FDA-C-Path-ISoP Workshop.

**Session II**


**Quantitative Tools to Support Biomarker Qualification**

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Overview

1. Qualification Process for Drug Development Tools (DDT)
   - Regulatory Components (e.g., nature of biomarker, context of use…)

2. Quantitative Tools to Support Biomarker Qualification
   - Linkage between Biomarker and Disease Progression => DDT
   - How do we construct these models/tools?
   - How do we implement these models/tools?

3. Case Study: Qualification of an Imaging Biomarker (DDT)
   - Total Kidney Volume as a Prognostic Biomarker in Patients with ADPKD
   - Implementation of the DDT (Trial Enrichment)
   - Other Applications
Guidance for Industry

Qualification Process for Drug Development Tools

I. INTRODUCTION
II. BACKGROUND
III. DRUG DEVELOPMENT TOOLS
   A. Biomarkers
   B. Patient Reported Outcome (PRO) and Other Types of Rating Scale Instruments
IV. WHAT IS QUALIFICATION?
   A. Stage 1: Consultation and Advice
   B. Stage 2: Review for Qualification Decision
V. PROCESS FOR QUALIFICATION
   A. Stage 1: Consultation and Advice
   B. Stage 2: Review for Qualification Decision
VI. PROCEDURES FOR MAKING RECOMMENDATIONS AVAILABLE
VII. ADDRESSES FOR DDT CORRESPONDENCE AND DOCUMENTS
APPENDIX 1 BIOMARKERS: ADDITIONAL CONSIDERATIONS
APPENDIX 2 LETTER OF INTENT TO PROPOSE BIOMARKER QUALIFICATION
APPENDIX 3 LETTER OF INTENT TO PROPOSE PRO OR OTHER RATING SCALE QUALIFICATION
APPENDIX 4 STRUCTURE OF BIOMARKER QUALIFICATION BRIEFING DOCUMENT
APPENDIX 5 BRIEFING DOCUMENT TO PROPOSE RATING SCALE (PRO OR OTHER RATING SCALES) QUALIFICATION

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

October 2010
Clinical/Medical

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...)
     - Prognostic biomarker
     - Predictive biomarker
     - Pharmacodynamic (or activity) biomarker
     - Surrogate biomarker
   - **Disease** (e.g., worsening, LFT, adverse events, transplant, mortality...)

3. **Methodology: Quantitative Tools**
   - Exploratory Analyses (Univariate Cox, Multivariate Cox & Kaplan Meier)
   - Joint Modeling: Linkage between a longitudinal measurement (biomarker) and an event (disease outcome)
   - Model Validation (Cross-validation & Predictive Performance of the model)
1. Fundamental component of biomarker-disease models
   - Biomarker-disease models are drug-independent
   - Can be customized by introducing a drug-biomarker
Challenges Biomarker-Disease Models

• Need to simultaneously model
  • Biomarker trajectory (longitudinal time-varying covariates)
  • Disease Endpoint, hazard function (time-to-event)

• Not widespread in the field of Pharmacometrics (mainly used in biostatistics).

• 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).
Joint Modeling approach using the R package JM (http://jmr.r-forge.r-project.org/index.html).

Briefly, joint modeling is performed using a 3-step approach.

1- A linear mixed-effects model for the longitudinal variable is constructed

```r
fitLME <- lme(I(log(MPVol)) ~ MPYRS, random= ~ MPYRS | UDERID, data = alltkvdataj, control = list(msVerbose = 1, maxIter=100, msMaxIter=1000, niterEM=1000))
```

2- A time-to-event model using important covariates is constructed (Cox, Weibull...). The JM package will allow specifying various parametric survival functions

```r
fitSURV <- coxph(Surv(MPYRS, EVFL) ~ 1+I(AGERFST-40) ,data=e57endpointj, x = TRUE)
```

3- The final step is to “join” model #1 and #2. Various hazard functions and ways to link the longitudinal outcome to the hazard can be developed

```r
fit.tkv_e57_all<- jointModel(fitLME, fitSURV,timeVar="MPYRS",verbose=T,method="piecewise-PH-aGH")
```
CASE STUDY

Qualification of Total Kidney Volume as a Prognostic Biomarker for use in Clinical Trials Evaluating Patients with Autosomal Dominant Polycystic Kidney Disease (ADPKD)
1. ADPKD is a debilitating genetic disease affecting more than 12 million people worldwide for which there is currently no known cure or effective treatment.

2. Goals of Collaboration
   - Qualify Total Kidney Volume (TKV) as a biomarker that can be used as a measure of the progression of ADPKD
   - Develop a tool that can improve the efficiency and predictive accuracy of clinical trials that investigate ADPKD.

3. The PKD Consortium is a successful collaboration of the following:
   - Critical Path Institute
   - The PKD Foundation
   - Clinical Data Interchange Standards Consortium (CDISC)
   - Various Academic Centers
     - Tufts University
     - University of Colorado
     - Emory University
     - Mayo Clinic
   - Pharmacometrics Consulting Organization (Pharsight, A Certara Company)
Introducing ADPKD

Autosomal dominant polycystic kidney disease (ADPKD)
• Caused by mutations in the gene PKD1 or PKD2

• Hundreds to thousands of renal cysts develop and grow over time, some as large as 10-20 cm in diameter.
• Cysts grow exponentially.
Introducing ADPKD

Autosomal dominant polycystic kidney disease (ADPKD)

- Nephrons get crushed

- ~50% will develop ESRD, require dialysis or kidney transplantation.
- Progression to ESRD happens in the 4\textsuperscript{th} to 6\textsuperscript{th} decades of life.
- Other: infections, hypertension, pain
- Current treatment for ADPKD
  - Symptomatic drug (pain killers antibiotics, antihypertensive)
  - No disease-modifying drugs…
Changing The Paradigm for Measuring Disease Progression of PKD

![Graph showing kidney function and age]

- Desired Endpoint
- Present Endpoint

- Hematuria, Infections, Hypertension, ESRD, Mortality

Courtesy V. Torres
Slide 12
Joint Model: Longitudinal TKV and Probability of Disease Outcome

Follow-up time: 0

Follow-up time: 1.9

Follow-up time: 7

Follow-up time: 9.1

Survival Probability
Log Kidney Volume
No 30% Worsening of eGFR Probability
Clinical Trial Planning Example
30% Worsening of eGFR

<table>
<thead>
<tr>
<th>Age</th>
<th>TKV</th>
<th>Follow-Up Period</th>
<th>Probability of No 30% Worsening of eGFR</th>
</tr>
</thead>
<tbody>
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<td>Random uniform distribution between 500 and 3000 mL</td>
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<td>Median</td>
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<tr>
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<td>0.96</td>
<td>0.99</td>
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</tbody>
</table>

Follow-Up (Years)

Follow-Up Period

Probability of No 30% Worsening of eGFR

Random uniform distribution between 18 and 40 years

Random uniform distribution between 500 and 3000 mL

500-3000 mL

Slide 14
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
Trial Enrichment
30% Worsening of eGFR
End-Stage-Renal-Disease

Slide 17
Example of a Decision Tree for Clinical Trial Enrichment

Patient Selection for Clinical Trials

Goal: Prevention of Early Outcomes
Candidate Endpoint: 30% Worsening of eGFR
Trial and Inclusion Criteria
Early Outcome Trial
TKV < X mL, age (range)

Goal: Reduction of Complications
Candidate Endpoint: 57% Worsening of eGFR
Trial and Inclusion Criteria
Disease Progression Trial
X ml < TKV < Y ml, age (range)

Goal: Reduce Progression to ESRD
Candidate Endpoint: ESRD
Trial and Inclusion Criteria
Late Stage Trial
TKV > Y mL, age (range)

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
- Use to select patients for appropriate clinical trials
1. Alzheimer's Disease
   - Linkage between Biomarker and Disease Progression
   - **Biomarker**: Hippocampal volume (HV), as measured by imaging
   - **Endpoint**: Conversion from mild cognitive impairment (MCI) to dementia (using clinical dementia rating sum of boxes scores)
   - **Application**: Trial Enrichment (patient characteristics)

2. Oncology
   - **Biomarker**: Quantitative measurement of lesion such as volume and density, or tumor vascularization
   - **Endpoint**: OS, PFS…
   - **Application**: Pick the right drug (e.g., anti-angiogenic vs. cytotoxic drugs)
Thank You