Model-Based Qualification of Biomarkers

Klaus Romero, MD MS FCP
Director of Clinical Pharmacology and Quantitative Medicine
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
Coalition For Accelerating Standards & Therapies
C-Path Data Mapping and Integration Process

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>Coalition Against Major Diseases</th>
<th>Coalition For Accelerating Standards and Therapies</th>
<th>Multiple Sclerosis Outcome Assessments Consortium</th>
<th>Polycystic Kidney Disease Outcomes Consortium</th>
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<tbody>
<tr>
<td>Focusing on diseases of the brain</td>
<td>Data standards</td>
<td>Drug Effectiveness in MS</td>
<td>New imaging biomarker for PKD</td>
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<td><em>CAMD</em></td>
<td><em>CFAST</em></td>
<td><em>MS</em></td>
<td><em>PKD</em></td>
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<tr>
<th>Critical Path for Parkinson’s Consortium</th>
<th>Critical Path to TB Drug Regimens</th>
<th>Patient-Reported Outcome Consortium</th>
<th>Electronic Patient-Reported Outcome Consortium</th>
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<tr>
<td>Enabling clinical trials in Parkinson’s Disease</td>
<td>Accelerating the development of TB drug regimens and diagnostics</td>
<td>Assessing treatment benefit</td>
<td>Electronic capture of treatment benefit</td>
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<td><em>CPP</em></td>
<td><em>CPTR</em></td>
<td><em>PRO</em></td>
<td><em>ePRO</em></td>
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<th>Duchenne Regulatory Science Consortium</th>
<th>International Neonatal Consortium</th>
<th>Predictive Safety Testing Consortium</th>
<th>Pediatric Trials Consortium</th>
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<td>Neonatal clinical trials</td>
<td>Drug safety</td>
<td>Developing effective therapies for children</td>
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<td><em>D-RSC</em></td>
<td><em>INC</em></td>
<td><em>PSTC</em></td>
<td><em>PTC</em></td>
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- 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
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 Baseline age=30yrs</th>
<th>TKV Baseline TKV 1.7L</th>
<th>Follow-Up Period</th>
<th>1-Probability of 30% Worsening of eGFR</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>1</td>
<td>Median 0.98</td>
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<td>10</td>
<td>Median 0.29</td>
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Follow-Up (Years)
Polycystic Kidney Disease Outcomes Consortium: Regulatory Sciences Pipeline

## Polycystic Kidney Disease

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<thead>
<tr>
<th>DRUG DEVELOPMENT TOOLS</th>
<th>FEASIBILITY¹</th>
<th>SCOPING²</th>
<th>RESEARCH³</th>
<th>SUBMITTED⁴</th>
<th>QUALIFIED⁵</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, 5630 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.

The graphs illustrate the predicted probability of no 30% worsening at baseline across different age groups and kidney function levels, showing a significant reduction over time with increasing TKV values.
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
    - \( W \text{ mL} \leq \text{TKV} \leq X \text{ mL}, \text{age}, \text{eGFR} \)

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

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

**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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- **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

DAT imaging illustrating reduced uptake in PD patients

PD patients (PPMI) with and without DAT deficit

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.”


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.”

Thank You

www.c-path.org