Drug Development Tools for Kidney Disease

C-Path Overview

CRITICAL PATH INSTITUTE
a decade of excellence

10 YEARS

Dr. Martha Brumfield
Critical Path Institute

Topics

DDT-KD Consortium

- History of C-Path, What We Do and How We Do It
- What DDT-KD Consortium Can Do and What It Will Not Do
- C-Path Experience with Data Sharing and Aggregation
  - Example in Alzheimer's Disease
  - Example in Polycystic Kidney Disease
- C-Path Track Record

C-Path Mission

DDT-KD Consortium

- The Critical Path Institute is a catalyst in the development of tools to advance medical innovation and regulatory science, accelerating the path to a healthier world. We achieve this by leading teams that share data, knowledge, and expertise, resulting in sound, consensus-based science.

Critical Path Initiative

DDT-KD Consortium

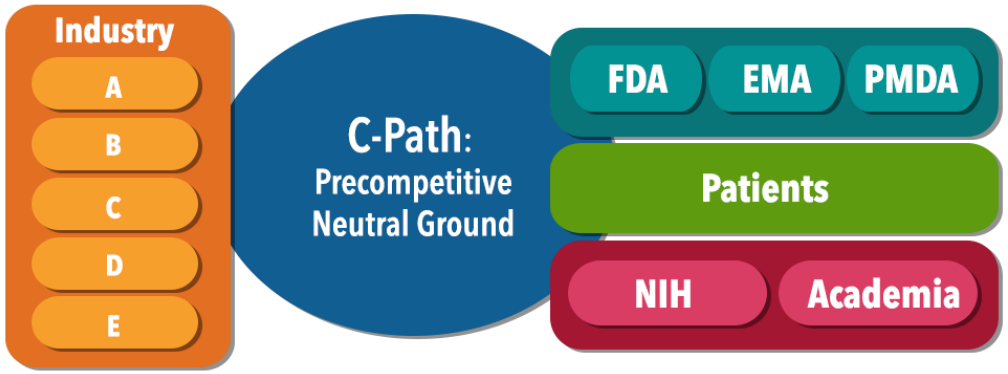
Independent 501(c)3 founded in 2005 "… to foster development of new evaluation tools to inform medical product development"

Memorandum of Understanding created between the FDA and C-Path in 2005

C-Path: A Public Private Partnership

DDT-KD Consortium

- Act as a trusted, neutral third party
- Convene scientific consortia of industry, academia, and government for sharing of data/expertise
  - ✓ The best science
  - ✓ The broadest experience
  - ✓ Active consensus building
  - ✓ Shared risk and costs



- Enable iterative EMA/FDA/PMDA participation in developing new methods to assess the safety and efficacy of medical products

- Official regulatory endorsement of novel methodologies and drug development tools

C-Path Core Competencies

DDT-KD Consortium

- Regulatory qualification of preclinical and clinical biomarkers for safety, efficacy, and trial enrichment
- Comprehensive modeling & simulation programs
- Novel *in vitro* tools to expedite proof-of-concept
- Outcome assessment instrument development
- Clinical data standards development
- Secure data management, standardization, curation, database development
- Forming collaborative ventures across organizations (e.g., IMI, FNIH)

C-Path Consortia – September 2015

CRITICAL PATH INSTITUTE

Eleven global consortia collaborating with 1,300+ scientists and 61 companies

CAMD — **Coalition Against Major Diseases**
Focusing on diseases of the brain

CFAST — **Coalition For Accelerating Standards and Therapies**
Data standards

CPTR — **Critical Path to TB Drug Regimens**
Testing tuberculosis drug combinations

D-RSC — **The Duchenne Regulatory Sciences Consortium**
Duchenne Muscular Dystrophy

INC — **International Neonatal Consortium**
Neonatal clinical trials

CRITICAL PATH INSTITUTE MS — **Multiple Sclerosis Outcome Assessments Consortium**
Measuring drug effectiveness in MS

PKD CONSORTIUM — **Polycystic Kidney Disease Outcomes Consortium**
New imaging biomarkers

PRO CONSORTIUM — **Patient-Reported Outcome Consortium**
Measuring drug effectiveness

ePRO CONSORTIUM — **Electronic Patient-Reported Outcome Consortium**
Electronic capture of drug effectiveness

PSTC — **Predictive Safety Testing Consortium**
Drug safety

PTC — **Pediatric Trials Consortium**
Developing effective therapies for children

- ✓ Biomarkers
- ✓ Clinical outcome assessment instruments
- ✓ Clinical trial simulation tools
- ✓ Data standards
- ✓ In vitro tools

C-Path Collaborators

DDT-KD Consortium

Industry

- AbbVie
- Acorda Therapeutics
- Actelion Pharmaceuticals
- Allergan
- Almac
- Amgen
- AstraZeneca
- Biogen Idec
- Boehringer Ingelheim
- Bracket
- Bristol-Myers Squibb
- Celgene
- Cepheid
- CRF Health
- Daiichi Sanyko
- Edetek
- Eisai
- Eli Lilly and Company
- EMD Serono
- Ephibian
- ERT
- Exco InTouch
- Forest Laboratories, Inc.
- GE Healthcare
- Genentech
- Genzyme
- GlaxoSmithKline
- Hoffmann-La Roche, Inc.
- Horizon Pharma
- ICON
- Ironwood Pharmaceuticals
- Johnson & Johnson Pharmaceutical Research & Development, LLC
- Medidata Solutions
- Merck and Co., Inc.
- Meso Scale Discovery
- **Millennium: The Takeda Oncology Company**
- **Mitsubishi Tanabe Pharmaceutical Commercialization, Inc.**
- **Pharsight/Certara**
- **Tanabe Pharma**
- Novartis
- Novo Nordisk
- Oracle
- Otsuka Pharmaceutical
- Pfizer
- PMDA Pharmaceuticals
- PHT
- Sanofi
- STC
- Shire
- Sunovion Pharmaceuticals
- TAG
- **Takeda**
- Teva Pharmaceuticals
- UCB
- Vertex

Nonprofit Research Organizations

- Alzheimer's Association
- Alzheimer's Drug Discovery Foundation
- Alzheimer's Research UK
- Bill & Melinda Gates Foundation
- CDISC
- Engelberg Center for Health Care Reform
- EDCTP
- Flinn Foundation
- Foundation for National Institutes of Health
- National MS Society
- Parkinson's UK
- PKD Foundation
- Reagan-Udall Foundation
- Science Foundation Arizona
- SRI International
- Stop TB Partnership
- TB Alliance
- US Against Alzheimer's

Government and Regulatory Agencies

- Centers for Disease Control and Prevention
- European Medicines Agency
- Innovative Medicines Initiative
- International Genomics Consortium
- National Institute of Allergy and Infectious Diseases
- National Institute of Diabetes and Digestive and Kidney Diseases
- National Institutes of Health
- National Institute of Neurological Disorders and Stroke
- U.S. Food and Drug Administration
- World Health Organization

Academic Institutions

- The University of Arizona
- Arizona State University
- Baylor University
- University of California San Francisco
- University of Colorado-Denver
- Emory University
- University of Florida
- Johns Hopkins
- Mayo Clinic
- University of Texas Southwestern Medical Center
- Tufts University

Why Form the DDT-KD Consortium?

DDT-KD Consortium

- Bring together industry, regulators, and academic experts in a pre-competitive collaboration, to share knowledge, data, etc.
- Include patient groups and disease foundations as active participants
- Prioritize areas of initial focus and specific objectives via consensus
- Develop a detailed research plan with specific timelines and deliverables early in the process toward a regulatory objective

How it happens:

- Form a consortium with defined governance structure; scientific and project management leadership support, provide data platform to support needs of consortium, embed processes to drive project forward and lead to meaningful regulatory science deliverables

Ultimate goal is to develop biomarkers that help to de-risk decisions during drug development and regulatory review

What We Will Not Do

DDT-KD Consortium

- Biomarker discovery – rather, we focus on biomarker development when a biomarker is close enough to being "regulatory ready"

- Only write papers and publish – rather, we aim for regulatory focused documents to push toward our deliverable to qualify appropriate, evidence-based biomarkers and then we publish accordingly

- Fund independent research – rather, we work in a collaborative manner, being good stewards of monetary and in-kind contributions to achieve clearly stated objectives to qualify biomarkers

C-Path Policies for Handling of Clinical Data

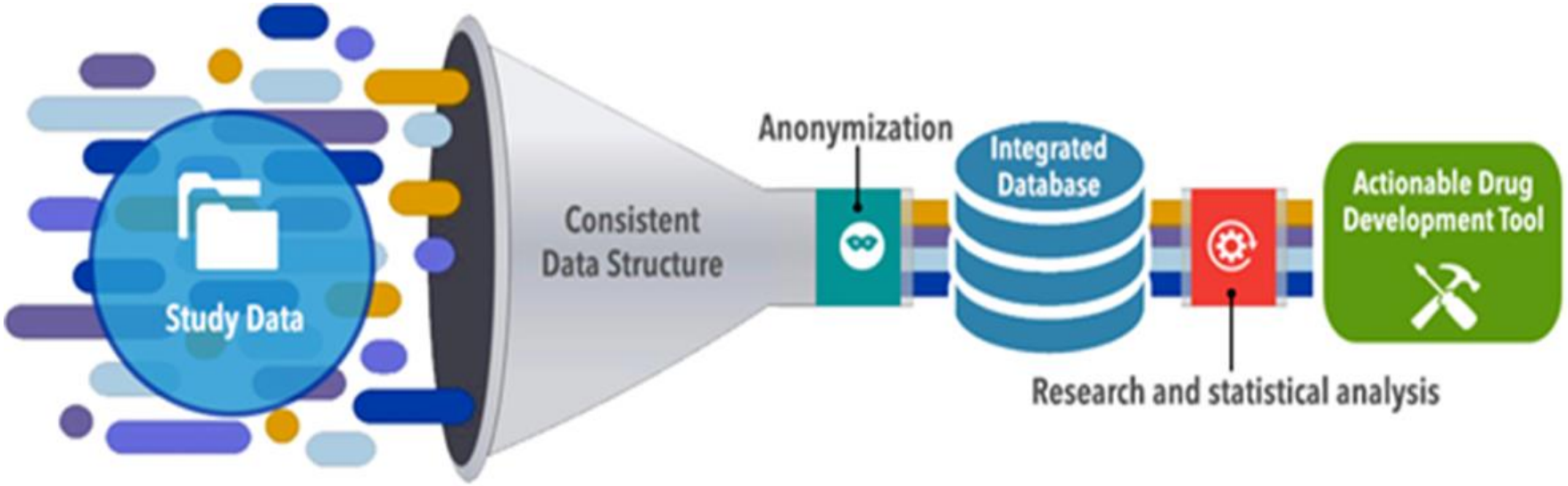
DDT-KD Consortium

Key guiding principles:

- We operate as a responsible steward for the clinical data contributed to, used by C-Path, and shared by C-Path
- We will abide by all regulations applicable to C-Path that govern the use of clinical data
- We will always strive to do the right thing
  – for patients, for our members, funders, regulators, and C-Path
- We will always seek to improve the way we work with clinical data, associated research data, and C-Path business data

C-Path Data Mapping and Integration Process

DDT-KD Consortium



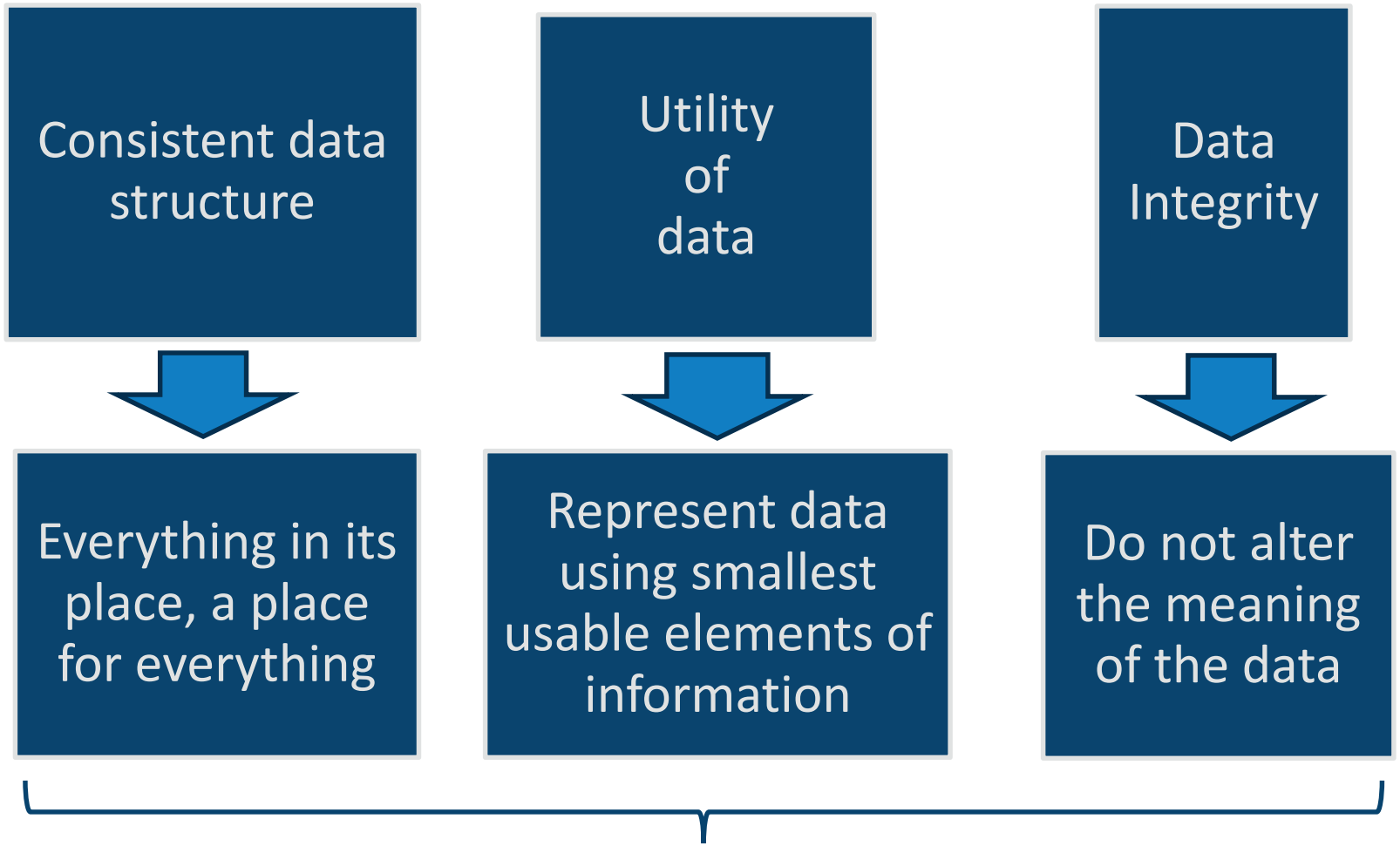
Data as contributed

Master Standardized Datasets

Analysis Datasets

Data Sharing – Key Success Factors

DDT-KD Consortium



CAMD Alzheimer's Disease Clinical Trial Database

DDT-KD Consortium

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C-PATH ONLINE DATA REPOSITORY

CODR Version: v0.14.3 Database Version: 7.1

CRITICAL PATH INSTITUTE

Report Library | Data Access | Batches | Resources | Admin | eaviles | 0 Mail | CAMD | Logout

Saved Reports | New Report | Manage Report Categories | Manage Data Sources

Batch Job Status — Batch job not currently running | Run Job

Abbott A Promise for Life

AstraZeneca

gsk GlaxoSmithKline

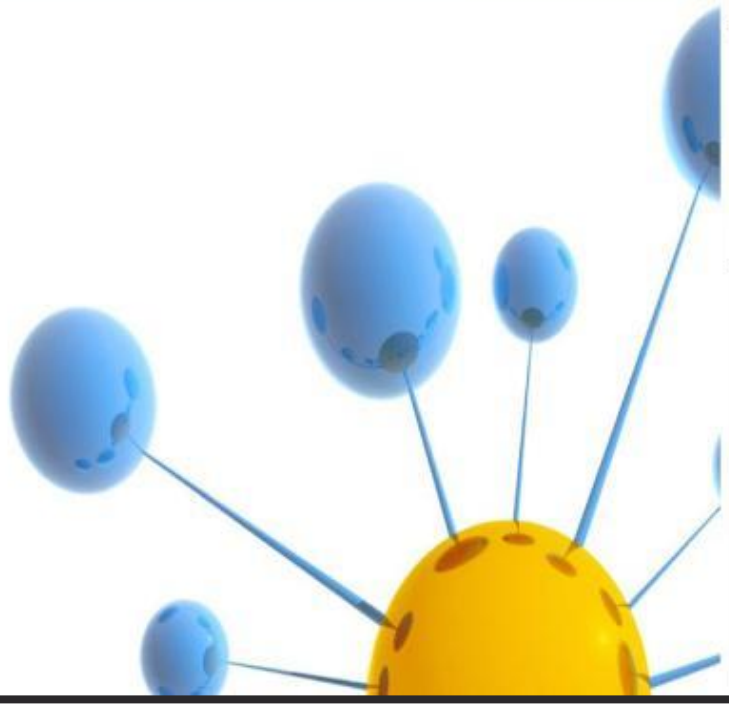
Johnson & Johnson

Pfizer

sanofi aventis

The CAMD database is currently composed of the placebo arm data from clinical trials conducted by the member companies. These trials include drugs on the market or at different stages of development including termination.

Nine companies
24 trials
~6500 Patients total
Data first had to be remapped in order to be pooled

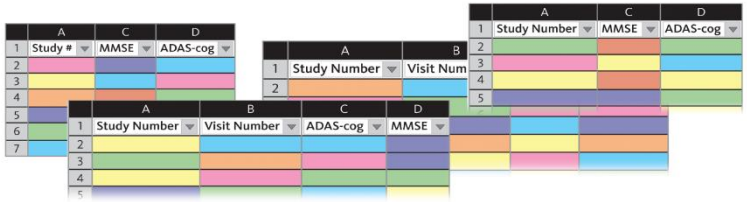


Value of Data Sharing, Standards, and Pooling

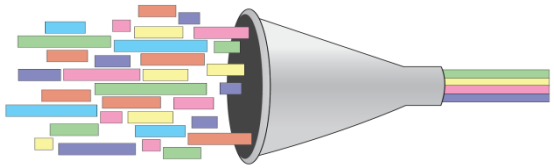
DDT-KD Consortium

Start Point

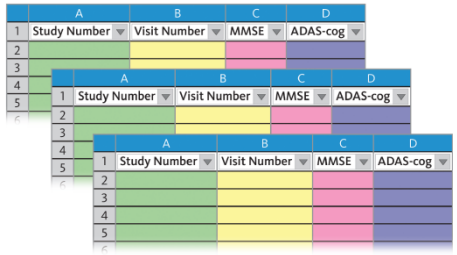
- Nine member companies agreed to share data from 24 Alzheimer's disease (AD) trials
- The data were not in a common format
- All data were remapped to the CDISC AD standard and pooled



Disparate Legacy Data



CDISC Data Standards



Integrated Data

Result

- A new clinical trial simulation tool was created and has been the first model endorsed by the FDA and EMA
- Researchers utilizing database to advance research

- Integrated database
- 24 studies, >6500 patients
- Database open to >200 qualified research teams in 35 countries

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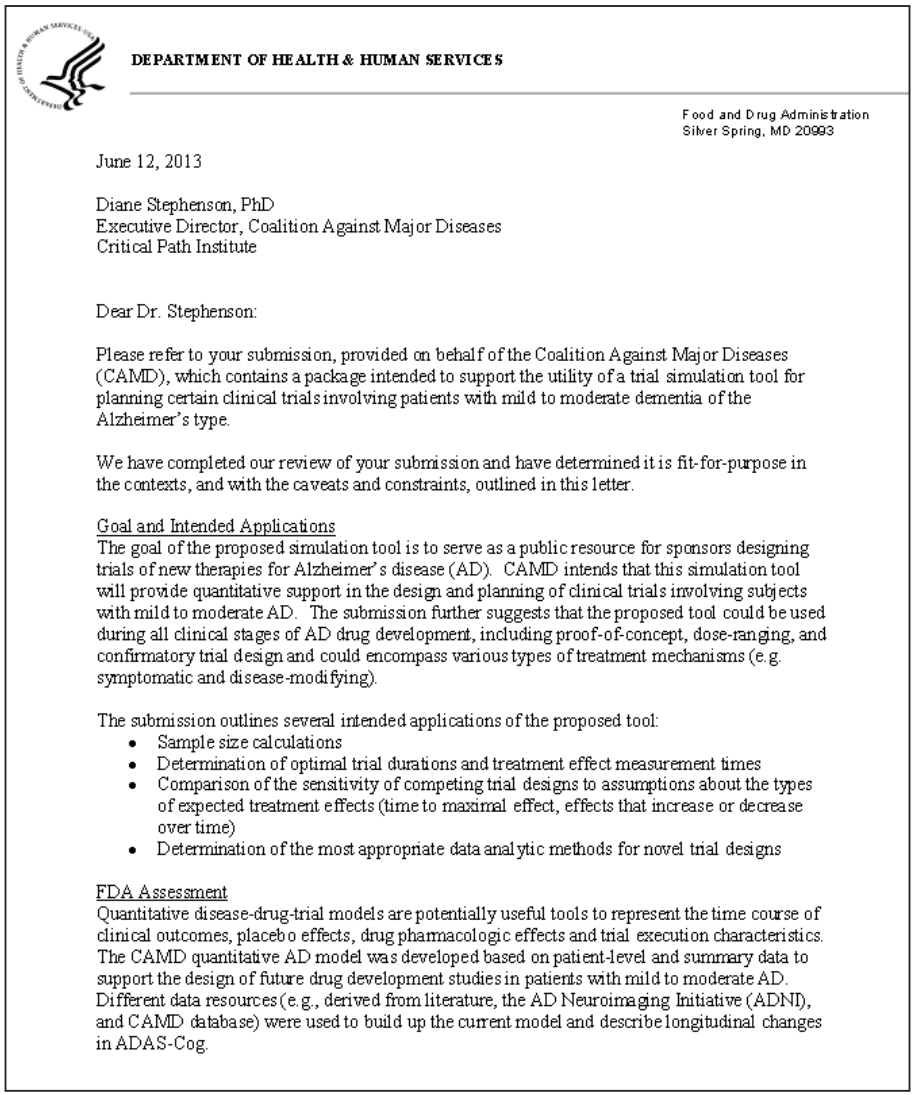
C-Path Tool Deliverables
CAMD Modeling Decisions -2013

DDT-KD Consortium



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

June 12, 2013

Diane Stephenson, PhD
Executive Director, Coalition Against Major Diseases
Critical Path Institute

Dear Dr. Stephenson:

Please refer to your submission, provided on behalf of the Coalition Against Major Diseases (CAMD), which contains a package intended to support the utility of a trial simulation tool for planning certain clinical trials involving patients with mild to moderate dementia of the Alzheimer's type.

We have completed our review of your submission and have determined it is fit-for-purpose in the contexts, and with the caveats and constraints, outlined in this letter.

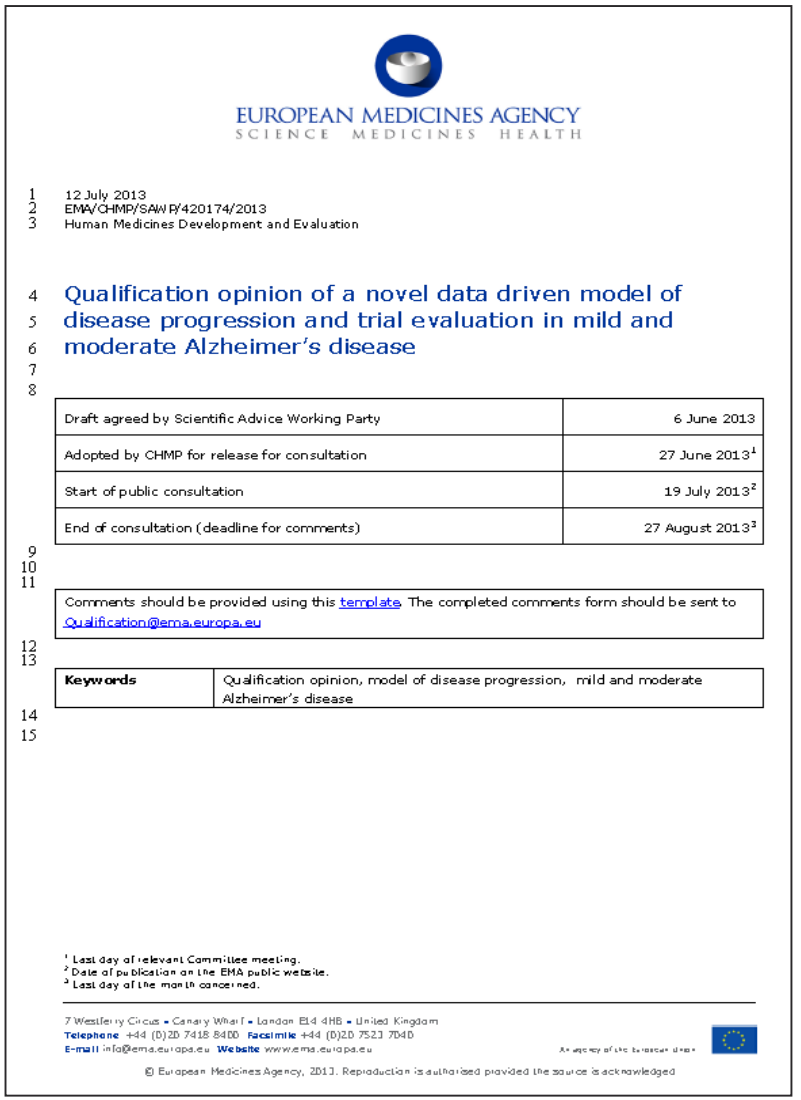
Goal and Intended Applications
The goal of the proposed simulation tool is to serve as a public resource for sponsors designing trials of new therapies for Alzheimer's disease (AD). CAMD intends that this simulation tool will provide quantitative support in the design and planning of clinical trials involving subjects with mild to moderate AD. The submission further suggests that the proposed tool could be used during all clinical stages of AD drug development, including proof-of-concept, dose-ranging, and confirmatory trial design and could encompass various types of treatment mechanisms (e.g. symptomatic and disease-modifying).

The submission outlines several intended applications of the proposed tool:

- Sample size calculations
- Determination of optimal trial durations and treatment effect measurement times
- Comparison of the sensitivity of competing trial designs to assumptions about the types of expected treatment effects (time to maximal effect, effects that increase or decrease over time)
- Determination of the most appropriate data analytic methods for novel trial designs

FDA Assessment
Quantitative disease-drug-trial models are potentially useful tools to represent the time course of clinical outcomes, placebo effects, drug pharmacologic effects and trial execution characteristics. The CAMD quantitative AD model was developed based on patient-level and summary data to support the design of future drug development studies in patients with mild to moderate AD. Different data resources (e.g., derived from literature, the AD Neuroimaging Initiative (ADNI), and CAMD database) were used to build up the current model and describe longitudinal changes in ADAS-Cog.

FDA fit-for-purpose decision on CAMD CTS tool. 2013



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

12 July 2013
EMA/CHMP/SAWP/420174/2013
Human Medicines Development and Evaluation

Qualification opinion of a novel data driven model of disease progression and trial evaluation in mild and moderate Alzheimer's disease

Draft agreed by Scientific Advice Working Party	6 June 2013
Adopted by CHMP for release for consultation	27 June 2013[1]
Start of public consultation	19 July 2013[2]
End of consultation (deadline for comments)	27 August 2013[3]

Comments should be provided using this template. The completed comments form should be sent to Qualification@ema.europa.eu

Keywords	Qualification opinion, model of disease progression, mild and moderate Alzheimer's disease

[1] Last day of relevant Committee meeting.
[2] Date of publication on the EMA public website.
[3] Last day of the month concerned.

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An agency of the European Union

EMA qualification opinion on CAMD CTS tool. 2013

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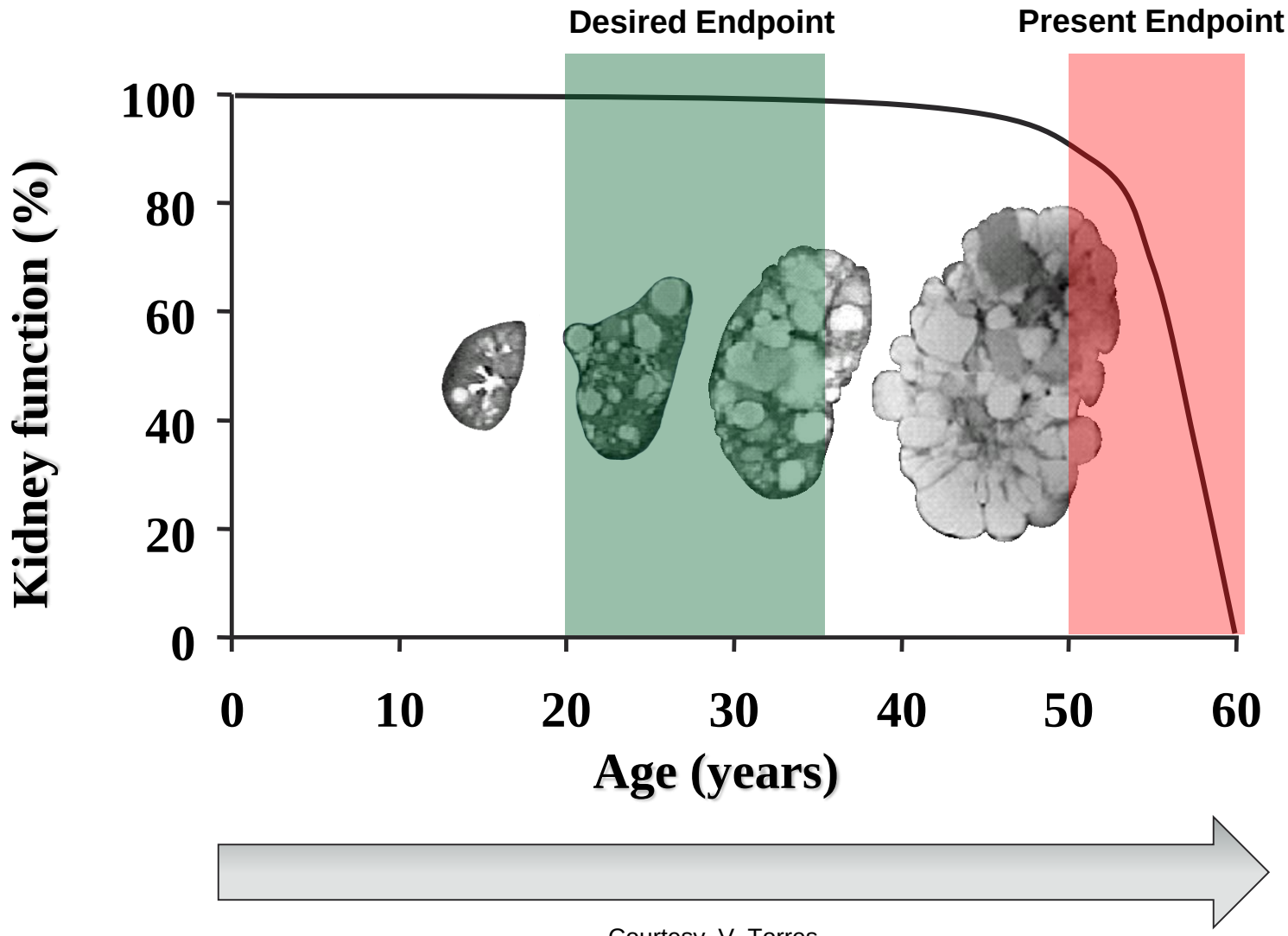
Changing the Paradigm for Measuring Disease Progression of PKD

DDT-KD Consortium



Courtesy V. Torres

C-Path's Polycystic Kidney Disease Consortium

DDT-KD Consortium

Mission: Develop tools to create treatments for patients with PKD

Project: Qualification of total kidney volume as a prognostic biomarker for PKD

Regulatory strategy: Qualification

Phase 1 (2009 – 2011): Data standards development, data acquisition, curation, and mapping	**Phase 2 (2011 – 2012):** Data analysis and modeling including initial briefing package and BQRT meetings
Tufts (Co-Director, scientific leadership)	**Tufts** (Co-Director, scientific leadership)
Mayo; Emory Univ.; UC Denver (expertise, data, & remapping)	**Mayo; Emory Univ.; UC Denver** (expertise)
PKD foundation (funding)	**PKD foundation** (funding)
CDISC (data standards development)	
pharma (funding; expertise)	**pharma** (funding; expertise)
NIH (data and expertise)	**Pharsight** (data analysis and modeling)
FDA (advice)	**FDA, EMA** (consultation/advice)

C-Path's Polycystic Kidney Disease Consortium

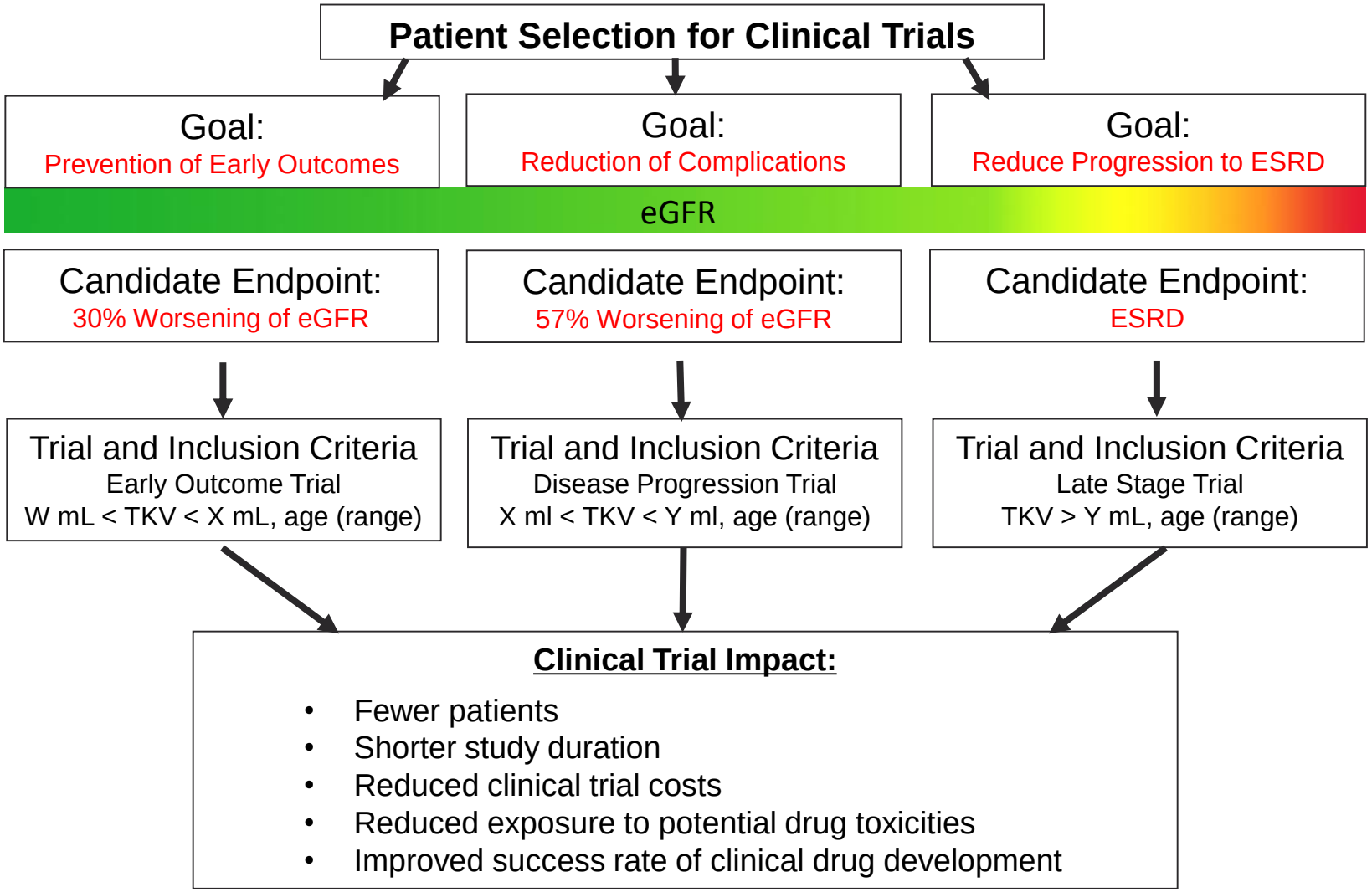
DDT-KD Consortium

Mission: Develop tools to create treatments for patients with PKD
Project: Qualification of total kidney volume as a prognostic biomarker for PKD
Regulatory strategy: Qualification

Phase 1 (2009 – 2011): Data standards development, data acquisition, curation, and mapping	**Phase 2 (2011 – 2012):** Data analysis and modeling including initial briefing package and BQRT meetings	**Phase 3 (2012 – 2015):** Regulatory submission and refinement of the model; qualification decision
Tufts (Co-Director, scientific leadership)	**Tufts** (Co-Director, scientific leadership)	**Tufts** (Write and review packages)
Mayo; Emory Univ.; UC Denver (expertise, data, & remapping)	**Mayo; Emory Univ.; UC Denver** (expertise)	**Mayo; Emory Univ.; UC Denver** (Write and review packages)
PKD foundation (funding)	**PKD foundation** (funding)	**PKD foundation** (funding)
CDISC (data standards development)		
pharma (funding; expertise)	**pharma** (funding; expertise)	**pharma** (funding; review packages)
NIH (data and expertise)	**Pharsight** (data analysis and modeling)	**Pharsight** (writing and reviewing packages)
FDA (advice)	**FDA, EMA** (consultation/advice)	**FDA and EMA** (formal review) **Health Canada** (discussion)

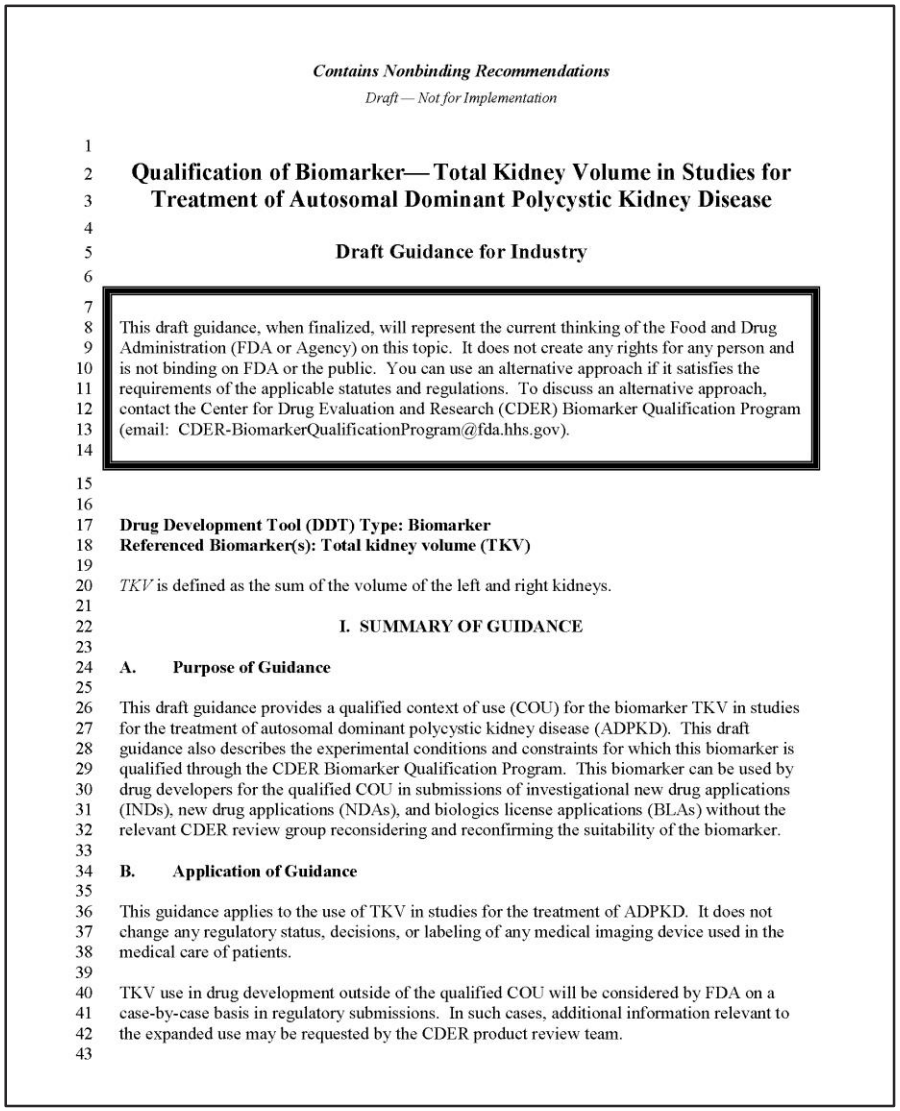
Example of a Decision Tree for Clinical Trial Enrichment

DDT-KD Consortium



PKDOC – FDA Qualification for TKV

DDT-KD Consortium



Contains Nonbinding Recommendations

Draft — Not for Implementation

Qualification of Biomarker—Total Kidney Volume in Studies for Treatment of Autosomal Dominant Polycystic Kidney Disease

Draft Guidance for Industry

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not create any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the Center for Drug Evaluation and Research (CDER) Biomarker Qualification Program (email: CDER-BiomarkerQualificationProgram@fda.hhs.gov).

Drug Development Tool (DDT) Type: Biomarker
Referenced Biomarker(s): Total kidney volume (TKV)

TKV is defined as the sum of the volume of the left and right kidneys.

I. SUMMARY OF GUIDANCE

A. Purpose of Guidance

This draft guidance provides a qualified context of use (COU) for the biomarker TKV in studies for the treatment of autosomal dominant polycystic kidney disease (ADPKD). This draft guidance also describes the experimental conditions and constraints for which this biomarker is qualified through the CDER Biomarker Qualification Program. This biomarker can be used by drug developers for the qualified COU in submissions of investigational new drug applications (INDs), new drug applications (NDAs), and biologics license applications (BLAs) without the relevant CDER review group reconsidering and reconfirming the suitability of the biomarker.

B. Application of Guidance

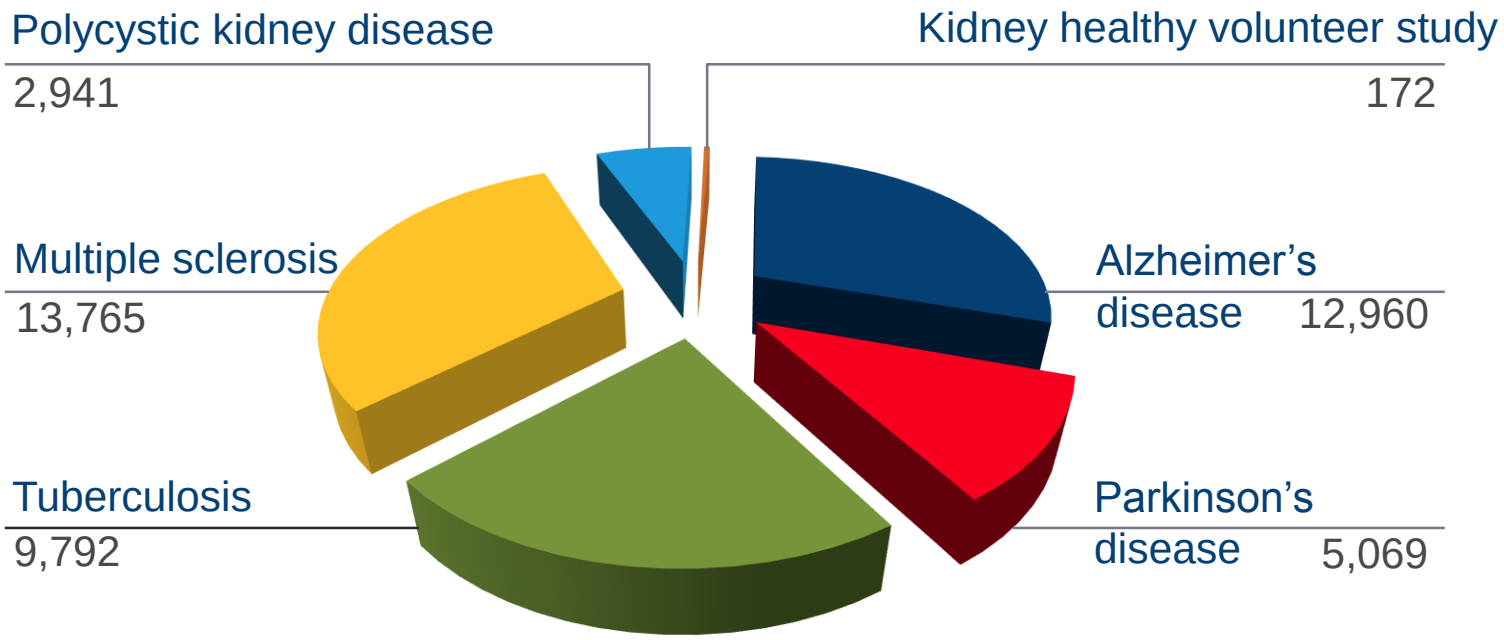
This guidance applies to the use of TKV in studies for the treatment of ADPKD. It does not change any regulatory status, decisions, or labeling of any medical imaging device used in the medical care of patients.

TKV use in drug development outside of the qualified COU will be considered by FDA on a case-by-case basis in regulatory submissions. In such cases, additional information relevant to the expanded use may be requested by the CDER product review team.

"draft guidance to C-Path's Polycystic Kidney Disease Outcomes Consortium (PKDOC) for total kidney volume (TKV) as a prognostic biomarker to select patients for clinical trials of new therapies for Autosomal Dominant Polycystic Kidney Disease (ADPKD). "

Clinical Data Contributions (To Date)

DDT-KD Consortium



78 studies totaling 44,699 subjects
Note: this does not include data housed external to C-Path for C-Path funded studies

Non-Clinical Data Contributions

95 studies, 5,047 subjects
(expansion to 75,000+ global patient isolates with CPTR ReSeqTB)

Key Success Factors for Data Sharing

DDT-KD Consortium

- Address Range of Objectives for Data Sharing
- Clear Quality Criteria
- Consistent and Transparent Data Process
- Maximize Data Utility Through Standardization
- Ongoing Curation, Validation and Reporting

C-Path DCA Attributes

DDT-KD Consortium

DATA CONTRIBUTION AGREEMENT PROTECTS PATIENTS, DATA HOST, AND CONTRIBUTORS

- A non-confidential description of the data being contributed
- Verification of Informed Consent review to allow sharing of data for secondary research as defined by regulations that govern in the location where the data is being held by the contributor
- Confirmation that the data being contributed is anonymized to the level appropriate for the contributing entity
- The scope of disclosure that is being permitted by the contributor
- Acknowledgement and understanding that C-Path will handle data with appropriate safeguards and security
- Appendices that provide registry information, a full description of anonymization requirements, etc.
- Ethical, cultural, social considerations to be factored in

C-Path DUA Attributes

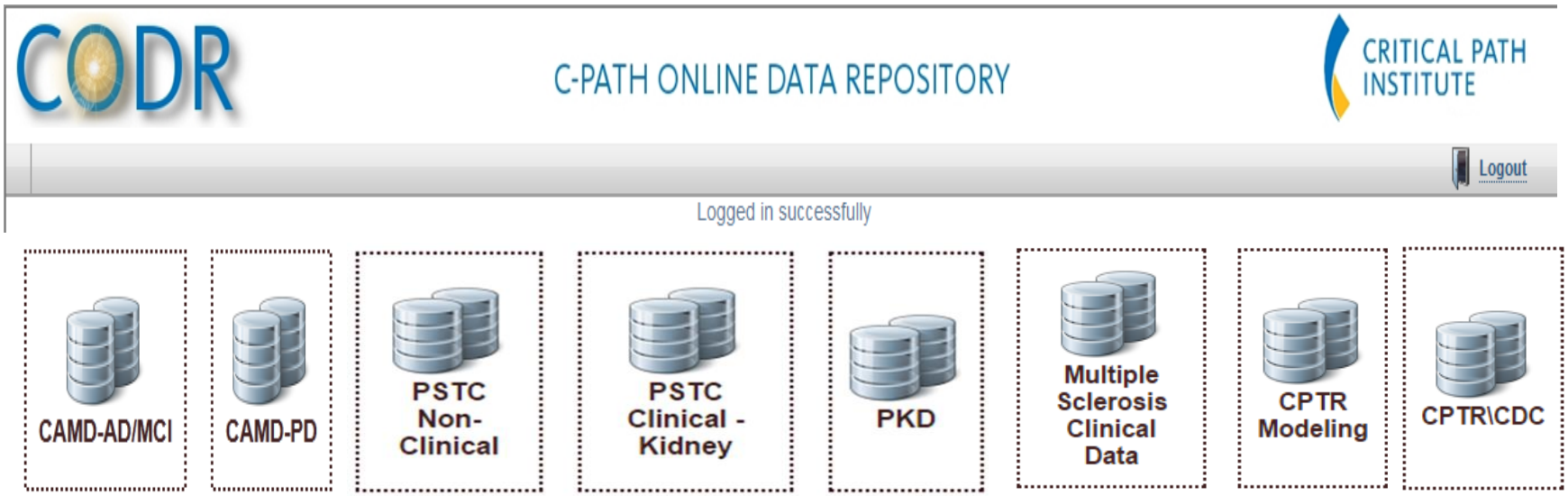
DDT-KD Consortium

DATA ACCESS VIA WEBSITE REQUIRES ACCEPTANCE OF DATA USE CRITERIA

- Verification of identity for access group or individual
- Agreement to use statement and non-disclosure beyond defined scope
- Compliance with rules and regulations
- Agreement to site source data platform in publication
- In some instances, submission of manuscripts prior to journal submission or notification of submission
- Exact provisions to be overseen by governance of this consortium

C-Path Online Data Repository

DDT-KD Consortium



C-Path Data Project Examples

CPTR: TB Modeling and Simulation Projects

CAMD: AD Clinical Trial Simulation Tool

PKD: Biomarker Qualification Project

MSOAC: New Outcome Assessment Instrument for MS

C-Path Accomplishments

DDT-KD Consortium

- ✓ First preclinical safety biomarkers (7) qualified by the FDA, EMA, and PMDA
- ✓ First imaging biomarker for trial enrichment qualified by the EMA (Alzheimer's disease) and first imaging biomarker for trial enrichment in Polycystic kidney disease qualified by FDA.
- ✓ First Clinical Data Interchange Standards Consortium (CDISC) therapeutic area data standard (Alzheimer's disease), and additional standards for TB, PD, PKD, MS, Influenza, Hep C, Schizophrenia, Dyslipidemia
- ✓ Unified CDISC database of Alzheimer's disease (AD) clinical trial information provided by multiple pharmaceutical companies
- ✓ First drug-disease-trial model for AD endorsed by the FDA & EMA
- ✓ First Drug Development Tool (DDT) for TB qualified by EMA and included in FDA Guidance for TB Drug Development- HFS-TB
- ✓ Letters of Support from EMA (2) and FDA (6) for two PSTC kidney biomarkers, one PKD biomarker, two AD biomarkers, one PD biomarker

EMA Qualifications of Novel Methodologies for Medicine Development

DDT-KD Consortium

C-Path Consortia have achieved four qualifications by the EMA:

- CPTR - *In-vitro* hollow fiber system model of tuberculosis (HFS-TB)
- CAMD - A novel, data-driven model of disease progression and trial evaluation in mild and moderate Alzheimer's disease
- CAMD - Low hippocampal volume (atrophy) by magnetic-resonance imaging for use in clinical trials for regulatory purpose in predementia stage of Alzheimer's disease
- PSTC - Final conclusions on the pilot joint European Medicines Agency/U.S. Food and Drug Administration VXDS experience on qualification of nephrotoxicity biomarkers

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000319.jsp&mid=WC0b01ac0580022bb0

FDA Letters of Support

DDT-KD Consortium

http://www.fda.gov/drugs/developmentapprovalprocess/ucm434382.htm

Issued Letters of Support

Submitter	Biomarkers	Area(s) for Further Evaluation	Issuance Date with Link to Letter of Support	Submitter Contact
Critical Path Institute's (C-Path) Predictive Safety Testing Consortium (PSTC), Nephrotoxicity Working Group (NWG)	Urinary Biomarkers: Osteopontin and Neutrophil Gelatinase-associated Lipocalin (NGAL)	Early Clinical Drug Development	8/20/2014: Letter of Support (PDF)	Refer to Predictive Safety Testing Consortium Web Site
C-Path, PSTC, Skeletal Muscle Working Group (SMWG)	Serum and Plasma Biomarkers: Myosin Light Chain 3 (Myl3), Skeletal Muscle Troponin I (sTNI), Fatty Acid Binding Protein 3 (FABP3), Creatine Kinase, Muscle Type (CK-M, the Homodimer CK-MM)	Early Clinical Drug Development	1/22/2015: Letter of Support (PDF)	Refer to Predictive Safety Testing Consortium Web Site
C-Path, Coalition Against Major Diseases Consortium (CAMD)	Cerebral Spinal Fluid (CSF) Analyte Biomarkers: Aβ1-42, Total tau, Phosphotau	Exploratory Prognostic Biomarkers for Enrichment in Early Stage Alzheimer's Disease Clinical Trials	2/26/2015: Letter of Support (PDF)	Refer to Coalition Against Major Diseases Web Site
C-Path, CAMD	Magnetic Resonance Imaging Biomarker: Low Baseline Hippocampal Volume	Exploratory Prognostic Biomarkers for Enrichment in Early Stage Alzheimer's Disease Clinical Trials	3/10/2015: Letter of Support (PDF)	Refer to Coalition Against Major Diseases Web Site
C-Path, CAMD	Molecular Neuroimaging Biomarker: Dopamine Transporter (DAT)	Exploratory Prognostic Biomarkers for Enrichment in Early Stage Parkinson's Disease Clinical Trials	3/16/2015: Letter of Support (PDF)	Refer to Coalition Against Major Diseases Web Site
C-Path, Polycystic Kidney Disease (PKD) Outcomes Consortium	MRI, Computerized Tomography (CT), or Ultrasound (US) Biomarker: Total Kidney Volume (TKV)	Exploratory Prognostic Biomarker for Enrichment in Autosomal Dominant Polycystic Kidney	4/23/2015: Letter of Support (PDF)	Refer to Polycystic Kidney Disease Outcomes Consortium Web Site

EMA Letters of Support

DDT-KD Consortium

C-Path consortia have received two Letters of Support issued by the EMA

- PSTC – Skeletal Muscle Injury Biomarkers
- PSTC – Translational Drug-induced Kidney Injury Biomarkers

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000319.jsp&mid=WC0b01ac0580022bb0