ADPedKD: An international web-based database for longitudinal data registry of children with Autosomal Dominant Polycystic Kidney Disease (ADPKD)

Protocol version 3, 19/06/2017

DATA PROCESSING ANNEX, 02/07/2018

Sponsor:

Name: UZ Leuven

Address: Herestraat 49, 3000 Leuven

Principal Investigator:

Name: Prof. Djalila Mekahli

Address: Herestraat 49, 3000 Leuven

Telephone: 0032 16 341866

Fax: 0032 16 34 38 42

Email: djalila.mekahli@uzleuven.be

Sub-investigator:

Name: Dr. Stéphanie De Rechter

Address: Herestraat 49, 3000 Leuven

Telephone: 0032 16 342086

Fax: 0032 16 34 38 42

Email: stephanie.derechter@uzleuven.be

Signatures

_____ 19/6/2017

Principal Investigator Date

Print Name: Djalila Mekahli

_____ 19/6/2017

Sub-Investigator Date

Print Name: Stéphanie De Rechter

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1. Study Synopsis

Title of clinical trial	An international web-based database for longitudinal data registry of children with Autosomal Dominant Polycystic Kidney Disease (ADPKD)
Protocol Short Title/Acronym	ADPedKD
Sponsor name	UZ Leuven
Principal Investigator	Djalila Mekahli
Medical condition or disease under investigation	Autosomal Dominant Polycystic Kidney Disease (ADPKD)
Purpose of registry	To establish clinical and/or bio-markers predicting the risk of early and progressive disease. To define recommendations for the follow-up of children with ADPKD to improve their outcome and survival.
Primary objective	To define disease progression factors for pediatric ADPKD.
Secondary objective(s)	- To identify clinical and/or bio-markers predicting the risk of early and progressive disease. - The development of clinical practice guidelines: unified diagnostic, follow-up and treatment approaches regarding modifiable disease factors from childhood.
Trial Design	Web-based registry, including retrospective and prospective longitudinal data
Endpoints	n/a

Sample Size	1500
Summary of eligibility criteria	Children, diagnosed with ADPKD before the age of 19 years. Adults, diagnosed with ADPKD before the age of 19 years.
Maximum duration of treatment of a subject	n/a
Version and date of final protocol	Version 3 Date : 19/06/2017
Version and date of protocol amendments	Idem

2. Background and rationale

Autosomal Dominant Polycystic Kidney Disease (ADPKD) is the most common monogenic cause of kidney failure, affecting more than 1 in 400 to 1000 live births and approximately 13 million individuals worldwide, representing a major socio-economic medical problem in the world. ADPKD arises as a consequence of mutations in the *PKD1* gene, accounting for 85% of cases, or *PKD2* gene, accounting for 15% of cases, encoding the proteins polycystin-1 (PC1) and -2 (PC2), respectively.[1] Recently, mutations in *GANAB* have been shown to be disease-causing as well.[2]

ADPKD is characterized by the slowly progressive development and enlargement of cysts in all nephron segments, ultimately leading to end-stage renal disease (ESRD) in many cases. Fifty % of patients need renal replacement therapy by the age of 60 years. Patients with *PKD2* mutations have a milder phenotype and reach ESRD approximately 20 years later than those with *PKD1* mutations. Moreover, ADPKD as a bona fide ciliopathy is a systemic disorder, associated with cyst formation in other organs, mostly in liver; intracranial arterial aneurysms, cardiac valvular defects, abdominal and inguinal hernias and colonic diverticulosis. There is a major unexplained phenotypic variability, even intra-familial.[3] Currently, there is no definitive curative treatment. Only the vasopressin-2-receptor antagonist, Tolvaptan, is now available in Europe for a subset of rapidly progressive adult patients, moderately slowing down disease progression.[4] Based on the cellular mechanisms, drug targets were tested *in vitro* and *in vivo* to slow cystogenesis. However, most clinical trials have been limited by inadequate power, short follow-up, patient's heterogeneity regarding their renal function, doses with inadequate pharmacological effects and uncertain concentration in the target organs. Moreover, the question remains whether it would be more efficacious to administer drugs before extensive renal damage has occurred.[5]

As cyst formation begins early in life, frequently in utero, ADPKD should no longer be considered an adult onset disease.[5] Significant disease progression with renal cyst formation and expansion occurs in the first decades. Moreover, it has been shown that hypertension is the earliest and most prevalent systemic feature of ADPKD children occurring in 5-44%.[6-8] It can present during the new-born or infantile period and correlates with the severity of structural renal disease despite a normal renal function.[9] Importantly, children with hypertension demonstrate a greater increase in cyst number and fractional cyst volume over time versus children with normal blood pressure[10, 11] and it has been shown that total kidney volume and total cyst volume are surrogate markers of disease progression in ADPKD,

now FDA-approved.[12-14] Unpublished data show that ADPKD children display non-dipping hypertension, for which there are no therapeutic guidelines available on this moment (ADPKiDs study). Other cardiovascular abnormalities found in affected children are mitral-valve prolapse and left ventricular hypertrophy, but also important independent predictors of future cardiovascular events and mortality, as an impaired endothelium-dependent dilatation and increased arterial stiffness.[15] Micro-albuminuria and proteinuria are common in affected children as well, and correlate with hypertension and the severity of renal disease.[7]

Families with early-manifesting offspring have a high recurrence risk that subsequent siblings will follow a similar early-manifesting clinical course.[16] Furthermore, long-term clinical outcomes in children with very-early onset (VEO) ADPKD, meaning diagnosed in utero or within the first 18 months of life, are worse compared to non-VEO ADPKD patients.[17] However, until now, it is controversial whether at-risk children should be tested for the presence of the disease, and if so, how this should be done. A recently performed survey among pediatric, adult nephrologists and geneticists illustrates the lack of uniform guidelines. (De Rechter et al, submitted).

Recently, it has been recommended to routinely plan medical check-ups, with blood pressure measurement and urinalyses in all at-risk children, as a standard of care.[7, 18]

3. Trial objectives and Design

3.1 Trial objectives

A longitudinal international registry on ADPKD children is built up in this ADPedKD project, to provide an observational evidence base for unified diagnostic, follow-up and treatment approaches regarding modifiable disease factors in order to slow down disease progression such as hypertension and proteinuria. We also aim to establish clinical and/or bio-markers predicting the risk of early and progressive disease and potentially lay the foundation for clinic trial patient selection.
To sum up, our objectives are the following:

As data on pediatric ADPKD are scarce, the first aim is to generate data on its incidence and presentation in childhood, and of its comorbidities such as hypertension and left ventricular hypertrophy. Secondly, we aim to define a pediatric scoring system, after identification of progression factors, by which we will be able to stratify patients from an early disease stage on into

low to high risk categories. Next, we will assess the effect of early treatment of hypertension and proteinuria on long term renal outcome. Last, we aim to provide international guidelines for work-up, follow-up and treatment of ADPKD in childhood.

3.2 Expected endpoints

There is currently no consensus on diagnosis, management or follow-up for ADPKD children. No longitudinal data set is described from children's age. The expected outcomes of ADPedKD to fill these milestones. The scientific activities within ADPedKD will lead to a firm evidence base for the development of clinical practice guidelines. We expect this as until now only small patient cohorts have been published, especially in pediatric ages, from which significant information on disease management could be withdrawn.

ADPedKD will generate a deeply characterized cohort that will be available for epidemiologic studies in the future. The participation of most major pediatric nephrology centers in the Registry will expedite the transfer of the obtained insights to clinical patient care, and help harmonizing the quality of care for this patient group throughout the world.

3.3 Trial Design

Well-established methods are used to achieve the specific goals of ADPedKD. The web-based database is under construction, and is based on the previous made ARegPKD database (S number 56357, with UZ Leuven, Prof Mekahli as head investigator for Belgium) (www.aregpkd.org).[19] In a collaboration between the Pediatric Nephrology Department of the University Hospital of Cologne (Max Liebau) and the Pediatric Nephrology Department of the University Hospital of Leuven (Djalila Mekahli), we will recruit patients with ADPKD, from children's age, both retrospectively and prospectively, initially from centers participating in the ARegPKD, which includes already 323 ARPKD patients, and from the ERKNet network. Here, it is important to notice ADPKD is far more frequent compared to ARPDK: 1/400-1000 live births compared to 1/20 000 respectively. The diagnosis of ADPKD relies on genetic analysis or a positive familial history and imaging. After signing the informed consent, patient data are pseudonymously introduced in the web-based database. Data protection is secured by use of SSL-connections and password restriction of the webpage.

To assure highest levels of data quality, the online case report forms will require mandatory inclusion of key variables, and include automated entry checks using predefined plausibility ranges. A data

validation plan for automated validity checks of entered data within the different subsections will be established. By these precautions, the risk of data entry errors will be minimized. The clinical data are collected, analysed and statistical analysis will be performed with the help of an experienced bio-informatician, to identify those factors important for disease progression at a pediatric age, after correction for multiple testing. Special interest is paid to the initial presentation, pre- and perinatal history, genetic analysis, renal function and longitudinal follow-up. An overview of collected data is given in the attached file.

To decrease existing large differences in ADPKD follow-up practices, especially in pediatric cohorts, ADPedKD is dedicated to the evaluation of current approaches. We focus on the key clinical problems in ADPKD, i.e. treatment of arterial hypertension and prevention of renal disease progression by established pharmaceutic intervention and cardiovascular complications.

In summary, ADPedKD will collect the largest longitudinal data set on ADPKD in the world.
In the future, the coded data might be used in international collaborations.

Expected number of participating centers and sample size:

After approval of the ethical committee of University Hospitals Leuven, we aim to start inclusion of other centers both in Belgium and internationally. Per new participating country, documents will be translated once by the main investigator of that country. Each center will however be responsible for their own ethical approval, as necessities for this might be different across and within countries. The project is currently being proposed at several congresses and work group meeting worldwide, to introduce its aim. On this moment, we have confirmation that the following countries would like to participate in this project: Australia, Belgium (apart from Leuven), France, Germany, Greece, Italy, Lithuania, the Netherlands, Spain and UK.

Depending on the center, we expect the number of children to be included per center from a minimum of 10 to a maximum of 100.

Total target sample size is 1500.

4. Selection and withdrawal of subjects

4.1 Inclusion criteria

Inclusion criteria for ADPedKD are:

- ADPKD diagnosed by positive family history and ultrasound (the presence of a single cyst, preferably >1 cm in diameter[7]) and/or molecular assessment

- ADPKD diagnosed at the age of 19 years or younger

- informed consent of patient and/or his/her parents/legal representatives

- Contiguous gene syndrome *TSC2-PKD1*

4.2 Exclusion criteria

Exclusion criteria for ADPedKD are:

- Other renal cysts diseases such as TSC, ARPKD, etc…

- Genetic proof of another cystic kidney disorder

- ADPKD diagnosed at an age older than 19 years

5. Statistics

5.1 Sample size

Formal sample size estimation has not been performed for this study, as this is the first study including patients from childhood.

5.2 Analysis

Statistical analysis will initially focus on descriptive analysis including calculation of relative and absolute frequencies for binary/categorical variables and for continuous variables calculation of mean, standard deviation, median, interquartile range, minimum and maximum. Inferential analyses will be planned based on first results of intermediate analyses and predefined in detail in a statistical analysis plan (SAP). Further longitudinal data regarding outcomes of markers of renal function and e.g. kidney size, and cardiovascular morbidity will be analyzed using appropriate statistical methods such as mixed modeling. In case of missing data appropriate methods (e.g. multiple imputation) will be used to handle them. Furthermore the aspect of multiple testing will be considered. Potential sources of bias will be examined and considered in the analyses.

6. Direct access to source data and documents

The Investigators and the University Hospitals Leuven - Cologne will permit EC review by other participating centers, by providing direct access to project overview- information - informed consent documents after registration. Centers will be able to register new patients. Participating centers can ask the Investigators to extract data of their own registered patients, but won't have a direct access to these dataset.

7. Ethics and regulatory approvals

The trial will be conducted in compliance with the principles of the Declaration of Helsinki (current version), the principles of GCP and in accordance with all applicable regulatory requirements. This protocol and related documents will be submitted for review to the Ethics Committee of the University Hospitals Leuven.

The Study can and will be conducted only on the basis of prior informed consent by the Subjects, and/or their legal representatives, to participate in the Study. The Participating Site shall obtain a signed informed consent form (ICF) for all patients prior to their enrollment and participation in the Study in compliance with all applicable laws, regulations and the approval of the local Ethics Committee, if required. The Participating Site shall retain such ICFs in accordance with the requirements of all applicable regulatory agencies and laws.

The Investigator and the Participating Site shall treat all information and data relating to the Study disclosed to Participating Site and/or Investigator in this Study as confidential and shall not disclose such information to any third parties or use such information for any purpose other than the performance of the Study. The collection, processing and disclosure of personal data, such as patient health and medical information is subject to compliance with applicable personal data protection and the processing of personal data (Directive 95/46/EC and Belgian law of December 8, 1992 on the Protection of the Privacy in relation to the Processing of Personal Data).

When data are pseudonymously coded, there continues to be a link between the data and the individual who provided it. The research team is obligated to protect the data from disclosure outside the research according to the terms of the research protocol and the informed consent document. The subject's name or other identifiers should be stored separately from their research data and replaced with a unique code to create a new identity for the subject. Note that coded data are not anonymous.

8. Data Handling

After signing the informed consent, patient data is pseudonymously introduced in the web-based database. Data protection is secured by use of SSL-connections and password restriction of the webpage.

9. Data Management

Only the Investigators of the University Hospitals Leuven and Cologne have the possibility to manage the data.

10. Publication Policy

It is anticipated that the results of the overall Study shall be published in a multicenter publication, involving the data of all clinical sites participating in the Study. Participating Site is not allowed to publish any data or results from the Study prior to the multicenter publication.

Publications will be coordinated by the Investigator of Sponsor, in collaboration with Cologne. Authorship to publications will be determined in accordance with the requirements published by the

International Committee of Medical Journal Editors and in accordance with the requirements of the respective medical journal.

11. Insurance/Indemnity

In accordance with the Belgian Law relating to experiments on human persons dated May 7, 2004, Sponsor shall assume, even without fault, the responsibility of any damages incurred by a Study Patient and linked directly or indirectly to the participation to the Study, and shall provide compensation therefore through its insurance.

Sponsor shall enter into an insurance agreement in order to cover the liability for any damages incurred by a Study Patient from a Belgian Participating Site.

If an insurance coverage is required by local laws of non-Belgian Participating Sites, these Participating Sites shall have and maintain in full force and effect during the term of this Agreement (and following termination of the trial to cover any claims arising from the trial) adequate insurance coverage for possible damages linked directly or indirectly to the patients' participation to the trial at Participating Sites.

12. Financial Aspects

The ADPedKD project is financially supported by an ESPN research grant (10.000 euro), and ERA-EDTA grant (5.000 euro). An application to the University Hospitals of Leuven 'Fonds Academische Studies' was performed in March 2017.

The ADPedKD project has the following financial necessities:

- Building of the web-based registry: 25.000 euro
- yearly maintenance: 1.000 euro per year
- Study nurse for data entry
- statistician for data analysis

13. References

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DATA PROCESSING ANNEX ("DPA") TO THE PROTOCOL

Definitions:

"**Protocol**" means the document entitled **ADPedKD: An international web-based database for longitudinal data registry of children with Autosomal Dominant Polycystic Kidney Disease (ADPKD)** containing the details of the academic study as developed by the Sponsor as approved by the relevant ethics committee.

"**Sponsor**" means Universitaire Ziekenhuizen, located at Herestraat 49, B-3000 Leuven, Belgium

Participating site acts as a data processor as defined under article 4, 8) of the Regulation (EU) 2016/679 ("**Data Processor**") for the Sponsor who acts as data controller as defined under article 4, 7) of the Regulation (EU) 2016/679 ("**Data Controller**").

"**Applicable Law**" means any applicable data protection or privacy laws, including:

(i) the European Data Protection Directive (95/46/EC) and upon its entry into force the Regulation (EU) 2016/679 also referred as the General Data Protection Regulation ("GDPR");
(ii) other applicable laws that are similar or equivalent to or that are intended to or implement the laws that are identified in (a) of this definition;

"**Personal Data**" means any information relating to an identified or identifiable natural person ('**Data Subject**'), including without limitation pseudonimized information, as defined in Applicable Law and described in the Protocol.

Rights and obligations:

1) The Data Processor is instructed to process the Personal Data for the term of the Protocol and only for the purposes of providing the data processing tasks set out in the Protocol.
2) The Data Processor must ensure that persons authorized to process the Personal Data have committed themselves to confidentiality or are under an appropriate statutory obligation of confidentiality.
3) The Data Processor shall implement appropriate technical and organizational measures to prevent that the Personal Data processed is:
   (i) accidentally or unlawfully destroyed, lost or altered,
   (ii) disclosed or made available without authorization, or
   (iii) otherwise processed in violation of Applicable Law.
4) The appropriate technical and organizational security measures must be determined with due regard for:
   (i) the current state of the art,
   (ii) the cost of their implementation, and
   (iii) the nature, scope, context and purposes of processing as well as the risk of varying likelihood and severity for the rights and freedoms of natural persons.
5) The Data Processor shall upon request provide the Data Controller with sufficient information to enable the Data Controller to ensure that the Data Processor's obligations under this DPA are complied with, including ensuring that the appropriate technical and organizational security measures have been implemented.

6) The Data Controller is entitled to appoint at its own cost an independent expert, reasonably acceptable to Data Processor, who shall have access to the Data Processor's data processing facilities and receive the necessary information for the sole purpose of auditing whether the Data Processor has implemented and maintained said technical and organizational security measures. The expert shall upon the Data Processor's request sign a non-disclosure agreement provided by the Data Processor, and treat all information obtained or received from the Data Processor confidentially, and may only pass on, after conferral with Data Processor, the findings as described under 8) (ii) below to the Data Controller.
7) The Data Processor must give authorities who by Union or Member State law have a right to enter the Data Controller's or the Data Controller's processors' facilities, or representatives of the authorities, access to the Data Processor's physical facilities against proper proof of identity and mandate, during normal business hours and upon reasonable prior written notice.
8) The Data Processor must without undue delay in writing notify the Data Controller about:
   (i) any request for disclosure of Personal Data processed under the Protocol by authorities, unless expressly prohibited under Union or Member State law,
   (ii) any finding of (a) breach of security that results in accidental or unlawful destruction, loss, alteration, unauthorized disclosure of, or access to, Personal Data transmitted, stored or otherwise processed by the Data Processor under the Protocol, or (b) other failure to comply with the Data Processor's obligations, or
   (iii) any request for access to the Personal Data (with the exception of medical records for which the Data Processor is considered data controller) received directly from the data subjects or from third parties.
9) Such a notification from the Data Processor to the Data Controller with regard to a breach of security as meant in 8) (ii)(a) above will contain at least the following information:
   (i) The nature of the Personal Data breach, stating the categories and (by approximation) the number of Data Subjects concerned, and stating the categories and (by approximation) the number of the personal data registers affected (datasets);
   (ii) The likely consequences of the Personal Data breach;
   (iii) A proposal for measures to be taken to address the Personal Data breach, including (where appropriate) measures to mitigate any possible adverse effects of such breach.
10) The Data Processor shall document (and shall keep such documentation available for the Data Controller) any Personal Data breaches, including the facts related to the Personal Data breach, its effects and the corrective measures taken. After consulting with the Data Controller, the Data Processor shall take any measures needed to limit the (possible) adverse effects of Personal Data breaches (unless such consultation cannot be awaited due to the nature of the Personal Data breach).
11) The Data Processor must promptly reasonably assist the Data Controller (with the handling of (a) responses to any breach of security as described in 8) (ii) above and (b) any requests from Data Subjects under Chapter III of the GDPR (upon its entry into force), including requests for access, rectification, blocking or deletion. The Data Processor must also reasonably assist the Data Controller by implementing appropriate technical and organizational measures for the fulfilment of the Data Controller's obligation to respond to such requests. The Data Processor must reasonably assist the Data Controller with meeting the other obligations that may be incumbent on the Data Controller according to Union or Member State law where the assistance of the Data Processor is implied, and where the assistance of the Data Processor is necessary for the Data Controller to comply with its obligations. This includes, but is not limited to, at the request to provide the Data Controller with all necessary information about an incident under 8) (ii), and all necessary information for an impact assessment in accordance with Article 35 and Article 36 of the GDPR.

Subprocessor:

12) The Data Processor may only engage a subprocessor, with prior specific or general written consent from the Data Controller. The Data Processor undertakes to inform the Data Controller of any intended changes concerning the addition or replacement of a subprocessor by providing a reasonable prior written notice to the Data Controller. The Data Controller may reasonably and in a duly substantiated manner object to the use of a subprocessor. The Data Processor must inform the Data Controller in writing of the discontinued use of a subprocessor.
13) Prior to the engagement of a subprocessor, the Data Processor shall conclude a written agreement with the subprocessor, in which at least the same data protection obligations as set out in this DPA shall be imposed on the subprocessor, including obligations to implement appropriate technical and organizational measures and to ensure that the transfer of Personal Data is done in such a manner that the processing will meet the requirements of the Applicable Law.
14) The Data Controller has the right to receive a copy of the relevant provisions of Data Processor's agreement with the subprocessor related to data protection obligations. The Data Processor shall remain fully liable to the Data Controller for the performance of the subprocessor obligations under this DPA. The fact that the Data Controller has given consent to the Data Processor's use of a subprocessor is without prejudice for the Data Processor's duty to comply with this DPA.