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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

Table 1. Timeline for Development of Therapeutic Area Data Standards for ADPKD

Date	Activity	Participants	Goals	Outcomes
May 7, 2007	Conference: Clinical Trial Endpoints and Therapies in PKD (FDA White Oak Campus, Silver Spring, MD)	Physician investigators, FDA, NIH/NIDDK, PKDF, industry	Achieve consensus that kidney/cyst growth is the best method to assess outcomes in PKD	Initiation of dialogue between FDA and PKDF regarding a process to validate TKV as an end point for PKD clinical trials
March 27, 2008	Conference: PKD Database Consortium Meeting (Chicago, IL)	Physician investigators, FDA, PKDF, industry	Begin the process of establishing a PKD clinical data base to: (1) aggregate data across registries and clinical trials from which new knowledge can be extracted; (2) simulate clinical trial designs to detect disease progression change or symptom relief	(1) Recommendation from FDA to construct disease model to ascertain the linkage between TKV and the secondary features of ADPKD; (2) need for developing a standardized data format so that data can be combined
January 28, 2009	Teleconference to formally initiate the PKD Outcomes Consortium process	Physician investigators, CDISC, C-Path, FDA, NIH/NIDDK, PKDF, industry	Review overall concept and necessity for data standards; define process; invite participation	Establish core data standards team
January-August 2010	Weekly teleconferences to review CDEs	Physician investigators; CDISC, C-Path; PKDF, industry	Review data elements for consensus	Consensus reached for inclusion or exclusion of CDEs
August 27-28, 2009; December 3-4, 2009; August 24, 2010	Face-to-face meetings to define and achieve consensus on standardized data elements (ie, CDEs)	Physician investigators, CDISC, C-Path, FDA, NIH/NIDDK, PKDF, industry	Achieve consensus on data elements from multiple registries; definition of new data elements	Creation of therapeutic area data elements for ADPKD
July 2011	Submission of PKD CDE for global public comment	Invited global public comment through CDISC and PKD pathways	Receive input from the standards and PKD communities	Incorporated changes into the PKD CDE
January 28, 2013	Webinar to review PKD SDTM User Guide	Data managers from registries, industry, representative from CRISP1, CDISC, and C-Path	Resolve any remaining issues and concepts related to the PKD SDTM User Guide	Approved publication of PKD SDTM User Guide
February 2013	Development of PKD SDTM User Guide completed	CDISC and C-Path, with participation from PKDF and investigators	Create a prospective PKD SDTM User Guide based on PKD CDE	Publication of the PKD SDTM User Guide v1.0

Abbreviations: ADPKD, autosomal dominant polycystic kidney disease; CDE, common data element; CDISC, Clinical Data Interchange Standards Consortium; C-Path, Critical Path Institute; CRISP, Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease; FDA, US Food and Drug Administration; NIH/NIDDK, National Institutes of Health/National Institute of Diabetes and Digestive and Kidney Diseases; PKD, polycystic kidney disease; PKDF, Polycystic Kidney Disease Foundation; SDTM, Study Data Tabulation Model; TKV, total kidney volume.

GFR decline and ESRD. At this time, it was recognized that data residing in long-term clinical registries and clinical trials had not been collected in a uniform manner. The FDA recommended standardizing these disparate data sets, so they could be integrated to create a disease model.

Common data elements (CDEs), defined as the metadata that describe types of data of interest to a given research topic, were compiled from existing case report forms from long-term PKD registries from the Mayo Clinic,[6,7] University of Colorado,[8] and Emory University[9] and from case report forms developed for

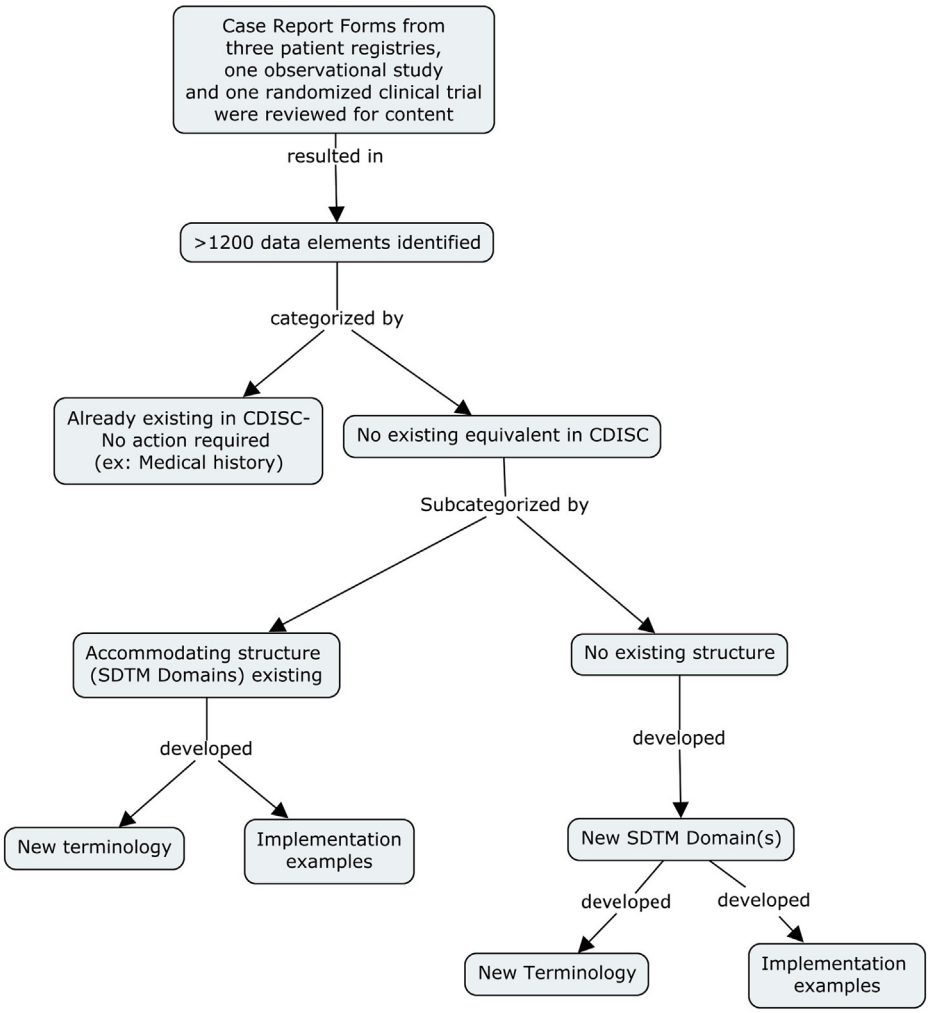

Figure 1. The process for polycystic kidney disease (PKD) common data element (CDE) development. Clinical subject matter experts from academia, industry, and government analyzed case report forms from 3 patient registries, 1 observational study, and 1 randomized clinical trial. CDEs identified from the original observational study were compared against ongoing industry trial data elements to confirm that all CDEs were considered. Concepts were harmonized across studies then vetted for inclusion in version 1.0 (v1.0) of the PKD data standard or deferred for possible inclusion in a later version. CDEs chosen for inclusion in v1.0 were then compared with existing Clinical Data Interchange Standards Consortium (CDISC) standards. CDEs not yet covered by CDISC standards were categorized by whether there were existing study data tabulation model (SDTM) domain structures (for handling data of similar types). In cases in which these domain structures existed, new terminology was created, when needed, and new implementation examples were developed. In cases in which there was no existing structure, new SDTM domains were developed, followed by new terminology and implementation examples.

CRISP 1 and 2[12] and the HALT-PKD (Halt Progression of PKD) study.[13] More than 1,200 derived data elements from these 5 sets of case report forms were grouped into categories that reflected separate aspects of disease, such as diagnosis, kidney volume, risk factors, events, procedures, imaging, kidney function and hypertension, polycystic liver disease, pain, and quality of life. CDEs were identified through cross-study analysis, identifying the data elements "in common" and used consistently across the different case report forms. Additionally, CDEs were agreed to be in scope or out of scope by the clinical experts. This was an important step in the early stages of the project. CDEs were reviewed and put into 2 categories. The first category included those for which complete specifications for standardization already existed in CDISC SDTM documentation, including SDTM domains, variables, controlled terminology, and implementation examples. The second category of CDEs included those for which complete specifications for standardization did not yet exist. This second category was further broken down into 2 subsets: a set for which CDISC SDTM domain structures existed, but for which the specific concepts represented by the CDEs had not yet been modeled into these structures by implementation examples, and a second subset for which no SDTM domain structure existed. This process is illustrated in Fig 1.

Table 2. SDTM Domains Used for the PKD Data Standard

CDISC SDTM Domain	Examples of Data Contained Within Domain
AP (Associated Persons)[a]	Cause of death for participant relatives, demography of participant relatives (race, sex, etc), family history of ADPKD and manifestations, survival status and kidney disease status of participant relatives
CE (Clinical Events)	ESRD, cyst infections, etc
CM (Concomitant Medications)	Nonstudy medications: antihypertensives, etc
DD (Death Details)[a]	Cause of participant death and autopsy findings
DI (Device Identifiers)	CT scanner, MRI scanner, and ultrasound device identifiers; model names/numbers, etc
DM (Demographics)	Participant demographics: age, race, sex, etc
DO (Device Properties)	Properties of imaging devices: software versions, etc
DR (Device-Subject Relationships)	Links participants to the imaging devices used
DS (Disposition)	Tracks participant progression through study milestones: informed consent, withdrawal, etc
DU (Device In-Use Properties)	Properties of imaging devices that may change between scans
FA (Findings About)	Additional details about events, medications, or procedures not contained within those domains
HO (Healthcare Encounters)[a]	Information about hospitalizations
LB (Laboratory Test Results)	Basic labs, urinalysis, kidney clearance labs, etc
MH (Medical History)	Diagnosis of ADPKD, general medical history
MO (Morphology)[b]	Kidney length, width, and volume
PF (Pharmacogenomics Findings)	Genetic basis for determination of PKD1 and PKD2
PR (Procedures)	Cyst aspirations, etc
QS (Questionnaires)	Pain intensity scales
RP (Reproductive System Findings)[b]	History of pregnancies
SC (Subject Characteristics)	Exercise habits
SU (Substance Use)	Caffeine use, tobacco use, etc
UR (Urinary System)[b]	Renal blood flow
VS (Vital Signs)	Blood pressure, temperature, BMI, etc

Abbreviations: ADPKD, autosomal dominant polycystic kidney disease; BMI, body mass index; CDISC, Clinical Data Interchange Standards Consortium; CT, computed tomography; ESRD, end-stage renal disease; lab, laboratory; MRI, magnetic resonance imaging; PKD, polycystic kidney disease; SDTM, Study Data Tabulation Model.

[a]Denotes a preexisting early draft domain that required additional development when the PKD project was underway.

[b]Denotes a domain that had to be developed anew as part of the PKD project.

Consensus on inclusion or deferment was achieved for each CDE during multiple face-to-face meetings and through weekly teleconferences over a period of approximately 1 year. A total of 219 CDEs were ultimately agreed upon by clinical experts for inclusion in version 1.0 of the PKD standard. Later, an additional 119 CDEs were added to facilitate mapping legacy study data for inclusion in an integrated PKD database, for a total of 338 CDEs covered in version 1.0 (shown in Table S1, available as online supplementary material). The definition of each CDE and the range and type of valid parameters for each were established, and CDEs were mapped to SDTM domains. A list of the existing and newly developed SDTM domains is shown in Table 2.

RESULTS AND DISCUSSION

The creation of CDEs that were subsequently mapped to SDTM served as the basis for a PKD-specific data standard user guide, which is now publicly available through the CDISC Therapeutic Area Standards website (www.cdisc.org/therapeutic). This standard provides a consensus vocabulary and guidelines for the organization, structure, and format for ADPKD that can be used for future clinical trials, long-term clinical registries, observational studies, and potentially for electronic health records. The use of this standard brings about the possibility of increasing the efficiency of clinical research, enhancing the pace of regulatory decisions, facilitating secondary analyses of separate trials and cohorts, and assisting with establishing the evidence for biomarkers such as TKV that can ultimately improve patient treatment. Users can define which CDEs are relevant to their clinical trial or registry, and thus use of a subset, rather than the entire standard, would be anticipated.

The development of therapeutic-area data standards is a labor-intensive effort requiring collaboration of many experts from diverse fields, and the process must often be coordinated across a broad spectrum of seemingly unrelated areas. This was particularly true for PKD because it was one of the first therapeutic-area standards developed. For example, the development of standards to accommodate TKV touched on ongoing CDISC standards development in areas such as internal organ morphology (TKV measurements)

and handling of medical devices (ultrasound, computed tomography, and magnetic resonance imaging). Creating an overarching logical data model that is consistent across multiple therapeutic areas, requires collaborating with teams working in diverse areas of standards development. A team working on data standards for neurodegenerative diseases may need to review standards development work in seemingly disparate and unrelated areas for guidance on the best approach for handling a type of data not previously represented in published CDISC standards. Identifying the areas of overlap is not always intuitive and can be challenging. For example, in the recent Alzheimer disease version 2.0 CDISC standards development project, the developers (including several coauthors of this report) needed a way to represent positron emission tomography scan tracer administration and found the definitions of existing domains designed to handle therapeutic interventions to be unsuitable. However, through collaboration with a parallel project in asthma standards development, it was discovered that a new draft domain—Procedure Agents (AG)—was underway and worked well for this purpose.

The effort required for any CDISC standards development project can vary considerably depending on the inputs (such as the number of data elements) identified and whether they or similar data types have been modeled for consistency in a previous CDISC standard publication. For example, new laboratory tests that have not been standardized before do not typically present a challenge; an existing SDTM domain structure (Laboratory Test Results [LB]) is available to accommodate data of this type. In such cases, standards developers need only develop new terminology to cover the laboratory test names, synonyms, and any associated methodologies and units as needed.

However, when a data element arises that describes a concept for which no existing suitable SDTM domain has yet been developed, the amount of effort required increases many fold. For example, neither TKV nor any analogous organ measurement had previously been represented in SDTM in a consistent manner. The modeling of data of this type therefore required the development of a new SDTM domain, Morphology (MO), but once developed, it can be used across new therapeutic area standards. Development of a new domain is resource intensive. First, the developers must make a case to CDISC's Submission Data Standards leadership team for why the new domain structure is needed and why existing domains are not suitable. Next, the developers must assemble a team of volunteers to define the purpose and rules for using the new domain and to assemble examples of data modeled into this domain. At the completion of this stage, the domain is considered draft and is reviewed by the CDISC Standards Review Council for consistency, clarity, and harmonization with the foundational SDTM rules. As part of the CDISC standards development process, the draft domain is then released for a broader public review, during which the global user community is invited to make comments and request changes. Every comment received must be addressed to the satisfaction of the Standards Review Council, and there may be more than 100 comments. By addressing thoughtful comments, a better standard emerges. Once approved, the new domain is available for use, but is considered provisional until such time that it is incorporated into the next release of the SDTM Implementation Guide.

The need to develop even one new domain as part of a standards development project can add significantly to the resource requirements and timelines. Of the 23 domains required to accommodate the PKD CDEs identified for this project, 7 were in very early draft stages and 3 needed to be developed completely anew (MO, Reproductive System Findings [RP], and Urinary System Findings [UR]); see Table 2 for a complete list of SDTM domains used).

In addition to the domain development work required, dozens of new terms were developed for PKD. Table 3 lists key terms that were developed for this project. It should be noted that many more terms

Table 3. Key SDTM Terminology for PKD

Term	SDTM Domain
Estimated GFR (eGFR)	Laboratory Test Results (LB)
Creatinine clearance corrected for BSA	Laboratory Test Results (LB)
Inulin clearance GFR	Laboratory Test Results (LB)
Width (kidney)	Morphology (MO)
Length (kidney)	Morphology (MO)
Depth (kidney)	Morphology (MO)
Volume (kidney)	Morphology (MO)
Mass (kidney)	Morphology (MO)
Renal blood flow	Urinary System Findings (UR)
Cause of death	Death Details (DD)
Source of death information	Death Details (DD)
Autopsy findings	Death Details (DD)
Last known kidney status	Subject Status (SS)
Survival status	Subject Status (SS)

Note: Key terms are limited to items that were first identified as part of the PKD data standards development project, regardless of whether they were specific to ADPKD. Note that many more such terms were identified but that they represented values that are not governed by CDISC controlled terminology.

Abbreviations: ADPKD, autosomal dominant polycystic kidney disease; BSA, body surface area; CDISC, Clinical Data Interchange Standards Consortium; CT, computed tomography; GFR, glomerular filtration rate; PKD, polycystic kidney disease; SDTM, Study Data Tabulation Model.

than those shown in Table 3 were identified, but these terms fell into categories of variables for which CDISC does not develop controlled terminology. For example, due to the broad (and in some instances required) use of Medical Dictionary for Regulatory Activities (MedDRA; www.meddra.org) terms, CDISC does not develop or publish controlled terminology in overlapping areas such as medical history. It is also important to note that CDEs (and other forms of clinical or research concept inputs) are just the first step in data standards development; while they are essential to the process, they do not stand alone as complete data standards. As stated previously, CDEs define relevant concepts and associated qualifying terms, value ranges, units (when applicable), and other parameters necessary for clarity of use. A comprehensive data standard such as the PKD CDISC therapeutic area standard, described in this report, defines CDEs and associated terminology as well as all the rules associated with organizing and structuring the data in SDTM. This enables data to be used efficiently and consistently. Developing CDEs into more comprehensive data standards within the confines of the SDTM standard data model is not a simple one-to-one conversion of terminology; a list of CDEs, once standardized, does not simply become another list of now-standardized elements. Almost always, what we describe as a single data "element" maps to multiple variables and often even multiple domains within the context of SDTM. One can get a complete sense of how the CDEs formed the basis of the PKD data standards by reviewing the ultimate product of this standards development effort: the *CDISC PKD Therapeutic Area User Guide* (http://www.cdisc.org/system/files/all/standard_category/application/zip/pkd_v1_standards_package.zip).

Building upon the lessons learned from the PKD project and other early therapeutic area projects (eg, Alzheimer disease), the Coalition for the Acceleration of Standards and Therapies (CFAST) was launched in 2012 as a collaborative effort of CDISC and C-Path. In addition to that prepared for PKD, additional therapeutic area standard user guides have been developed and published through CFAST. The program aims to develop and maintain an additional 15 to 18 therapeutic area data standards and guides over the next 2 years. CFAST brings a level of coordination to these diverse projects that did not exist previously and is helping to address earlier challenges in the standards development process associated with therapeutic areas. By closely assessing lessons learned and implementing process improvements from early ground-breaking projects such as PKD, new therapeutic area standards are being developed at a much faster pace; in most instances, projects are completed 12 months from project kickoff to release and publication of a new standard.

The existence of the PKD therapeutic area data standard allows for the incorporation of future clinical trial and observational data into the PKDOC registry for analyses and disease modeling and for standardization across registries (ie, Eurocyst). PKDOC has already pooled legacy data into a common database. The conclusion of a recent consensus conference on earlier end points in chronic kidney disease suggested that earlier end points including 30%, 40%, and 57% decline in eGFR could be used as a surrogate marker for ESRD.[14-17] Preliminary reports using the PKDOC database have strongly supported the concept that TKV is an important predictor of GFR decline in ADPKD using these earlier end points.[18,19]

Despite the immense effort required in the development of therapeutic-area data standards, once published, they enable study efficiencies previously not possible. These benefits will continue to be reaped into the future, especially as therapeutic area standards are implemented at the beginning of a new clinical trial. It is important to note that standards are not static; through an iterative process of use and feedback, it is expected that each therapeutic-area standard developed will continue to expand in scope and be adjusted based on updates to the foundational rules of the SDTM. In order for each standard to reach its full potential value, it must first be put to the test of use. The PKDOC database represents the first use of the ADPKD standard, and the user guide is now available for broader application of the standard in all clinical studies. Future development of data standards that encompass other areas of kidney disease can build upon this initial project.

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developing treatments for ADPKD. The remaining authors declare that they have no relevant financial interests.

SUPPLEMENTARY MATERIAL

Table S1: PKD v1.0 Common Data Elements List.

Note: The supplementary material accompanying this article (http://dx.doi.org/10.1053/j.ajkd.2015.04.044) is available at www.ajkd.org

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