Model-Based Qualification of Biomarkers

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Critical Path Initiative (CPI)
Critical Path Institute (C-Path)

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
Application of Clinical Data Interchange Standards Consortium (CDISC) data standards

This illustrates the process of taking non-standardized data from individual studies, applying CDISC standards so all the data can be aggregated, and utilizing that fully integrated database to support the delivery of drug development tools.
## C-Path Consortia

Twelve global consortia collaborating with 1,450+ scientists and 84 organizations

<table>
<thead>
<tr>
<th>Consortium</th>
<th>Description</th>
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<tbody>
<tr>
<td>CAMD (Coalition Against Major Diseases)</td>
<td>Focusing on diseases of the brain</td>
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<tr>
<td>CFAST (Coalition For Accelerating Standards and Therapies)</td>
<td>Data standards</td>
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<tr>
<td>CPP (Critical Path for Parkinson’s Consortium)</td>
<td>Enabling clinical trials in Parkinson’s Disease</td>
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<td>CPTR (Critical Path to TB Drug Regimens)</td>
<td>Accelerating the development of TB drug regimens and diagnostics</td>
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<td>D-RSC (Duchenne Regulatory Science Consortium)</td>
<td>Duchenne Muscular Dystrophy</td>
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<td>INC (International Neonatal Consortium)</td>
<td>Neonatal clinical trials</td>
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<td>Multiple Sclerosis Outcome Assessments Consortium (MS)</td>
<td>Drug Effectiveness in MS</td>
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<td>PKD Consortium (Polycystic Kidney Disease Outcomes Consortium)</td>
<td>New imaging biomarker for PKD</td>
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<td>PRO Consortium (Patient-Reported Outcome Consortium)</td>
<td>Assessing treatment benefit</td>
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<td>ePRO Consortium (Electronic Patient-Reported Outcome Consortium)</td>
<td>Electronic capture of treatment benefit</td>
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<tr>
<td>PSTC (Predictive Safety Testing Consortium)</td>
<td>Drug safety</td>
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<tr>
<td>PTC (Pediatric Trials Consortium)</td>
<td>Developing effective therapies for children</td>
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</tbody>
</table>

- Biomarkers
- Clinical outcome assessment instruments
- Clinical trial simulation tools
- Data standards
- In vitro tools
1. Regulatory Process: Context-of-Use
   • Context of use: manner and purpose of use of the drug development tool

2. Drug Development Tool: Biomarker-Disease Model
   • **Biomarker** (biochemical marker, imaging biomarker...)
     • susceptibility/risk biomarker
     • diagnostic biomarker
     • monitoring biomarker
     • prognostic biomarker
     • predictive biomarker
     • pharmacodynamic/response biomarker
     • safety biomarker
   • **Disease** (e.g., worsening, LFT, adverse events, transplant, mortality...)
Autosomal Dominant Polycystic Kidney Disease (ADPKD)

• Hereditary systemic disorder

• Bilateral kidney cysts leading to marked expansion of total kidney volume (TKV)

• Progressive reduction in kidney function
  • Accounts for 8-10% patients on dialysis

• Direct medical costs exceed $1.5 billion/year

Courtesy J. Grantham
Changing The Paradigm For Predicting and Measuring Disease Progression

Desired future endpoint

Concentrating defect, Hypertension, Proteinuria

Present endpoint

Pain, Hematuria, Stones, Infections

Courtesy V. Torres
Development of Quantitative Tools to Support Biomarker Qualification

1. Fundamental component of biomarker-disease models
   - Biomarker-disease models are drug-independent
   - Can be customized by introducing a drug-biomarker
Polycystic Kidney Disease Outcomes Consortium: The Need

- **Autosomal Dominant Polycystic Kidney Disease (ADPKD)** is a debilitating genetic disease affecting more than 600,000 Americans and 12 million people worldwide and for which there is currently no known cure or effective treatment.
- **Critical need for a biomarker** that will predict disease progression at an earlier stage when patients may be more likely to respond to new therapies.

A total of 2355 patients with TKV measurement available in the database.

Observational data from the following five sources has been aggregated (CDISC SDTM):
- University of Colorado – Denver
- Mayo Clinic
- Emory University
- Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease 1 (CRISP1)
- Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease 2 (CRISP2)
Challenges

• This effort involved simultaneously modeling
  • Biomarker trajectory (longitudinal time-varying covariates)
  • Disease Endpoint, hazard function (time-to-event)

• Joint modeling is considered as the gold standard method for assessing the effect of longitudinal time-varying covariates in a time-to-event analysis of clinical endpoint (Sweeting et al., 2011; Tsiatis, & Davidian, 2004)
Clinical Trial Planning Example
30% Worsening of eGFR

<table>
<thead>
<tr>
<th>Age</th>
<th>TKV</th>
<th>Follow-Up Period</th>
<th>1-Probability of 30% Worsening of eGFR</th>
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<tr>
<td>Baseline age=30yrs</td>
<td>Baseline TKV 1.7L</td>
<td>1</td>
<td>Median</td>
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<td>10</td>
<td>Median</td>
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Follow-Up (Years)

Predicted Probability of 30% worsening of eGFR at baseline
Polycystic Kidney Disease Outcomes Consortium: Regulatory Sciences Pipeline

### Polycystic Kidney Disease

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<tr>
<th>DRUG DEVELOPMENT TOOLS</th>
<th>FEASIBILITY</th>
<th>SCOPING</th>
<th>RESEARCH</th>
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<td>Imaging of Kidney Volume</td>
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- **U.S. Food & Drug Administration (FDA)**
- **European Medicines Agency (EMA)**

Qualified prognostic enrichment biomarker
Application: Trial Enrichment

**Guidance for Industry**

**Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products**

**DRAFT GUIDANCE**

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the Federal Register of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5650 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the Federal Register.

For questions regarding this draft document contact (CDER) Robert Temple, 301-796-2270, (CBER) Office of Communication, Outreach and Development, 301- 827-1800, or (CDRH) Robert L. Becker, Jr., 301-796-6211.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)
December 2012
Clinical Medical

**Trial Enrichment**

- Improve the likelihood of clinical trial success by identifying a patient population that can discriminate between active and inactive drug treatment.
- Calculations may be performed to determine the sample size for
  - specific clinical cut-offs
  - patient characteristics
  - study duration
- Provide sufficient power to detect statistically and clinically-relevant differences between a candidate drug vs. placebo
Baseline Total Kidney Volume (TKV) is predictive of kidney function decline regardless of age or baseline kidney function.
How TKV Can be Used for Patient Selection in Various Stages of Drug Development and the Anticipated Benefits

**Patient Selection for Clinical Trials**

- **Goal:** Prevention of Early Outcomes
  - Candidate Endpoint: 30% Worsening of eGFR
  - Trial and Inclusion Criteria: Early Outcome Trial
    - $W \, mL \leq TKV \leq X \, mL$, age, eGFR

- **Goal:** Reduction of Complications
  - Candidate Endpoint: 57% Worsening of eGFR
  - Trial and Inclusion Criteria: Disease Progression Trial
    - $X \, mL < TKV \leq Y \, mL$, age, eGFR

- **Goal:** Reduce Progression to ESRD
  - Candidate Endpoint: ESRD
  - Trial and Inclusion Criteria: Late Outcome Trial
    - $TKV > Y \, mL$, age, eGFR

**Clinical Trial Impact:**
- Fewer patients
- Shorter study duration
- Reduced clinical trial costs
- Reduced exposure to potential drug toxicities
- Improved success rate of clinical drug development
## Parkinson’s Disease (PD)

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<td>Disease Model of Early PD</td>
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- **U.S. Food & Drug Administration (FDA)**
- **European Medicines Agency (EMA)**
- **Letter of Support**

**Prognostic enrichment biomarker**

**Disease progression model as fit for purpose**
Molecular Neuroimaging of the Dopamine Transporter as a Prognostic Enrichment Biomarker in Early PD Trials

PD patients (PPMI and PRECEPT) with and without DAT deficit

PD patients with DAT deficit progress faster

DAT imaging illustrating reduced uptake in PD patients

Observed harmonized motor scores. Records were binned by month and bins with less than 15 records were not plotted.

Faster progressors

FDA & EMA Issue Letter of Support for Use of DAT Imaging as Prognostic Enrichment Biomarker in Early PD Trials

"We encourage the use of this biomarker in clinical trials to evaluate its utility for the identification of patients likely to show clinical progression of Parkinson’s motor symptoms. We believe that sharing and integrating data across trials can foster a more efficient path to biomarker qualification."

Sincerely,

[Signature]

Janet Woodcock, M.D.
Director, CDER
U.S. Food and Drug Administration


“The EMA supports the primary objectives of the applicant and has decided to issue a letter of support to the Critical Path for Parkinson’s (CPP) Consortium to encourage further development and validation of the proposed Biomarker.”
