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Special Report

Therapeutic Area Data Standards for Autosomal Dominant Polycystic Kidney Disease: A Report From the Polycystic Kidney Disease Outcomes Consortium (PKDOC)

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Data standards provide a structure for consistent understanding and exchange of data and enable the integration of data across studies for integrated analysis. There is no data standard applicable to kidney disease. We describe the process for development of the first-ever Clinical Data Interchange Standards Consortium (CDISC) data standard for autosomal dominant polycystic kidney disease (ADPKD) by the Polycystic Kidney Disease Outcomes Consortium (PKDOC). Definition of common data elements and creation of ADPKD-specific data standards from case report forms used in long-term ADPKD registries, an observational cohort (Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease [CRISP] 1 and 2), and a randomized clinical trial (Halt Progression of Polycystic Kidney Disease [HALT-PKD]) are described in detail. This data standard underwent extensive review, including a global public comment period, and is now available online as the first PKD-specific data standard (www.cdisc.org/therapeutic). Submission of clinical trial data that use standard data structures and terminology will be required for new electronic submissions to the US Food and Drug Administration for all disease areas by the end of 2016. This data standard will allow for the mapping and pooling of available data into a common data set in addition to providing a foundation for future studies, data sharing, and long-term registries in ADPKD. This data set will also be used to support the regulatory qualification of total kidney volume as a prognostic biomarker for use in clinical trials. The availability of consensus data standards for ADPKD has the potential to facilitate clinical trial initiation and increase sharing and aggregation of data across observational studies and among completed clinical trials, thereby improving our understanding of disease progression and treatment.

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INTRODUCTION

Autosomal dominant polycystic kidney disease (ADPKD) is the most common hereditary kidney disease and the fourth most common cause of end-stage renal disease (ESRD) in the United States.[1] The clinical course of ADPKD is marked by a long period of stable glomerular filtration rate (GFR) despite the inexorable expansion of kidney volume due to the growth of cysts.[2] GFR stability results from hyperfiltration of the surviving nephrons. The finding of stable GFR when ADPKD kidneys are dramatically enlarged, distorted by multiple cysts, and fibrotic provides false reassurance as to the stability of disease progression.[3] Total kidney volume (TKV) was identified as a reliable way to measure cyst development and expansion in ADPKD.[2] It has been shown that a TKV adjusted for height (htTKV) of

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600 cc/m (approximately equivalent to an uncorrected TKV of 1,100 cc) predicts the risk for development of chronic kidney disease stage 3 within 8 years.[4]

The stability of GFR in the context of a simultaneous 4- to 5-fold volumetric expansion in TKV creates enormous challenges to clinical trial design in ADPKD. Using established regulatory end points such as doubling of serum creatinine level or achievement of ESRD,[5] ADPKD clinical trials would require intervention before severe structural deterioration has occurred and decades of follow-up to reach previously accepted kidney function end points. TKV has been suggested to be a biomarker that can be easily measured in the early stages of disease and that predicts later clinical outcomes. However, only a small number of ESRD events have occurred over a 10-year follow-up in CRISP (Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease [PKD]; 24 of a total of 241 participants).[4] Long-term registry data including measurements of TKV have been compiled,[6-9] but these data had not been collected in a uniform manner and required mapping and standardization prior to analysis. To consolidate and combine data from long-term clinical registries and clinical trials collected using different formats and definitions, we therefore set out to create a PKD-specific Clinical Data Interchange Standards Consortium (CDISC) data standard, a process described in this report.

Interactions between the US Food and Drug Administration (FDA) and the PKD Foundation (PKDF) regarding data standardization and end points for clinical trials in ADPKD began in 2007 (Table 1). This interaction led to the creation of the PKD Outcomes Consortium (PKDOC) in 2009; PKDOC is a collaboration between the PKDF, CDISC, the Critical Path Institute (C-Path), academic medical centers, regulatory authorities, and the pharmaceutical industry to determine the utility of TKV as a biomarker for ADPKD progression. The output of this project is one of CDISC's first fully developed Therapeutic Area Data Standards, from which many subsequent projects are following. This standard is focused entirely on ADPKD and does not include autosomal recessive PKD.

Data standards provide a structure for consistent understanding and exchange of data. They also enable the integration of data across studies for integrated analysis. In addition, they have been shown to decrease the time and costs of medical research and improve data quality.[10] Electronic submission of clinical trial data that use standard CDISC data structures and terminology will be required by the FDA and the Japan Pharmaceutical & Medical Devices Agency by 2016. As part of the Prescription Drug User Fee Act (PDUFA) IV, sponsors are expected to provide data conforming to standards in all new electronic submissions to the FDA by the end of 2016.[11]

The Study Data Tabulation Model (SDTM), developed by CDISC, has become widely used around the world. It is the primary CDISC standard used for storage and submission of tabulation data as part of the regulatory review process. Nine disease-specific (therapeutic area) standards have been developed by CDISC and at least 10 more are in the process of development (www.cdisc.org/therapeutic). The primary building blocks of SDTM are "domains"—structure specifications for the construction of data sets containing conceptually related types of data using standard variables, including references to controlled terminology for population of these data sets. In total, the SDTM Implementation Guide contains specifications for more than 45 domains as of this report.

In this article, we describe the development of disease-specific data standards for ADPKD. A number of the data elements are applicable to kidney disease of any cause, particularly those related to kidney function, blood pressure, and treatment modalities for ESRD. The availability of consensus data standards has the potential to facilitate clinical trial initiation and increase sharing and aggregation of data across observational studies and among completed clinical trials, thereby improving our understanding of disease progression and treatment of kidney disease. This special report describes the process used to develop these consensus therapeutic area data standards.

PROJECT METHODOLOGY

The complete timeline of this project is shown in Table 1. A conference jointly sponsored by the FDA and the PKDF, Clinical Trial Endpoints and Therapies in Polycystic Kidney Disease, was held on May 7, 2007. Issues related to the development of a drug and appropriate clinical trial end points in ADPKD were discussed by clinical investigators and representatives from the FDA, pharmaceutical industry, National Institutes of Health, and PKDF. The FDA did not at that time (and still does not at the time of writing) recognize TKV as an end point that could be used to establish the efficacy of a therapy intended to treat ADPKD. The outcome of this meeting was the initiation of dialogue between the FDA and PKDF regarding a process to validate TKV as an end point for PKD clinical trials. Considering the significant challenges to collecting prospective data from sufficient patients to support this validation, this process ultimately resulted in a recommendation from the FDA to combine data from existing long-term clinical registries to ascertain the linkage between TKV and rate of size increase and the secondary features of ADPKD most commonly encountered, including

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