FDA Biomarker Qualification and MRI Imaging Parameters qualified by FDA (PKDOC Measures)

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Topic list

- TKV qualification for enrichment
- Lessons learned from TKV – FDA and PKDOC (Polycystic Kidney Disease Outcomes Consortium)

TKV qualification

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

Guidance for Industry

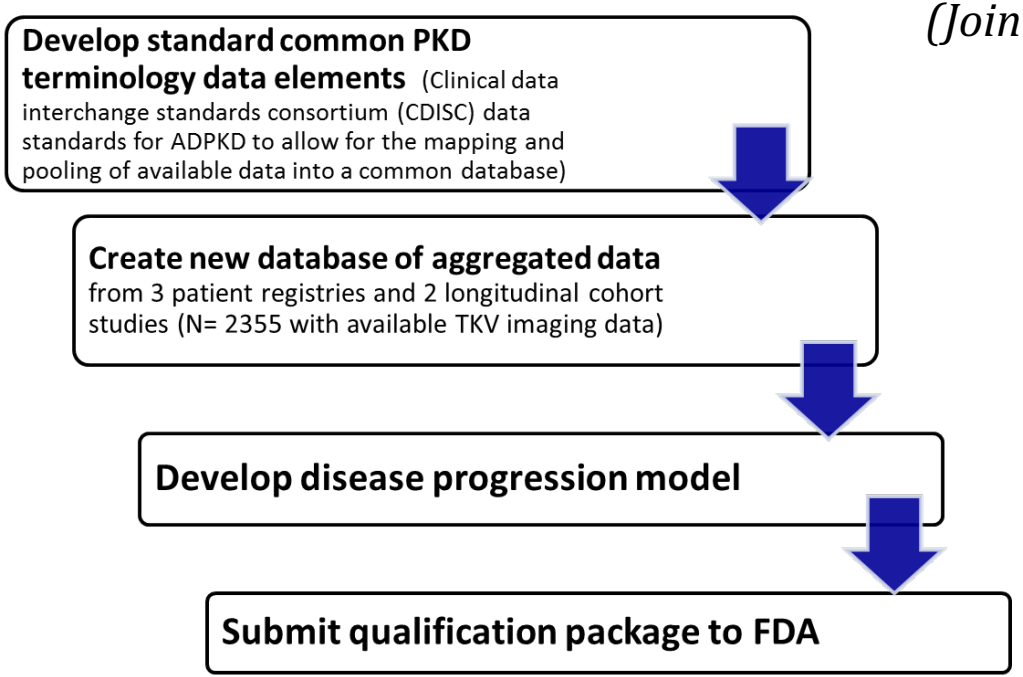
https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM458483.pdf

TKV qualification: Use statement

TKV, measured at baseline, is qualified as a prognostic enrichment biomarker to select patients with ADPKD at high risk for a progressive decline in renal function (defined as a confirmed 30% decline in the patient's eGFR) for inclusion in interventional clinical trials. This biomarker may be used in combination with the patient's age and baseline eGFR as an enrichment factor in these trials.

TKV as a prognostic biomarker: PKDOC Approach

(Joint FDA-EMA submission)



Slide Courtesy of Shashi Amur

Creation of ADPKD-Specific Data Standard

- 5 sets of case report forms (Emory, University of Colorado, Mayo, CRISP, HALT)
- More than 1200 individual data elements
- 3 face-to-face meetings, multiple conference calls
- Full-time coordinator
- Required approximately one year prior to submission for public (global) comment
- Another 8+ months to complete mapping and data transfer to central database
- Context: Small group of collaborative investigators working in a focused field

FDA review: TKV for enrichment

Does TKV provide enrichment? If so, how much?

- Determined best fit models with and without TKV
  - Cross-validation
  - External validation using a separate dataset
- Assessed improvement in model fit and model discrimination
- Evaluated the potential utility of using TKV for trial enrichment

The Value of Enrichment

Predicted event rate in placebo arm over 3 years, **number needed to enroll and number needed to treat to get one event** using the best fit models with and without TKV.

	Model without TKV	Model with TKV, using added criterion of TKV > 1 L
Predicted event rate in placebo arm over 3 years	0.091	0.110
Number needed to enroll†	11	9
Number needed to screen	13	25

Assumes entry criteria of eGFR > 50 mL/min per 1.73 m^2 and age between 20 and 50 years.

From Executive Summary; Analysis by John Lawrence

FDA review: Imaging performance

- Is the uncertainty associated with the measurement acceptable?
- First, what's acceptable? Depends on the context of use
  - Do imaging assessments of TKV with high uncertainty (e.g., ultrasound) provide enrichment? *Yes –data from all modalities informed the enrichment model*
- What are the minimum imaging technical performance requirements necessary to ensure that future users of the biomarker achieve the desired enrichment?

TKV qualification: Measurement Applicability

- Various imaging modalities and post-processing methods are available to determine TKV. These modalities have different levels of precision.
- For patients with ADPKD at high risk for a confirmed 30% decline in their eGFR, TKV was qualified based on a collection of data from multiple study sites, as well as on results from imaging modalities (i.e., magnetic resonance imaging (MRI), computed tomography (CT), or ultrasound (US)) and from analysis methodologies (i.e., stereology and ellipsoid calculations).

Lessons learned

Lessons Learned: FDA Perspective

- TKV has been used for some time as a prognostic biomarker in individual drug development programs; perhaps the greatest benefit of the effort was that it quantified the amount of information that “was added” by using TKV to enrich the trial population.
- Registry data can be critical for establishing the value of a biomarker as a tool in drug development but there are challenges associated with using and interpreting registry data.

Lessons Learned: FDA Perspective

- Biomarker qualification packages are based on the totality of data available to the submitter; however sometimes FDA has access to other large datasets (i.e., data from drug development programs) that speak to the utility of a biomarker.

  It is unclear when and how we should use these sources of information to confirm the utility of a biomarker for a proposed context of use.

Lessons learned: FDA imaging

- A tool used in the context of a clinical investigation may have a different purpose (context for use/intended use) than the same tool in clinical practice.

- The level of evidence, rigor of analytical validation, and performance criteria depend on the context for use, intended use, and claims in addition to the technical considerations of the imaging technique.

Take away

- Data Standards key
- Retrospective mapping of data standards is time consuming
- Ideally, data standards should be developed prospectively
- Standards should map to SDTM for regulatory analysis and/or submission
- Work with organizations like C-Path for optimal efficiency
- Data Standards facilitate collaborations and aggregation of data

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