currency" and a need exists to standardize the capture of data. Moving forward, collaboration will be the key to success.

SESSION I: STANDARDIZED DATA: CONVERTING DATA TO ACTIONABLE INSIGHTS

Integration of Models in Biomarker Qualifications – Klaus Romero

[Presentation LINK]

Theme: Model-based biomarker qualification offers a comprehensive regulatory pathway.

Klaus Romero, MD, Critical Path Institute, articulated the need to quantitatively understand disease progression to support biomarker qualification efforts that focus on using the biomarker to make predictions regarding varying disease states. These models mathematically describe disease progression, while accounting for relevant sources of variability, including one or multiple biomarker signals. The presentation described the specific example of the model-based approach to support the successful qualification of the first clinical prognostic imaging biomarker by FDA (Total Kidney Volume –TKV– for trial enrichment in Polycystic Kidney Disease –PKD–). One advantage of this approach is that instead of evaluating pre-defined cutoffs for the biomarker of interest, model-based approaches allow sponsors to define trial-specific cutoffs that best fit the context of the drug candidate and trial design targeted for enrichment. Another advantage is that for different cutoffs, the enrichment magnitude can be estimated

based on the balance between sample size and power optimization through simulations based on the disease progression models. He reinforced that CDISC data standards are essential for integrating existing data sources (from clinical trials, observational studies, etc.), but also provide a resource for sponsors to prospectively collect information in a standardized way, expediting regulatory submissions.

Digital Drug Development Tools Team – Building a Regulatory Roadmap – Dan Karlin

[Presentation LINK]

Theme: Digital tools are the future of clinical trial data gathering. Standards must be developed to provide meaning and interoperability for digital drug development tools to be utilized effectively.

Dan Karlin, MA, MD, PhD, Pfizer, described the deep history of informatics and the need to apply the concept for data standardization, exchange, and sharing. The current digital landscape provides ample opportunity for data gathering. However, rigor and conclusions with biological meaning for the digital space have been difficult to create. The determination of what sensors actually measure and how to connect to areas of interest is essential to understand. The future requires the creation of data standards. In order to drive meaningful standards, the community must first understand the process used to create raw data and the device used for data collection. Dr. Karlin emphasized the need for a meaningful and structured vocabulary based in concepts that drive the lexicon and that provide reliable correlation.

Data Standards for Mobile Devices – Sam Hume

[Presentation LINK]

Theme: Understanding standards and protocols for data collection from mobile devices is essential for technology to be utilized in the regulatory space.

Sam Hume, MS, CDISC, noted how new types of devices are far beyond current use abilities and the need to reduce the burden on subjects participating in studies. Currently, over 259,000 healthcare applications are available, providing a broad spectrum of possibilities and usage. Technology moves in advance of regulations. Interested parties must ask how to apply new innovations with assurance they work correctly. The Operational Data Model (ODM) provides a data collection space with metadata and a description of how the data was collected. This model has provided data to the academic and research community for advanced research. ODM helps support regulatory science submissions and review. Traceability and understanding of data is important to understanding regulatory science.

Panel: Gaps and Opportunities for Mobile Devices in Clinical Trials– Eric Bastings, Billy Dunn, Sean Khozin, Tim Marjenin (FDA), Maria Isaac (EMA), and Yoshiko Komuro (PMDA) – Moderated by Johan Luthman (Eisai)

[Panel Questions LINK]

Topics discussed included the importance of creating a standardized lexicon, clinical validations in CDER and CBER adding in clinical meaningfulness, the importance of data standardization through partnership with CDISC, and the proprietary nature of algorithms of devices and how the FDA will utilize them in a submission. Challenges related to understanding what devices are actually measuring and the evaluation of devices by regulatory agencies were discussed. The need for real-world evidence was raised to help understand device performance. It was suggested for companies to initially gain understanding of

performance in a smaller environment like a clinical trial and then during a second stage, use a wider population. Sponsors were encouraged to demystify the use of biosensors as the field grows to passive data collection tools like "implantables" and patches. An additional challenge to standardization is the variety of devices existing in the market.

SESSION II: PROGRESS IN THE QUALIFICATION OF BIOMARKERS

AD Hippocampal Volume Team – Steps Enabling a Qualification Package – Klaus Romero

[Presentation LINK]

Theme: CAMD will develop a quantitative disease progression model to assess the potential added value of intracranial adjusted volume (ICV) volumetric MRI (vMRI) as an enrichment biomarker for MCI, compared to standard, baseline *status quo* assessments. If successful, the team will submit a qualification package to the FDA for Hippocampal Volume as a prognostic biomarker for MCI studies of AD.

Klaus Romero, MD, Critical Path Institute, explained the process of standardizing data and performing analyses to create drug development tools, specifically CAMD's AD Hippocampal Volume (HV) Team's qualification work on HV as an enrichment biomarker. Utilizing a volumetric measure, CAMD will develop a model that allows sponsors to determine trial-specific cut-off points. Dr. Romero reviewed the proposed context-of-use (COU), the three data sets, ADNI-1, ADNI-2 and InDDEx, to be used to develop the analyses, and explained how the model will be utilized. The tool will be able to run simulations of varying progression rates, using information with model-based cut-off points. Imaging data are being analyzed and the results will be integrated into the datamart to create the Statistical Analysis Plan to be utilized in the qualification submission to the FDA.

The IDEAS Study – PET Imaging Update – James Hendrix

[Presentation LINK]

Theme: The Alzheimer's Association is conducting the IDEAS study to alter the reimbursement decision for PET imaging, allowing patients to utilize PET to receive better treatment options.

Jim Hendrix, PhD, Alzheimer's Association (AA), described the IDEAS study. The goal of the study is to have Centers for Medicare & Medicaid (CMS) change the reimbursement decision for PET imaging. IDEAS is an open-label longitudinal cohort study which aims to identify if there is a change in a patient's medical plan based on the diagnostic clarity provided by a PET scan. The study requires a case report form to be completed before a PET scan and after to show pre- and post-scan differences. The hope is for patients to receive the proper care and support to prevent hospitalizations and emergency room visits. Diagnostic clarity will allow the development of a better care plan and will provide better outcomes for patients. Despite amyloid PET not diagnosing Alzheimer's disease (AD), a negative brain amyloid PET result indicates the cause of a patient's symptoms is unlikely to be AD - allowing for a specified plan. The study launched in February 2016 and has to date completed 3,800 PET scans at 380 clinics and 268 PET centers. The goal is to complete 18,000 PET scans within two to three years. This study will also provide a wealth of data for additional research studies in the future.

CSF Biomarker Team – Refocusing on Low Hanging Fruit – Mary Savage

[Presentation LINK]

Theme: CAMD has refocused the Context-of-Use (COU) for the CSF biomarker team due to a lack of available data for the initially pursued qualification, and now seeks to provide an alternative approach to for patient exclusion, when PET imaging is not viable.

Mary Savage, PhD, Merck, explained the refocus of the qualification approach for the CSF Biomarker team. The new COU focuses on advancing through the formal regulatory process the use of CSF $A\beta_{42}$, or a composite of CSF analytes, for their concordance to amyloid PET to measure amyloid in the brain of those with cognitive impairment as an alternative approach when PET is not available. Dr. Savage provided an overview of the regulatory history achieved by this team, receiving regulatory encouragement with a Letter of Support in 2015 from FDA. The team is currently in the data gathering stage and will work towards a regulatory pathway.

Panel: Biomarker Qualifications – Where should AD focus? – Shashi Amur (FDA), James Hendrix (Alzheimer's Association), Mary Savage (Merck), and Derek Hill (IXICO) – Moderated by Richard Meibach (Novartis)

The panel discussed qualification efforts, the use of stratification and enrichment, and the difference between program qualification and sponsorship. Dr. Amur suggested reaching out to the regulatory division for the CSF submission and to send an updated Letter of Intent to help the project team progress faster. The FDA will be holding an Analytics Biomarker Workshop in 2017 to discuss future plans. The decision on whether to pursue a qualification is based on general use, public disclosure, multiple inputs, data gathering and whether the tool may be used by all members of the scientific community. It was agreed that modeling demonstrates biomarker performance and assists in clinical trial development and biomarker qualification efforts. The panel discussed whether the main obstacle to sharing data was privacy or cost. Jim Hendrix, Alzheimer's Association, admitted the challenge to find donors that will put the money toward de-identifying data. The panel noted that biomarkers for any use may be discussed with the review division, and the Agency is prepared to discuss novel and innovative issues.

SESSION III: WORKING ACROSS ECO-SYSTEMS: LESSONS LEARNED

Wearable Devices in Parkinson's Disease Research – Lauren Bataille

[Presentation LINK]

Theme: The Michael J. Fox Foundation (MJFF) is integrating wearable technology into clinical trials and patient care to begin data collection to for biomarker qualification.

Lauren Bataille, MS, (MJFF), explained how they are integrating wearable technology in research and patient care. Working with Intel, MJFF uses wearables to collect movement data outside of clinical trials. This allows for the continuous collection and monitoring of health data through the *Fox Insight Wear* application. MJFF utilizes the application to collect data, creates algorithms to measure data and ultimately will make data available to the community. Real-time analytics inform patients of activity-level, nighttime movement, and tremors. Patients were engaged during the development process; over ten versions of the application have been created based on feedback. Mrs. Bataille provided an overview of two longitudinal studies that are currently in process, Fox Insight and Parkinson@home. The data received

from these studies will be reviewed to determine potential biomarkers. MJFF's goal is to promote data sharing and put an initiative into place to provide curated/harmonized data to researchers.

Challenges to GCP Compliant Deployment of Biosensors in Cognitively Impaired Populations – Derek Hill

[Presentation LINK]

Theme: IXICO is currently conducting two case studies utilizing devices to help understand concordance of wearables with more traditional outcome methodology.

Derek Hill, PhD, IXICO, noted the work being done with biosensors applying a regulatory compliance tool for clinical trials. Specifically, IXICO is focused on diseases of the brain. Challenges exist with a more vulnerable population of the cognitively impaired. Two case studies are currently in progress utilizing devices which provide the ability to monitor in real-time what the patient is doing. However, concern was expressed regarding the need for data validation and clarity on knowing if a change of sensor measurement is due to the subject's condition instead of a specific, condition-agnostic input. Dr. Hill expressed a need to communicate with regulatory agencies earlier in the development process to ensure the regulatory point-of-view is incorporated. A key deliverable of IXICO's study will be the comparison of data from wearables that assess sleep, patient diaries, and polysomnography to understand their concordance.

Deep Phenotyping of AD Patients – Modeling Real World Evidence – John Gallacher

[Presentation LINK]

Theme: ROADMAP is a collaborative data environment for the global community.

John Gallacher, PhD, Oxford University, described the importance of working collaboratively across the globe and how most data sharing is operating in a relatively immature environment due to the lack of a coordinated approach. Technology already exists and ROADMAP is attempting to bring data and technology together. ROADMAP has established a framework that will provide utility and resources from six countries with two million people within cohorts. The initiative invites data owners to provide data for curation within ROADMAP. Data becomes more valuable over time and the incentive to support ROADMAP is strong.

CTTI's Mobile in Clinical Trials Program: Opportunities for Transforming the Clinical Trials Enterprise through the Appropriate Use of Mobile Technology – Jennifer Goldsack

[Presentation LINK]

Theme: CTTI is utilizing a multi-stakeholder approve to develop and drive practices for increased efficiency in clinical trials.

Jennifer Goldsack, MA, MBA, CTTI, discussed the Clinical Trials Transformation Initiative's (CTTI) public-private partnership and how its success is based on the multi-stakeholder approach with over 80 members. The mission of CTTI is to develop and drive practices to increase efficiency in clinical trials. Ms. Goldsack discussed four main projects working in the mobile devices space. Challenges include using mobile technology appropriately without creating additional inefficiencies, the potential risk of "boiling the ocean", and the need for collaboration. It is necessary to meet with key experts and stakeholders to determine real and perceived barriers in the field in order to progress.

Panel: Global Synergies– Lauren Bataille (MJFF), Derek Hill (IXICO), John Gallacher (Oxford University), and Jennifer Goldsack (CTTI) – Moderated by Dan Karlin (Pfizer)

The panel discussed the importance of collaboration and identification of opportunities for alignment. Benefits of standardizing best practices, data sharing and expertise will enable the community to create an environment where individuals are working for mutual advantage. The panel agreed on the importance of understanding and being aware of what other groups are focusing on and communicating earlier regarding successes and failures. There is a need for industry to integrate devices in an exploratory manner in clinical trials to gather data. A controlled approach in trials will assist with the larger goal to have passive measurement devices in homes. A request was made for sponsors to focus on getting more diverse groups of subjects in studies to the attempt to eliminate the lack of data for specific social-economic and racial groups.

Closing – Stephen Arnerić

[Presentation LINK]

Dr. Arnerić reminded the group every 66 seconds another individual in the US is diagnosed with Alzheimer disease (that is more than thirty-nine thousand people each month: http://www.alz.org/facts/) and it is paramount to work toward a cure through a more concerted effort. There is a need for more data sharing, the collection of real-world evidence, application of digital drug development tools for monitoring, and the need to understand information in the context of daily living. This is a global ecosystem that needs to leverage information across efforts, to discover strengths and to be a forum for data sharing, to find a cure.