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ABBREVIATIONS AND DEFINITIONS OF TERMS

AE Adverse Event
CFR Code of Federal Regulations
CRF Case Report Form
COC Certificate of Confidentiality
CLIA Clinical Laboratory Improvement Amendments
CRI Clinical Research Institute
DCC Data Coordinating Center
DHHS Department of Health and Human Services
DSMB Data Safety Monitoring Board
DSMP Data and Safety Monitoring Plan
eCRF Electronic Case Report Form
FWA Federalwide Assurance
GCP Good Clinical Practice
HIPAA Health Insurance Portability and Accountability Act
ICF Informed Consent Form
IRB Institutional Review Board
LAR Legally Authorized Representative
MOP Manual of Procedures
OHRP Office for Human Research Protections
PD Protocol Deviation
PI Principal Investigator
QA Quality Assurance
QC Quality Control
RE Reportable Event
SAE Serious Adverse Event
SOP Standard Operating Procedure
SRC Scientific Review Committee
UP Unanticipated Problem

ABSTRACT

Context:

Health-related quality of life is known to be significantly impaired in children with chronic kidney disease, especially those on dialysis and after renal transplantation, and causes significant caregiver burden. However, there are no specific data related to quality of life for children with autosomal recessive polycystic kidney disease (ARPKD). These children are unique in that they have dual organ disease (kidney and liver) and often have a severe perinatal course with antenatal oligohydramnios causing pulmonary morbidity and mortality in neonates. Polycystic kidney disease research has identified a number of potential treatments, and clinical trials for ARPKD are on the near horizon.

The overarching goal of the proposed study is to lay the foundation for incorporating the patient voice into clinical trial design. The study will solicit patient, caregiver, and healthcare professional perspectives regarding health-related quality of life (hrQoL) for this patient cohort using validated hrQoL questionnaires. The data collected from these stakeholder groups will enable the identification of priorities regarding outcomes for this patient population, which will then be organized into a set of core outcomes to inform future clinical trial design.

Objectives:

1. Assess the quality of life of children affected by autosomal recessive polycystic kidney disease (ARPKD) and their parents, using validated survey instruments.
2. Determine the priorities of patients, caregivers, and healthcare professionals regarding outcome measures in order to determine a set of core outcomes for future ARPKD-related clinical trials.

Study Design:
This is a two-part cross-sectional cohort study based on online questionnaires.

Part 1 is addressed to patients with ARPKD and their caregivers. It assesses proxy-reported and self-reported hrQoL, caregiver burden, and the impact on families using the questionnaires listed under “measures” below.

Part 2 is addressed to patients with ARPKD, their caregivers, and healthcare professionals who regularly care for patients with ARPKD. Participants are asked to rank the outcomes identified in Part 1 into 3 categories (critical, important, of limited importance).

Setting/Participants:

- Single-site study of children, adolescents, and young adults between the age of 0 and 25 years of age who are affected by ARPKD.
- Primary caregivers (over the age of 18 years) of participants with ARPKD (including grandparents or stepparents if they live in the same household)

- Healthcare professionals regularly involved with the care of children with ARPKD.
- Subjects will be identified by the ICD-10 diagnosis code for ARPKD in the CHOP Epic EHR (e.g. Arcus and Healthy Planet) and through the CHOP Inherited Kidney Diseases Program.
- Anticipated recruitment: 40 children with ARPKD. About 60 parents or other regular caregivers of those children with ARPKD. About 20 healthcare professionals. Total enrollment: 120.

Study Procedures, Interventions and Measures:

- The study does not include procedures performed on any participant.

- Part 1 will utilize the following questionnaires:
    - hrQoL in affected children and young people:
        - PedsQL-ESRD module (validated questionnaire on health-related QOL for children ≥ 24 months and adults < 25 years with renal disease)
        - PedsQL infant module (for children < 24 months) [6,7]
        - Strengths and Difficulties Questionnaire (SDQ) - a validated brief emotional and behavioral screening tool [8].
    - Caregiver burden will be captured by recording both the burden on family life with the "Impact on Family Scale"(IFS) [10], as well as parental health-related quality of life using the "Ulm Quality of Life Inventory for Parents of Chronically Ill Children (ULQIE)" [9].

- Part 2 consists of an online survey in which participants will be asked to rank 22 previously identified outcome domains [4,11] on a 9-point Likert scale. Additionally, they will be presented with a number of limited sets of outcomes and asked to identify the most and least important one in each list.

Main Study Outcomes:

- Proxy-reported and self-reported summary scores of PedsQL ESRD and SDQ scales in children with ARPKD. Summary scores of the Impact on Family Scale and the ULQIE scale.

- Ranking of the predefined 22 outcome domains (categorized into the categories of critical, important, limited) as viewed by children, caregivers, and healthcare professionals.

- Ranking of the patient-reported outcome domains as viewed by children and caregivers.

PROTOCOL SYNOPSIS

Study Title	Capturing quality of life and priorities for clinical research in parents and patients with autosomal recessive polycystic kidney disease – ARPKD PROM Study
Funder	HRFD U54/NIH
Study Rationale	The aim of this single site, cross-sectional questionnaire study is to assess the quality of life of children affected by autosomal recessive polycystic kidney disease (ARPKD) and their parents. This study will document the impact on quality of life and caregiver burden, as well as serve to validate existing instruments for this rare-disease population. In addition, parents, affected older children and young adults, and healthcare professionals will be asked about their personal priorities for clinical trials. The results of this study will enable the incorporation of the views of parents, children and young adults, and healthcare professionals into the design of future clinical trials, giving these key stakeholders a voice in study design.
Study Objective(s)	1. Assess the quality of life of children affected by autosomal recessive polycystic kidney disease (ARPKD) and their parents, using validated survey instruments. 2. Determine the priorities of patients, caregivers, and healthcare professionals regarding outcome measures in order to determine a set of core outcomes for future ARPKD-related clinical trials.
Study Design	This is a two-part cross-sectional cohort study based on online-questionnaires. Part 1 is addressed to patients with ARPKD and their caregivers. It assesses proxy-reported and self-reported hrQoL, caregiver burden, and impact on family using 4 different, previously validated questionnaires (PedsQL ESRD Module; strength and difficulties questionnaire (SDQ); impact on family scale (IFS); Ulm Quality of Life Inventory for Parents of Chronically Ill Children (ULQIE)). Part 2 is addressed to patients with ARPKD, their caregivers, and healthcare professionals who regularly care for patients with ARPKD. It consists of a single online questionnaire to rank previously identified outcome domains into 3 categories as well as several head-to-head comparisons of patient-reported outcomes.
Subject Population key criteria for Inclusion and Exclusion:	Inclusion criteria for ***participants with ARPKD:*** • They should be between 0-25 years of age and have an ICD-10 diagnosis code for ARPKD in the CHOP Epic EHR.

	Inclusion criteria for ***caregivers of participants with ARPKD***: • They should be over 18 years of age and permanently live in the same household as the child/ young person with ARPKD. Inclusion criteria for ***healthcare professionals***: • They should be regularly engaged in the care of children with ARPKD (i.e. with ≥2 years of experience in caring for these children) Exclusion criteria: • Insufficient understanding of the questions due to intellectual capabilities or language barriers. However, translation by a professional interpreter is permissible. • Lack of written informed consent. • Subjects that choose not to have their responses recorded.
Number Of Subjects	40 ARPKD children, 60 caregivers, 20 healthcare professionals. 120 subjects total.
Study Duration	Each subject's participation will last about 30-45 min. The entire study is expected to last about 2 years.
Study Phases **Screening** **Study**	1. Screening: screening for eligibility and obtaining HIPAA authorization/consent 2. Observation Period: questionnaires
Safety Evaluations	not applicable
Statistical And Analytic Plan	In Part 1 summary scores of instruments will be presented as mean with standard deviations as well as median with interquartile range. Scores will be correlated to measures of disease severity (such as estimated glomerular filtration rate) using Spearman rank order correlation. As there is no intervention group, there is no planned group comparison or power calculation. Exploratory subgroup analysis may also be performed. Part 2 defines a mean and median Likert score for each predefined outcome domain, as well as a "winning rate" for each patient-reported outcome in the head-to-head comparisons.
DATA AND SAFETY MONITORING PLAN	The study team and PI will be responsible for data quality management and ongoing assessment of safety.

1 BACKGROUND INFORMATION AND RATIONALE

1.1 Introduction

Chronic kidney disease (CKD) in childhood is a significant burden and reduces the quality of life for both children and their parents [1]. CKD is especially burdensome when it progresses to end stage kidney disease (ESKD, previously referred to as end-stage renal disease or ESRD), placing considerable demands on a child's entire family [2]. Although studies are available for all-cause CKD and for some disease subsets, there is no study capturing quality of life in children or adolescents specifically affected by autosomal recessive polycystic kidney disease (ARPKD). These children are often severely affected prenatally and postnatally have problems due to massive kidney enlargement, hypertension, kidney failure, and portal hypertension. They often need to receive kidney replacement therapy during childhood.

The need to include patients and their lived experience in the design of clinical trials exists for all diseases, but is implemented infrequently, especially in the field of rare diseases. The negative consequences of limited patient/parent input in clinical trial design for rare diseases has been recently highlighted by a report from the International Rare Diseases Research Consortium (IRDiRC) [3].

1.2 Relevant Literature and Data

In the field of adult nephrology, the SONG initiative (standardized outcomes in nephrology) is currently advancing the collection of patient-relevant endpoints, including priority lists and tools related to adult autosomal dominant kidney disease (ADPKD) [4] as well as pediatric CKD [5]. However, children with ARPKD have their own disease-specific impairments related to quality of life. For example, many of these patients have extremely large kidneys with very distended abdomens, the impact of which is typically not recorded in most general QOL or ESKD-specific questionnaires. Due to advances in the field of polycystic kidney diseases in general, clinical trials in children and adolescents with ARPKD can be expected in the coming years. The design and implementation of these trials should take into account both the quality of life and the priorities of the patients and their parents as important stakeholders.

1.3 Compliance Statement

This study will be conducted in full accordance all applicable Children's Hospital of Philadelphia (CHOP) Research Policies and Procedures and all applicable Federal and state laws and regulations including 45 CFR 46. All episodes of noncompliance will be documented.

The investigators will perform the study in accordance with this protocol, will obtain consent and assent, and will report unanticipated problems involving risks to subjects or others in accordance with CHOP IRB Policies and Procedures and all federal requirements. Collection, recording, and reporting of data will be accurate and will ensure the privacy, health, and welfare of research subjects during and after the study.

2 STUDY OBJECTIVES

Primary Objective (or Aim)

The first primary objective of this study is to assess the quality of life of children affected by autosomal recessive polycystic kidney disease (ARPKD) and their parents, using validated survey instruments.

The second primary objective is to determine priorities of patients, caregivers, and healthcare professionals regarding outcome measures in order to determine a set of core outcomes for future ARPKD-related clinical trials.

Secondary Objectives (or Aim)

The secondary aim is to validate the use of existing quality of life questionnaire for this cohort of children with ARPKD and to compare their hrQoL to previously published cohorts of children with all-cause chronic kidney disease.

3 INVESTIGATIONAL PLAN

In Part 1, participants will be asked to complete the following questionnaires:

- Parents (as proxies for their children) as well as older children (as self-reports) will complete these assessments of health-related quality of life:
    - PedsQL- ESRD module (validated questionnaire on health-related QOL for children ≥ 24 months and adults < 25 years with renal disease)
    - PedsQL infant module (for children < 24 months) [6,7]
    - Strengths and Difficulties Questionnaire (SDQ) (validated brief emotional and behavioral screening tool) [8].
- Parents (in their role as caregivers) will complete these assessments on caregiver burden:

    - Impact on Family Scale"(IFS) [10]
    - Ulm Quality of Life Inventory for Parents of Chronically Ill Children (ULQIE) [9].

Age-appropriate versions are listed below.

The PATIENT will be asked to complete the following questionnaires about themself:

Age of the patient	**Peds QL ESRD Module**	**SDQ**
6 – 7 years	Young child (with coordinator)	-
8 – 12 years	Child	Self 11-17
13 – 18 years	Teen	
18 – 25 years	Young Adult	Self 18+

The CAREGIVER(S) will be asked to complete the following questionnaires:

<table>
<tr><td></td><td colspan="5">About their child
(at least once per child)</td><td colspan="3">About themself
(each caregiver)</td></tr>
<tr><td>Age of the patient</td><td>Peds QL infant scales</td><td>Peds QL ESRD Module</td><td>SDQ</td><td>Basic data</td><td>FaBel (IFS)</td><td>ULQIE</td><td>Basic data</td></tr>
<tr><td>< 12 mo</td><td>< 12 mo</td><td>-</td><td>-</td><td rowspan="8">Demographic questionnaire (child)</td><td rowspan="8">IFS</td><td rowspan="8">ULQIE</td><td rowspan="8">Demographic questionnaire (caregiver)</td></tr>
<tr><td>12-23 mo</td><td>12-23 mo</td><td></td><td></td></tr>
<tr><td>2–5 yrs</td><td></td><td>-</td><td>Parents 2-4 yrs</td></tr>
<tr><td>6–7 yrs</td><td></td><td>Young child</td><td rowspan="3">Parents 4-17 yrs</td></tr>
<tr><td>8–12 yrs</td><td></td><td>Child</td></tr>
<tr><td>13–18 yrs</td><td></td><td>Teen</td></tr>
<tr><td>18– 25 years</td><td></td><td>Young Adult</td><td>Self 18+ yrs</td></tr>
</table>

Part 2 will follow on seamlessly for the participant and include two ranking exercises:

First, participants will be asked to rank 22 previously identified outcome domains [4,11] on a 9-point Likert scale according to their perceived importance in clinical trials, ranging from 0-3 (only limited importance, e.g. to a subgroup of patients), 4-6 (important, should be included in most studies), to 7-9 (critical, should be reported in all ARPKD studies).

Second, priorities of about 15 patient-reported outcomes will be further defined with a ranking exercise that avoids ceiling effects. Respondents will be presented with 5 sets of 3 outcomes (e.g. fatigue, school participation, abdominal pain) and asked to rank the most and the least important outcome in each set. The 15 outcomes will be presented in randomized order.

3.1 General Schema of Study Design

This study is a partnership with the University of Heidelberg, Germany. It is a mirrored cohort study using the same study design to establish parallel datasets from Europe (primarily Germany) and the US. The observational study described herein will only be conducted at CHOP. The aggregated summary data will be shared for combined analyses; participant-specific data will not be shared.

Participants will be informed about the possibility to take part in the study during their routine visit to the CHOP pediatric nephrology clinics (e.g. Inherited Kidney Diseases Program, Kidney-Liver Clinic, General Nephrology).

Prior to the survey administration:

- Families will be provided with an age-appropriate information leaflet as well as consent forms to review.
- Families will be informed that the following current data from affected children will be useful – serum creatinine, height, and abdominal circumference. For abdominal circumference, families will be directed to perform these measurements at home with guidance from the coordinator.

Once written informed consent has been provided by the parents and/or legal guardians taking part as caregivers, the study survey will be administered via REDCap and can be completed in the participant's own time. Participants who agree to share their e-mail address may receive the study link and reminders via this electronic address.

3.2 Study Duration, Enrollment and Number of Sites

3.2.1 Duration of Study Participation

The study is a one-point survey that does not require follow-up.

3.2.2 Total Number of Study Sites/Total Number of Subjects Projected

CHOP will be the only US study site. 120 subjects total are projected.

3.3 Study Population

The target study population of 40 children/adolescents/young adults and 60 of their respective caregivers is aimed for, in order to represent different age groups and disease severity representatively. 20 healthcare professionals will also be enrolled. 120 total subjects.

3.3.1 Inclusion Criteria

The three groups of included subjects are:

1. Children and adolescents between the age of 0 and 25 who are affected by ARPKD (based on ICD-10 diagnostic code in the EHR).

2. Primary caregivers over the age of 18 years of persons listed in 1 (including grandparents or stepparents if they live in the same household).

3. Healthcare professionals who provide care for persons listed in 1.

It is possible to include families where only the patient or only the caregiver(s) wish to participate. Also, caregivers may choose not to answer personal questions about themselves, but still complete the proxy-questionnaires for the child.

For affected patients, written informed consent must be provided by a parent or legal guardian. In the case of joint custody of both parents, the signature of both legal guardians is to be preferred.

Caregivers (parents or other caregivers as defined above) must also provide written informed consent for their own participation in the study.

3.3.2 Parent Subject Inclusion Criteria

Primary caregivers over the age of 18 years of subjects (including grandparents or stepparents if they live in the same household). Caregivers may have chronic illness.

3.3.3 Healthcare Professional Inclusion Criteria

Physicians, nurses, specialist nurses, social workers who regularly work with children who suffer from ARPKD and have done so for at least 2 years.

3.3.4 Index or Parent Subject Exclusion Criteria

The exclusion criteria for this study are:

- Insufficient understanding of the questions due to intellectual capabilities or language barriers. However, translation by a professional interpreter is permissible.
- Lack of written informed consent.
- Subjects that choose not to have their responses recorded.

4 STUDY PROCEDURES

Forms will be labeled with the subject's unique study ID, collection date and time. Only study team members will have access to the "code book" linking the subject's unique study ID to the participant using computerized password-protected software.

Participant e-mail addresses will be recorded solely within REDCap. Study links and reminders will be sent directly out of REDCap, as it can handle identifying information and study replies separately, therefore minimizing the risk of re-identification.

The study team will receive proper training on consenting subjects, providing questionnaires, and data entry from our colleagues at the University of Heidelberg, Germany.

4.1 Screening Visit

Subjects will be identified by the ICD-10 diagnosis code for ARPKD in the CHOP Epic EHR and through the CHOP Inherited Kidney Disorders Program.

4.2 Observational Period

No observation is needed due to the cross-sectional questionnaire study design.

4.3 Subject Completion/Withdrawal

Subjects may withdraw from the study at any time without prejudice to their care. They may also be discontinued from the study at the discretion of the Investigator for lack of cooperation with the study survey. It will be documented whether or not each subject completes the clinical study Early Termination Study Visit.

5 STUDY EVALUATIONS AND MEASUREMENTS

5.1

Questionnaires:

- Peds QL ESRD Module - Quality of life in children with end-stage renal disease
- SDQ - Strengths and Difficulties Questionnaire is a brief behavioral screening questionnaire about 2–17-year olds
- Basic data (demographics)
- FaBel (IFS) - personality scale based on the Internal Family Systems Model
- ULQIE - Quality of Life and Mental Health in Mothers and Fathers Caring for Children and Adolescents with Rare Diseases

5.1.1 Medical Record Review

Date of birth
ICD-10 code for ARPKD
Age at diagnosis of ARPKD
Gender
Height, abdominal circumference (recorded by participant/caregiver)
Serum creatinine
Renal replacement therapy (dialysis or transplant)
Type of liver complications
Number of different medications taken

5.2 Safety Evaluation

Not applicable.

6. STATISTICAL CONSIDERATIONS

The target recruitment is 40 affected children and their care providers, with the goal of representing different age groups and disease severity. As there are no group comparisons in the primary endpoints, a formal power calculation of minimum sample size is not meaningful.

6.1 Primary Endpoint

In Part 1, summary scores of the 4 different instruments will be presented as means with standard deviations, as well as medians with interquartile range.

Part 2 defines a mean and median Likert score for each predefined outcome domain, as well as a "winning rate" for each patient-reported outcome in the head-to-head comparisons.

6.2 Secondary Endpoints

In Part 1, scores will be correlated to measures of disease severity (such as estimated glomerular filtration rate) using Spearman rank order correlation.

Exploratory subgroup analysis may be done between the renal treatment modalities (conservative, dialysis, transplant), type of presentation (classical neonatal vs later), and presence/absence of liver complications, only if sufficient numbers of patients take part in each subgroup.

Measures of hrQoL in affected patients will also be correlated with measures of caregiver burden.

Psychometric properties of the instruments in the ARPKD population will be assessed with Crohnbach's alpha and examination for floor/ceiling effects.

In Part 2, group rankings may be compared by age of affected patient, treatment modality, type of presentation (classical neonatal vs later), and presence/absence of liver complications, only if sufficient numbers of patient take part in each subgroup.

6.3 Control of Bias and Confounding

Not applicable.

6.4 Statistical Methods

6.4.1 Baseline Data

Baseline and demographic characteristics will be summarized by standard descriptive summaries (e.g. means and standard deviations for continuous variables such as age and percentages for categorical variables such as gender). Distribution of age at study, age at presentation, sex, and treatment modality will be used to assess the representativeness of the sample in comparison to previously published cohorts.

6.4.2 Analysis of Primary Outcome of Interest

The primary analysis will include all subjects meeting all inclusion criteria and fully completing at least one questionnaire in Part 1 or Part 2. The inclusion of participants who chose to omit one or more questionnaires will not be considered to introduce undue bias.

6.4.3 Sample Size and Power

As there are no group comparisons in the primary endpoints, a formal power calculation of minimum sample size is not meaningful. ARPKD is a very rare disease. If recruitment stays

below the expected number, subgroup analyses may not be possible, but they are only secondary outcomes for exploratory analysis.

7 SAFETY MANAGEMENT

The study is observational, therefore safety monitoring is not required.

7.1 Clinical Adverse Events

7.2 Adverse Event Reporting

Since the study procedures are not greater than minimal risk, SAEs are not expected. If any unanticipated problems related to the research involving risks to subjects or others happen during the course of this study (including SAEs) these will be reported to the IRB in accordance with CHOP IRB SOP 408: Unanticipated Problems Involving Risks to Subjects. AEs that do not meet prompt reporting requirements will be summarized in narrative or other format and submitted to the IRB at the time of continuing review (if continuing reviews are required), or will be tracked and documented internally by the study team but not submitted to the IRB (if continuing reviews are not required).

8 STUDY ADMINISTRATION

8.1 Data Collection and Management

1. Confidentiality.

   There will be a master list containing PHI and subject ID number separate from data forms (paper and electronic) that have only a study ID number. The master list will be on a separate computer, removable disk drive, or in a locked file cabinet. This form of data is considered "coded" not de-identified. As long as the data can be re-linked to identifiers, the data is coded. Only after the key to the code or the Master List is destroyed will the data be considered de-identified.

   Study team will use password-protected files.

   Data files will be encrypted.

2. Security. The Team will have a copy of the password-protected file on office computer, with the original in one of the Hospital's secure servers.

3. Anonymization, de-identification or destruction. The identifiers and other data will be destroyed 6 years after study completion in compliance with CHOP Data Retention Policy A-3-9.

8.2 Confidentiality

All data and records generated during this study will be kept confidential in accordance with Institutional policies and HIPAA on subject privacy and that the Investigator and other site personnel will not use such data and records for any purpose other than conducting the study.

No identifiable data will be used for future study without first obtaining IRB approval or IRB determination of exemption. The investigator will obtain a data use agreement between provider (the PI) and any recipient researchers (including others at CHOP) before sharing a limited dataset (dates and zip codes).

Participant confidentiality is strictly held in trust by the participating investigators, their staff, the sponsor, and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests, in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The sponsor representatives and regulatory authorities (e.g., IRB, OHRP) may inspect all documents and records required to be maintained by the investigator. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each study site for internal use during the study. At the end of the study, all research records will be stored in a secure location for the time period dictated by the sponsor and institutional regulations.

The research data will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by research staff will be secured and password protected. At the end of the study, all study databases will be archived at CHOP.

8.3 Regulatory and Ethical Considerations

8.3.1 Data and Safety Monitoring Plan

The CHOP PI will monitor and review the study progress, subject safety, and the accuracy and security of the emerging data.

8.3.2 Risk Assessment

Answering questionnaires is the intervention associated with the study which could carry specific risks. For example, patients or families may be upset by reflecting on limitations in their quality of life. There are no questions about suicidal ideas. The study design allows participant withdrawal at any time or for participants to skip questions which are considered too personal. In our experience, many patients and families deeply value speaking openly about their perspective and lived experience with ARPKD. There is no direct benefit to participation in this study.

Efforts will be made to limit the use and disclosure of the subject's personal information, including research records, medical records, and Protected Health Information (PHI), to authorized members of the study team and to people who have a need to review this information. Identifiable personal information will not be given to anyone unless we obtain the subject's written permission, except as described in the consent form or if the law

requires it. We will make every effort to keep information private, but no one's privacy can be totally guaranteed. There is a risk of breach of confidentiality.

8.3.3 Potential Benefits of Study Participation

There is no immediate or direct benefit to the subjects from the research study except the possibility that data generated from this investigation may provide important insights for the design of future ARPKD clinical trials.

8.4 Recruitment Strategy

Potential subjects will be identified by the ICD-10 diagnosis code for ARPKD in the CHOP Epic EHR and Inherited Kidney Disorders Program. The study team will reach out to potential participants and describe the study during their clinical visits, study recruitment email, phone call or flyer. If they express interest, the study team will provide specific study information through the consent process. Consent will be available in person, over the phone, or via e-consent (REDCap). We will use CHOP's Research Discovery Finder to aid in recruitment efforts.

External collaborator Dr. John Sayer from Newcastle, UK will distribute CHOP consent and survey links to his patients and colleagues. He will determine diagnosis and review his patient's medical records.CHOP investigators will not receive medical records from UK subjects. A limited dataset will be entered into CHOP's REDCap. Chop staff will not contact non-CHOP patients and there will not be any transfer of medical record. Dr. Sayer will consent and input his subjects data into CHOP's REDCap.

8.5 Informed Consent/Assent and HIPAA Authorization

External collaborator Dr. John Sayer from Newcastle, UK will distribute CHOP consent and survey links to his patients and colleagues.

The consent process:

- Patients with ARPKD meeting the inclusion criteria for enrollment will be identified.
- These patients and their parents or legally-authorized representatives (LAR) will be approached by the PI and/or clinical research coordinator to discuss the protocol in the privacy of a consultation room (in-person) or over the phone. Potential participants also will be able to be consented remotely through the REDCap e-consent process. The study team will direct participants through the e-consent RedCap process.
- The physician and/or the clinical research coordinator will describe the purpose of the study (in lay language), the alternatives to participating and the risk and benefits of the research, and alternative approaches. In addition, potential participants will be advised that participation is voluntary and that they are free to withdraw at any time without penalty. Considerations around confidentiality and any foreseeable risks and benefits will also be discussed with potential participants.

- The patient and family will be given time to consider the protocol and ask questions, as well as to discuss the study with other care providers/family members prior to agreeing to participate.

- Once all questions are answered, the participants/parents/LAR will be offered to participate in the study and be asked to verbally confirm they understand all the aspects of the study.

- If the participant/parents/LAR decides to participate, the IRB-approved research study consent form will be made available by a printable and/or downloadable format. For interested families who do not have the required computer access, printed forms will be provided by mail, upon request.

- The participant/parents/LAR will sign the informed consent documentand submit it to the research coordinator prior to the administration of any study questionnaires.

- Consent of at least one parent/LAR will be documented on the consent form (or as determined by the IRB). Assent for subjects aged 7-11 years old will be obtained and documented on the parental/LAR consent form.

- Additional staff members (nursing, social work, or other) may participate in this and subsequent sessions, in order to optimize our ability to ensure that the information provided is comprehensive.

8.5.1 Screening

The PI will determine eligibility of subjects. Subjects will be screened for a diagnosis of ARPKD through their medical record. The study team will describe the study, and if subjects are interested, they will be given the consent to review.

8.5.2 Individuals with Limited English Proficiency

Questionnaires are only available and validated in English.

8.6 Payment to Subjects/Families

There will be no payment to subjects.

9 PUBLICATION

Only aggregate data without individually-identifiable information will be published. Data analysis will be performed at CHOP in collaboration with our colleagues at the University of Heidelberg.

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