Patient information and informed consent to the participation in the ARPKD registry study ARegPKD

Initiator of the study:
Max C. Liebau, MD
Department of Pediatrics
University Hospital of Cologne
Kerpener Str. 62
50937 Koeln
Germany

Substitute:
Markus Feldkötter, MD
Department of Pediatrics
University Hospital Bonn
Adenauerallee 119
53113 Bonn
Germany

Dear patients,

Your doctor has made the diagnosis of "autosomal recessive polycystic kidney disease" (ARPKD) for you and has asked you to participate in our ARPKD patient registry study. With this form, we want to give you an overview over the purpose of the registry, as well as potential benefits and risks of your participation. Please take some time to read the following information carefully and please consult your doctor if you have any further questions.

What is known about ARPKD?
ARPKD is an inborn disease that progressively affects the kidneys and the liver. It is a rare but severe disorder and an important cause of end stage renal failure mainly during childhood and adolescence. ARPKD may present with different symptoms and at different ages. While many patients present during early childhood – or even prenatally – others show the first symptoms during late adolescence. There is also a major variability of the symptoms in ARPKD patients, even between affected siblings. ARPKD always affects the liver, leading to fibrotic remodeling of the liver tissue. In many patients renal cysts, fluid-filled cavities within the kidneys, occur. However, other organs may be involved.

ARPKD is an inborn disease. According to the current state of research it is caused by mutations in a single gene, called *PKHD1*. ARPKD is a so-called recessive disorder, which means that patients carry two affected copies of the gene, while their – usually unaffected – parents carry a healthy and an affected copy of the gene.
Within the last 10-15 years some progress has been made in the understanding of the mechanisms leading to cystic kidneys. However, there is still no causative treatment for ARPKD. Data on long-term clinical courses and treatment response remain sparse.

While we progress in our search for curative treatment, it is critical for us to learn as much as possible about this rare and severe disorder in order to improve our understanding of the underlying mechanisms and of the clinical courses of ARPKD.

What are the goals of the ARPKD registry? Why is ARegPKD being conducted?
As a multinational registry ARegPKD will give the possibility to collect ARPKD patient data from different centers all over the world (mainly across Europe). It is our goal to understand this disease much better than we currently do and to identify e.g. symptoms and disease courses that

may point to a mild or a severe progression of the disease. Would some patients benefit from early treatment? Which different treatment approaches have been taken so far and which did show good results? Furthermore, we aim to look for the genetic causes of the observed variability in symptoms. Are there genetic variants that modify disease progression?

These questions can only be addressed in the setting of an international registry including patients from multiple centers. As ARPKD is a rare disease, every single center has only limited experience with this disorder. For example, only around 30 patients with this disorder are born in Germany every year. The latest data collection for Germany included data from 164 patients. We therefore want to collect the data from different centers across Europe in a central registry to get a broader understanding. Patient data will be pseudonymously collected (see below), and our registry may serve as an essential central pool of data for future therapeutic studies. The registry is thus being supported e.g. by the German Pediatric Nephrology Association (GPN).

Who can take part in the registry? How to register?
Only doctors can submit data to ARegPKD. You do not have to introduce data yourself. Every ARPKD patient, female or male, children and adults, can participate in ARegPKD.
If the disease also affects other family members, we ask you to inform them about our registry. However, your doctor can only include the data once you have submitted the written informed consent.

Who cannot take part in the registry?
Patients who have been diagnosed clinically, genetically or by histological evaluation to suffer from another cystic kidney disease than ARPKD may not participate.

How is ARegPKD being conducted? Which data are collected? Which examinations will be performed?
If you agree, medical staff at your corresponding hospital will include available clinical data e.g. on symptoms, ultrasound examinations, laboratory values, family history, renal and hepatic biopsies, and on performed genetic studies into the online data base. This data will be pseudonymous, meaning that your name and address will not be included. Your name will be replaced by an ID-code that will consist of a code for the center and a personal ID (e.g. Harry Potter in Cologne → 01-13). Only your doctor will be able to link this ID data back to you. For this purpose, your doctor will have a list, which will not be accessible for the coordinators of the registry. In exceptional cases, members of the study coordinating team will introduce medical data into the registry on site. Of course these members are also subject to medical confidentiality.

In yearly follow-ups data, e.g. on renal and hepatic function or new symptoms that may have developed will be included.

If you are already participating in a pediatric nephrological study, e.g. the 4C study (Cardiovascular Comorbidity in Children with Chronic Kidney Disease Study), specific data points can, if you agree, be transferred from the database of the study you are already participating in into the ARegPKD database. This is exclusively possible for data that has been obtained for the first study, e.g. your age, your height and growth or your laboratory values. Such a transferral of data facilitates the work of the registry, as these already existing datapoints do not need to be entered into a database for a second time. Obviously your data well be kept

pseudonymized at all times. The data to be transferred can only be related to you by your corresponding medical staff.

In case of substantial changes of the scientific goal of ARegPKD, you will get additional information from ARegPKD through your corresponding doctor.

During the establishment of the project, the corresponding ethics committee advised the initiators of ARegPKD. ARegPKD received a positive vote of the corresponding ethics committee.

Information on the handling of biological samples. How will biological samples be obtained? What will happen to these samples?
When a blood sample is taken during a routine visit, we will take an additional blood sample on the same occasion. The amount of blood required for these analyses will be 5 to 30 ml. For small children we will reduce the amount to the minimum. During the course of the disease we will take 2-10 ml of blood once every year. This process will thenbe repeated when blood will be taken during a routine visit. The samples will be centrally stored in a laboratory at the Children's Hospital of the Hannover Medical School in Germany. If you agree, the samples can be examined for genetic changes that might influence ARPKD. For this purpose, we want to analyze the genetic material of the tissue samples (the DNA) with novel high-resolution techniques for known changes associated with cystic kidney diseases but also want to look for changes that have not yet been described. If we find genetic changes that are known for ARPKD, e.g. in the *PKHD1* gene, we can inform your doctor, if you wish so. In some countries the information on *PKHD1* changes will already be available for many patients.

In the unexpected event that we obtain medical findings in the samples taken from you, which would be crucial for the maintenance or recovery of your health, your doctor will be informed and will discuss further proceedings. Under certain circumstances, you may have to reveal this information in different contexts (e.g. before conclusion of a life insurance). If you do not want your doctor to be informed, you can express this in the form for the informed consent.

The genetic analyses will be performed in cooperation with our partners. These are currently:

Prof. Dr. Carsten Bergmann
Bioscientia Institut für Medizinische Diagnostik GmbH
Labor Ingelheim mit Zentrum für Humangenetik
Konrad-Adenauer-Straße 17
55218 Ingelheim
Germany

Prof. Dr. Klaus Zerres
Institut für Humangenetik
Uniklinik Aachen
Pauwelstraße 30
52074 Aachen
Germany
If you – for medical reasons – need a kidney or a liver biopsy, or a biopsy of any other organ, we want to collect a small piece of the biopsy or of the affected kidney/liver, which will be removed by surgery, and store it for further molecular, genetic or immunological analyses and for further

research on the disease and potential treatment options. With your approval, these samples can be obtained during the intervention without further harm and without impairment of the diagnostic possibilities. There will be no further intervention to obtain samples without a medical indication. Furthermore, ARegPKD offers the microscopic analyzation of biopsy material by an internationally recognized expert for ARPKD (a so-called reference histology assessment). The reference histology assessment will be performed by Prof. Dr. R. Büttner at the Institute of Pathology of the University Hospital of Cologne. The results will be communicated to your doctor. Remaining material, which will not be used for the analysis, will be stored at the site of the reference histology:

Prof. Dr. Reinhard Büttner
Institut für Pathologie
Uniklinik Köln
Kerpener Str. 62
50937 Köln
Germany

Within the ARPKD registry biological samples shall be collected and stored in a so-called 'biobank', meaning blood samples (blood, plasm, serum), tissue samples of kidney and liver, potentially samples of biopsies from other tissues. From these genetic material can be extracted, which will also be stored. After pseudonymisation the samples will be kept at the Pediatric Research Centre of the Hannover Medical School, under the direction of Prof. Dr. T. Illig:

Prof. Dr. Thomas Illig
Pädiatrisches Forschungszentrum
Medzinische Hochschule Hannover
Carl-Neuberg-Str. 1
30625 Hannover
Germany

With your approval, the biological samples will only be used for scientific research on cystic kidney diseases. The results of genetic analyses will be saved separately from your personal data and cannot be related to yourself without the assistance of your doctor. Access to the pseudonymized samples and to the data required for analysis can be requested for scientific studies. The requesting centers have to send a written application to the steering committee (the scientific direction of the ARegPKD consortium, consisting of various experts for pediatric nephrology from different countries). The request can only be submitted following the evaluation of a scientific study by an ethics committee. The steering committee will then decide on the request.

The samples will be stored in Hannover but may, under certain circumstances, be sent to other places (e.g. laboratories) and potentially to other countries. However, you have the right to ask for the elimination of your samples at all times. Data that has already been obtained will remain within the study even after the elimination of your samples, for as long as you agree.

As ARPKD is a rare and sever disease the samples are of very high scientific value. They will therefore not be eliminated after a certain time but will be stored indefinitely.

Will there be additional examinations or additional consultations required for ARegPKD?
No. Your doctor will introduce the data into the registry. There will be no additional examinations or hospital visits that would otherwise not be performed. Importantly, there will be no additional takings of blood samples.

Which risks result from ARegPKD?
ARegPKD is a registry study. Within ARegPKD existing data will be collected. There will be no change of treatment or additional interventions for ARegPKD. There will be no additional takings of blood, but small blood samples will only be collected for ARegPKD during the takings that your doctor will do anyway.

How do you or your doctor profit from the participation? Are there any costs? Will you get any gratification?
Apart from the possibility to get your tissue material analyzed by a specialist, and the potential possibility to obtain information about genetic changes that may have caused the disease, the participation in ARegPKD is of no further profit to you. Potentially, all ARPKD patients may profit from the results obtained within this registry study.
Registered centers will get information on ongoing clinical trials or novel therapeutic options quickly. There will be no costs for participants. There will be no gratification either.

Information concerning data protection
Within the ARPKD registry personal data and medical findings will be collected and saved on a secure online server in a web-based data base before being analyzed. The electronic storage and analysis of data will be carried out pseudonymously, meaning that your name will be replaced by a patient ID consisting of an ID for the center and a personal ID (e.g. Harry Potter in Cologne → patient 01-13). Neither the exact date of birth noryour address will be entered. The month and year of birth will be collected. Your doctor will enter the data via a password-restricted area of SSL-secured webpage into the database (SSL: Secure Sockets Layer, a protocol for encrypting information over the Internet). The database will be placed on a server, which will be maintained by the computer center of the University Hospital of Cologne and will be situated at the computer center of the University of Cologne. You have the right on information about the saved data and on correction of erroneously processed data.
Transmission of data may only occur in a pseudonymized way to scientific institutions of the registry's direction and to their scientific cooperating partners. Everyone involved will treat these data confidentially, of course. The transmission may also occur to cooperating partners in other countries. If data protection in these countries is not equal to the level of data protection in Germany, ARegPKD will try to maintain the level of data protection ensured in Germany.
In the case of publication of the results of this research project in scientific journals and on scientific meetings, the publication will not contain personal data that would allow inferences on your person. Furthermore, the results may be used commercially, e.g. they may be patented. You will not profit from a potential commercial benefit.
ARPKD is a rare disease meaning that international data collections like ARegPKD are difficult to organize and of high scientific value. Registry data will therefore not be deleted within a certain time frame, as is usually done for other studies, but will be saved indefinitely.

What happens if I want to retract my consent?
The participation in the study is completely voluntary. You can withdraw yourparticipation in the study at any time without specification of reasons. There will be no negative consequences regarding your medical attendance. If you change your mind, please talk to your doctor.
By request, all data collected for the study will be deleted or anonymized (meaning this data cannot be linked to you in any way), and all remaining samples will be destroyed or handed over to you. If you decide to quit the study you can give your consent to the further storage of data samples already collected.

Who is your contact person?
Your first contact person for this study is your corresponding doctor.

Local doctor:
Name:
_____
Institution:
_____
Phone:
_____

Further questions?
Please do not hesitate to contact us for any further questions you may have.

Max Christoph Liebau, MD
Markus Feldkötter, MD

Klinik und Poliklinik für Kinder- und Jugendmedizin
Geb. 26, Uniklinik Köln
Kerpener Str. 62
50937 Köln
Germany
max.liebau@uk-koeln.de,
markus.feldkoetter@ukb.uni-bonn.de
or kinderklinik-studiensekretariat@uk-koeln.de

Participation in ARegPKD

Consent

I hereby declare my consent to the participation in the ARPKD registry study ARegPKD. I am aware that my participation is voluntarily and that I can retrieve my consent without the need to indicate any reason and without potential disadvantages in my medical treatment.

I have been informed about and I agree to the fact that my data and samples collected in the context of the study are saved and stored under a pseudonym. My name will not be registered and will not show up in case of the publication of study results.

A copy of the information and of the consent has been given to me. I had sufficient time to decide on the participation in the registry, had the chance to discuss the questions that I had and to discuss them with my doctor. The questions have been answered elaborately and understandingly.

Further topics of the informational conversation have been:

_____
_____
_____
_____
_____

I agree that my pseudonymized data that has been obtained within the ARegPKD registry study is saved, analyzed, and potentially published.

□ Yes □ No

I agree that samples from kidney, liver, or other biopsy samples from a medically indicated biopsy are sent to the reference histology center of the registry.

□ Yes □ No

I agree that pseudonymized samples may be used for further research on cystic kidney diseases.

□ Yes □ No

I agree that samples from kidney, liver, or other biopsy samples from a medically indicated biopsy, or from a biopsy during a medically indicated surgical procedure (e.g. explantation of an organ) are sent to the biobank of the registry and will be stored there.

□ Yes □ No

I agree that pseudonymized samples will be analyzed for genetic changes that may cause or aggravate cystic kidney diseases.

□ Yes □ No

In the case of detection of relevant genetic changes that may explain my cystic kidney disease, I want to be informed through my doctor.

□ Yes □ No

In the case of detection of medical findings that are of substantial value fort the maintenance or recovery for my health, my doctor shall be informed.

□ Yes □ No

In case of a participation in another pediatric nephrology study (in this case:_____): I agree to the transferral of selected data points from the database of the study into the ARegPKD database.

□ Yes □ No □ Does not apply

_____ _____

(patient name)

_____ _____

(name, date – to be written by patient/legal representative)(signature of patient)

_____ _____

(name of 1st parent/legal representative) *(signature)*

_____ _____

(name of 2nd parent/legal representative) *(signature)*

In case of full custody:
I confirm that I have full custody.

_____ _____

(name of parent/legal representative) *(signature)*

_____ _____

(place, date) *(stamp and signature of doctor)*