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# „Identifying best practices for obtaining ethical consent and for data and sample collection in pediatric rheumatic diseases – the role of the EU-wide ethics process in real-life“

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Widmen möchte ich diese Dissertation Frau Hannelore Kastner, die keine Sekunde an mir gezweifelt hat.

**List of abbreviations**

| | |
|---|---|
| SHARE | **S**ingle **H**ub and **A**ccess point for pediatric **R**heumatology in **E**urope |
| DNA | **D**eoxyribo**n**ucleic **A**cid |
| EU | **E**uropean **U**nion |
| USA | **U**nited **S**tates of **A**merica |
| BD | **B**ehcet's **D**isease |
| HLA | **H**uman **L**eucocyte **A**ntigen |
| REB | **R**esearch **E**thics **B**oard |
| WHO | **W**orld **H**ealth **O**rganization |
| ICH | **I**nstitute of **C**hild **H**ealth |
| EMA | **E**uropean **M**edicines **A**gency |
| FDA | **F**ood and **D**rug **A**dministration |
| SOP | **S**tandard **O**perating **P**rocedure |
| CIOMS | **C**ouncil for **I**nternational **O**rganizations of **M**edical **S**cience |

# 1 Introduction

Pediatric rheumatic diseases are rare and often devastating. In order to improve the knowledge and care as well as outcomes of affected children research and collaboration efforts across national borders is necessary.[25,98, 102]

Over the past decade substantial contributions to the progress of clinical for pediatric rare diseases have been made across Europe. Clinical tools, biomarkers and imaging strategies for children with rheumatic diseases have been developed by national innovative research teams.[25] Their evaluation and implementation mandate international patient cohorts and research partnerships given that some pediatric rheumatic diseases have incidences as low as one per million.[1]

## 1.1 Rare diseases and the need for European collaborative pediatric research

The European Conference on Rare Diseases defines a rare disease as "life-threatening or chronically debilitating being of such low prevalence that there is a need for special combined efforts in order to address them".[1]

Low prevalence is taken as prevalence of less than 5 per 10,000 in the Community.[2] While this number is extremely low, the total number of patients affected by a rare disease is much higher. It is estimated that there are about 8,000 different rare diseases affecting three million people in Germany alone. In Europe the number rises to an estimated 30 million patients affected by rare diseases.[1]

For pediatric diseases the incidences can be as low as 1 in a million children, but because of the fact, that 80% of rare diseases are of genetic origin, 75% of rare diseases affect children primarily. Considering the extremely low patient numbers, in order to perform research projects with patient numbers large enough to ensure that findings from scientific studies are reliable, combined efforts across national borders are needed to advance knowledge and improve care and outcomes of affected children.[3-7] A common framework, taking the various cultural, procedural and legislative differences of the countries in which study participants live into account, is still missing.

The diagnosis of rare diseases is difficult not only due to the low patient numbers, but also because of the variety of unspecific symptoms patients are presenting. Highly vari-

able phenotypes complicate the task of finding the correct diagnosis. On the other hand, diseases with a similar phenotype might have a completely different genetic etiology. Molecular genetic research on biological material collected from affected children and their healthy siblings can help improve our understanding of predictive factors enabling researchers to diagnose a disease much earlier. This results in a better disease control, less long-term damage and improvement of the quality of life.

Since the majority of rare diseases affects children, research on minors is important in order to enable us to identify predictive factors for the development of rare diseases even before the first symptoms occur. One of the ethical dilemmas caused by this possibility is the question of who should be informed about clinically relevant results and especially at which point the children themselves should be informed.

Children represent a special, vulnerable group of patients. Until a certain age they lack the ability to fully understand the scope of research and especially of genetic research and what it means to give consent to the use of data and samples for research. Pediatric research in general is often neglected because of the ethical dilemmas involved. Consent, scope of consent, return of results, reconsent at the age of majority, compensation for the participation and the principle of subsidiarity, i.e. studies that are likely to produce generalizable results should be performed preferably in adults are topics that are often discussed in medical literature.

On the other hand children and adolescents gain more and more insight on the matters and events that affect them on their way to reaching the legal age of majority and can express very clearly whether or not they approve of something even at a very young age.[4,8-11] One of the most important questions of the ethical discussion concerning the participation of minors in research projects is whether or not a child's disapproval should be taken into consideration and from which point on this possible disapproval should overrule the parents' approval.[10,12-14]
Pediatric research is nonetheless very important to ensure that children receive adequate and appropriate treatment.[9,15]
Researchers who want to perform pediatric research are confronted with a variety of

ethical, legislative and personal barriers, which have not been thoroughly analysed and clearly identified so far.

In an effort to support and promote collaborative international research, to identify the barriers that researchers face performing pediatric research and to find possible solutions to overcome these barriers, the European community has funded SHARE, the "Single Hub and Access point for pediatric Rheumatology in Europe".

## 1.2 "Diseases of Interest" pediatric rheumatism

The European Association of Pediatric Rheumatology defines pediatric rheumatism as a disease that can affect virtually all possible tissues in the human body. Autoimmune and auto-inflammatory processes affect the skin, blood vessels, visceral organs, the eyes, the brain and the musculoskeletal system accompanied by musculoskeletal pain and dysfunction as well as long term damage of all affected tissues and organs. Pediatric rheumatic diseases have a huge impact on the lives of patients and their families. In order to improve care and outcomes of children suffering from rare diseases as well as to advance knowledge, international collaborations are needed since some pediatric rheumatic diseases have incidences as low as one per million.[16] Across Europe several researchers have developed biomarkers, imaging strategies and clinical tools to enhance the treatment and care of affected children.

Pediatric Behçet's disease is one of these rare diseases that illustrates the difficulties and challenges of diagnosing and treating a rare rheumatic childhood disease.

## 1.3 Behçet's disease

Behçet's disease (BD) is a severe illness defined by systemic vasculitis of unknown origin affecting arteries and veins causing thrombosis and/or aneurysm. Various organs can be involved such as the central nervous system, kidneys, lungs, joints and the eyes (Uveitis). It is extremely rare in Northern Europe and even in countries like Japan, the Far and Middle East as well as countries bordering on the Mediterranean where BD is more common, the prevalence does not exceed 15-300/100000.

In children under the age of 16 it is even less frequent but takes a more severe course than in adults. Initially they may present with only one symptom or even atypical signs, therefore a number of patients is often not diagnosed. A study performed by I. Koné-Paut et al. showed a mean delay of 3.5 years between the first symptoms and satisfying international BD criteria. It is difficult to diagnose BD early enough in these young patients to start treatment and prevent consequential organ damage.[17]

There are important differences between patients with early BD and adults with BD. For example:

- The occurrence of uveitis is less common, but more damaging.
- The clinical course is worse in young male patients aged 15 to 25.
- There is a higher prevalence (15%) in some families pointing towards a genetic pre-condition.[17]

Although being identified as a clinical entity consisting of buccal or genital aphthae and ocular inflammation as early as 1937 by Huluçi Behçet, clinical symptoms are highly diverse. Considering the mostly unspecific symptoms and the lack of specific bio-pathological markers, diagnosis remains to be challenging. One of the major genetic risk factors of early-onset Behcet's Disease is a specific form of chromosome 6 in the Human Leukocyte Antigen region (HLA-B*51). A positive status for HLA B*51 combined with clinical symptoms points towards the diagnosis of BD.
Differentiating between BD and other inflammatory diseases is difficult. While most patients are adults when the first symptoms occur, pediatric cases have been reported.[18] The clinical presentation is marked by unpredictable phases of high inflammatory activity affecting mainly young adults at the age of 30, followed by a remission of symptoms. Diagnosis is generally based on the combination of clinical symptoms and is often delayed.

This delay leads to severe consequential organ damage, such as strokes, iris atrophy, cataract, secondary glaucoma, intestinal perforation, rupture of blood vessels, pericarditis, myocarditis, endocarditis, valve lesions and coronary artery lesions, especially in younger patients often presenting with a more severe disease course. [19]

For adults, internationally valid criteria have been defined and published by an expert committee in 2013. In the absence of other clinical explanations, patients presenting with the following symptoms and scoring 4 or more points have a high risk of BD:

- Ocular lesions (2 points)
- Genital aphthosis (2 points)
- Oral aphthosis (2 points)
- Skin lesions (1 point)
- Neurological manifestations (1 point)
- Vascular manifestations (1 point)
- Positive pathergy test (1 point)

For children, provisional classification criteria have been defined based on the largest cohort study for BD in children:

- Ocular lesions (1 points)
- Genital aphthosis (1 points)
- Recurrent oral aphthosis (1 points)
- Skin lesions (1 point)
- Neurological manifestations (1 point)
- Vascular manifestations (1 point) [19]

Based on this situation a biobank that analyses clinical and genetic parameters to define predisposing factors leading to earlier treatment and thus better chances of a favourable outcome can only be effective by recruiting large numbers of mainly minor patients from all over the European Union.

### 1.4 Biobanks

The Council of Europe states that biobanks should be implemented with the goal of supplying biological material or data for multiple future research projects. Biobanks contain samples and may also include the collection of personal data (medical, genealogical or lifestyle data) and may be continuously updated. Any personal data should be considered confidential and protected by the law against inappropriate disclosure.[20]
In every case appropriate consent should be given and be as specific as possible with regard to future research projects. The temporal scope of the collection is not defined, but it is stated that a withdrawal of consent leading to the destruction of data and/or samples should be possible at any time.[20]
In the past thirty years a vast number of biobanks emerged throughout the EU and accumulated large numbers of biospecimen and corresponding data. Many ethical questions about the use of and the duration of storage as well as the sharing of these samples and data are still the subject of discussion.[21,22]

### 1.5 The SHARE project

The SHARE project's goal is to standardize laboratory conditions, diagnostics and therapies of rare diseases in Europe. It consists of eight work packages, each one focusing on a different topic.

Work Package 7's main objective was to identify barriers between nations regarding ethical, legal and privacy issues as regards data and sample collection and the storage and shipment of DNA and viable cells for data collection as well as data sharing and developing recommendations for collaborative research within Europe.[23] Work Package 7 was executed under the leadership of the University of Tübingen's SHARE working group of Prof. J. Kümmerle-Deschner.

In order to identify these barriers a modular concept was developed to capture the existing literature on this topic as well as the perspective of pediatric investigators, patients and their parents as well as research ethic boards. Furthermore the goal was to determine the various kinds of barriers the different stakeholders have to face concerning ethical, legal and privacy issues regarding data and sample collection and storage in a real-life approach.

Another goal was to find existing best practices for research projects in a systematic literature review.

The results of these studies were collected and translated into recommendations developed for gaining ethically correct consent for studies including the participation of minors, the collection of data and samples and the possible storage and exchange of these data and samples between European biobanks.

### 1.6 Aims of the study

Therefore the aims of the study were to address the following questions:

1. What is the current perspective of the relevant literature on pediatric collaborative research?

a. What are the perspectives of key stakeholders including investigators, patients and parents as well as research ethics boards on collaborative pediatric research?

2. What do collaborating researchers need concerning their own process of planning, implementing and registering their study at the local research ethics board?

3. What views, wishes and needs do patients and their families have when they are enrolled in pediatric research projects?

4. How do research ethics boards across Europe work and what are their main concerns when analysing and scrutinising an ethics proposal?

5. What kind of barriers do researchers encounter in the real-life initiation or a rare disease pediatric research protocol when performing pediatric studies and what are the existing best practices and enabling factors to meet and overcome these barriers?

## 2 Methods

In an effort to facilitate and encourage collaborative international research the European project “Single Hub and Access point for pediatric Rheumatology in Europe” has been funded with the goal of identifying barriers between nations for collaborative Pediatric Rheumatology research.

A multidisciplinary team including three academic pediatricians, a basic scientist, an ethics board representative and two graduate students was established and designed a multi-modular study to assess the perspectives of researchers, patients and families and Research Ethic Boards REB in a real-life approach. (see Figure 1)
In a first step we performed a systematic literature review regarding existing European regulations, legislative documents and standardized operating procedures to ensure quality standards in specimen handling and confidentiality of personal data. Furthermore, we searched for literature focussing on the process of obtaining consent from minors, ethical, legal and privacy issues regarding the collection and storage of data and samples in biobanks and shipment of DNA and viable cells.

As a next step a questionnaire was sent to collaborating scientists. The questionnaire was designed to measure the amount of experience researchers have in writing an ethics proposal and concerning the surrounding requirements. The goal was to gain insight on the investigators’ perspective.

As a third step a questionnaire investigating the perspective of patients and parents regarding pediatric research, specimen collection and consent to data and sample use for research purposes was conducted. This study was registered at the University of Tübingen research ethics boards under No 272/2015BO1.

Furthermore, an interview with University research ethics boards in Germany was performed to identify organizational differences between the REBs and gain insight on the research ethics board perspective.

As a final step an ethics proposal was designed which was submitted to REBs in Germany and collaborating European centres to capture the variations of their responses to an identical proposal. All these studies were designed to identify real-life barriers in pediatric research. All study instruments and procedures were iteratively discussed and optimized by all SHARE WP7 investigators in regular meetings. (see Figure 1)

The goal of these surveys was to identify barriers hindering possible international research projects. This report will give a short overview about the systematic literature review. It will be described and discussed in depth by my co-worker in another thesis. The main focus will be the methods and results of the real-life approach consisting of the study on the investigator perspective, the study on the patient and parent perspective and the study on the research ethics board perspective as well as the ethics proposal.

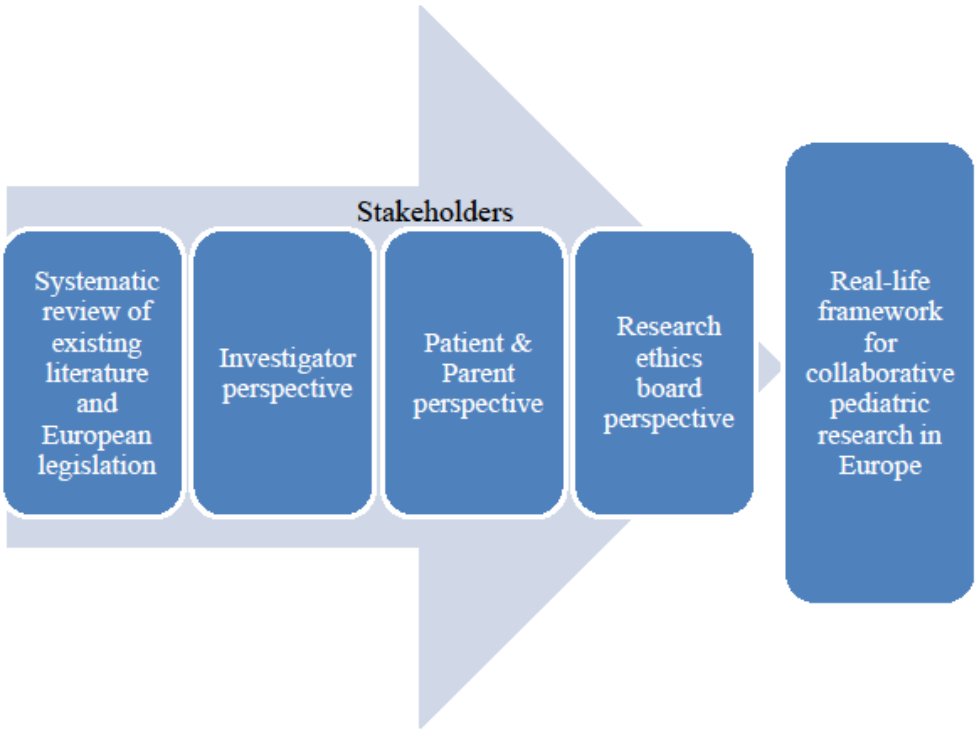


**Figure 1 Methods: Multimodular approach for the development of a real-life framework in pediatric research in Europe**

**Legend:** A systematic literature review of the existing scientific and legislative literature dealing with pediatric research including pediatric biobanking and the ethical and legal queries was performed. We investigated the perspective of European Researchers, patients and their parents, the perspective of research ethics boards and the result of an ethics proposal that was sent to research ethics boards in Germany and Europe to capture their responses. As a result a real-life framework for collaborative pediatric research in Europe was developed.

## 2.1 Systematic literature review

In order to get a comprehensive overview of the ethical discussion concerning pediatric biobanking we performed a systematic literature review in the following databases:

1. PubMed
2. Web of knowledge

Web of Knowledge includes inter alia the following databases: Web of Science Core Collection, Medline, Biosis Citation Index and Biosis Previews.
The following search terms „information dissemination“, „data sharing“, „data collection“, „biological specimen banks“, “confidentiality”, “informed consent by minors”, „specimen handling“, „standards“, „quality improvement“, „European union“, „Europe“, „ethics“, „legislation and jurisprudence“ were used.

We excluded duplicates, papers dealing with the situation in the USA, Canada, Asia, Africa or Australia (i.e. non-EU Countries), as well as papers not addressing the pediatric situation and papers not published between January 1st 1989 and April 31st 2014.

From the remaining references all papers referring to the situation in any European country were extracted and as a final step papers not mentioning the keywords were excluded. Two members of the SHARE working group from the University of Tübingen, a multidisciplinary team including three pediatricians, a biologist, an ethics expert and two graduate students, performed a full text screening. The literature references of the resulting papers were searched for additional papers meeting the inclusion criteria that had not appeared in the initial search. Additionally, European guidelines, declarations and legislative documents were included and a full text screening was performed to exclude the documents that are not relevant to the study. (see Figure 2)

Since the existing Cochrane ranking systems do not include European guidelines or declarations and were therefore not applicable, we developed a modified hierarchy of evidence with the help of the Cochrane collaboration. The modification enabled the inclusion of all available scientific evidence and international normative documents in the systematic literature review. (see Figure 3)

The strength of the recommendation was based upon the evidence found for each statement, for example: A strength “A” recommendation was based on level 1evidence, a recommendation of strength “B” was based on level 2 evidence or extrapolated from level 1 evidence.

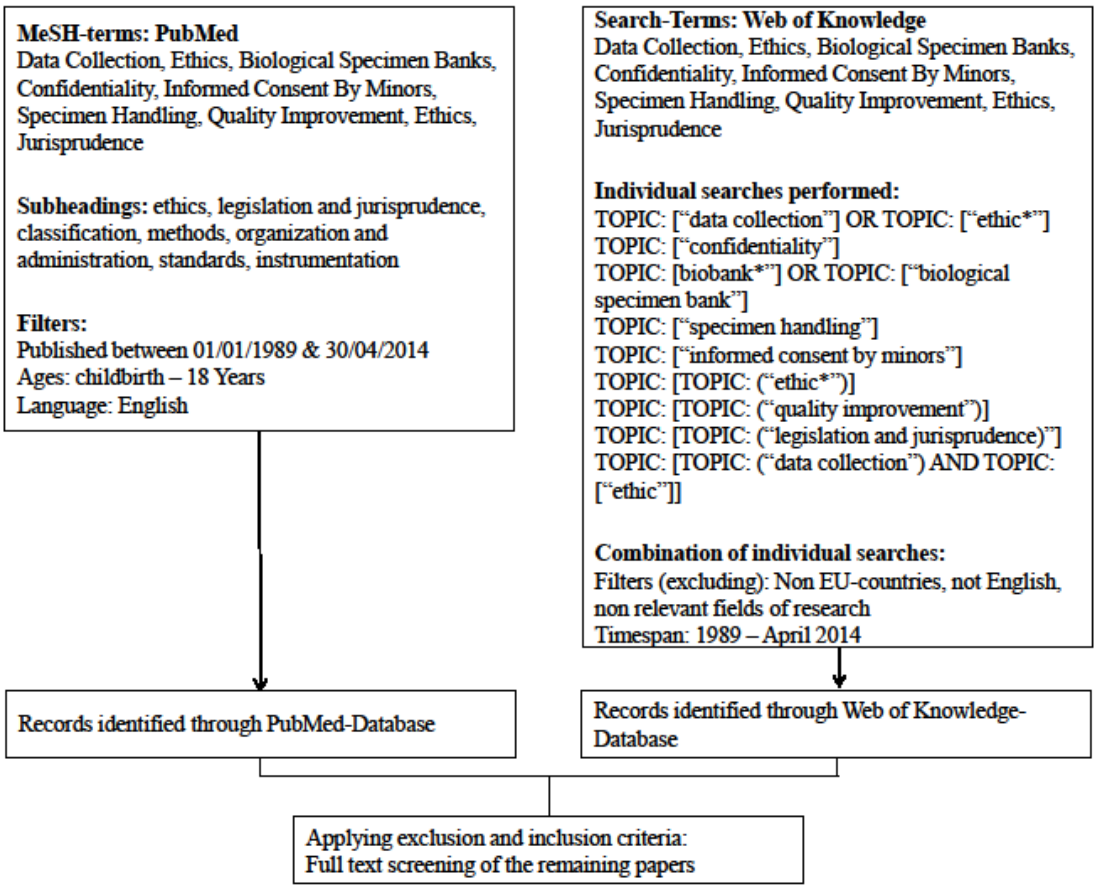


**Figure 2 Methods: Search strategy for the systematic literature review**

**Legend:** The search included the following MESH-terms: data collection, ethics, biological specimen banks, confidentiality, informed consent by minors, specimen handling, quality improvement, ethics and jurisprudence. In addition, the following subheadings were used: ethics, legislation and jurisprudence, classification, methods, organization, and administration, standards, instrumentation. The search was limited to literature relevant to the pediatric age group (child to 18 years of age) and to Europe.

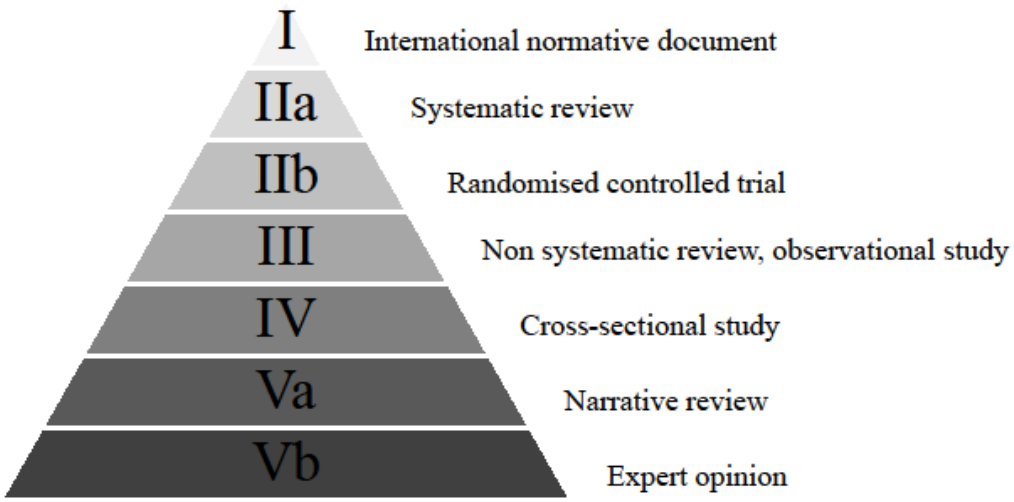


**Figure 3 Methods: Modified hierarchy of levels of evidence as proposed by the Cochrane Collaboration**

**Legend:** The traditional levels of hierarchy as proposed by the Cochrane collaboration were modified with their support for the available scientific publications and international normative documents utilized in the systematic review.

## 2.2 Investigator perspective

The systematic literature review showed only a handful of surveys evaluating the public opinion/perspective towards genetic research on children and only one evaluating the views and experiences of the scientists engaged in these projects.[24]

We wanted to assess the clinicians' experience concerning the conduct of a pediatric study or more precisely their experience in writing an ethics proposal and dealing with queries concerning the application.

The goal was to assess how much experience scientists working in pediatric rheumatology generally have in writing an ethics proposal, conducting a pediatric study and dealing with queries concerning the application.

We were also interested if there is a need for more support and of what kind this support should preferably be (administrative, financial etc.).

We divided the questionnaire into four main sections:

1. General questions about the scientists' experience concerning ethical applications
2. Legal matters such as the scientists' comprehension for their national legislation
3. Procedural difficulties evaluating what kind of support scientists receive on a local level
4. Post-application queries to investigate how much work needs to be done after an application has been submitted

The SHARE working group developed the questionnaire using nominal group technique. The next step was to identify crucial items for the work of a researcher and determine whether these items could be quantified and examined.

As a third step answers were sorted into four different kinds of scales (nominal scale, ordinal scale, interval scale and ratio scale).

Wherever possible the interval scale was used (more than 10, 10 to 20, more than 20) to facilitate the completion of the questionnaire as much as possible and allow clear but differentiated answers. (see Figure 4)

The first draft of the questionnaire was revised by the supervising doctor and a statistics expert leading to a substantial revision of the original version. Several questions were redrafted and answer categories redefined.

Before submitting the questionnaire a pretest was performed to identify problems and queries that might occur while answering the questions. Before the final version of the questionnaire was submitted critical points identified in the pretest were discussed, analysed and if necessary amended.

An accompanying letter explaining the context of the questionnaire was formulated. The final draft was then sent simultaneously with the ethics proposal to pediatric scientists in Germany and participating pediatric scientists of the SHARE project.

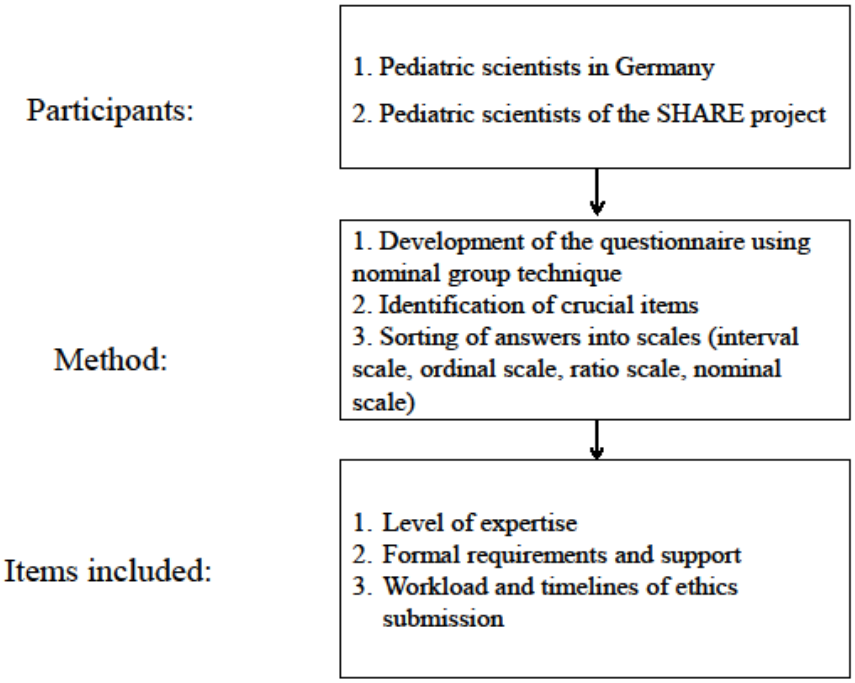


**Figure 4 Methods: Investigator perspective on pediatric collaborative research**

**Legend:** The questionnaire was developed by the SHARE working group and sent to pediatric scientists in Germany and participating pediatric scientists of the SHARE project.

### 2.3 Patient and parent perspective

A standardised patient questionnaire was developed to obtain information about the patients' and parents' perspective regarding data and sample use for research purposes. Demographic data including date of birth, education, gender, number of family members and number of family members affected by BD was obtained. The questionnaire addressed the domains of pediatric research, specimen collection and consent. Furthermore, there were questions investigating the attitude of patients and parents towards the sharing of results and the acceptable risk/benefit ratio. This study was registered at the University of Tübingen research ethics boards under No 272/2015BO1.

The following topics were addressed:

- Experience with clinical studies
- Willingness to participate
- The importance of pediatric research
- The subject of subsidiarity
- Data and sample protection
- The circumstances under which samples can be obtained
- The inclusion of parents and especially children in the consent process
- The scope of consent regarding future use of data and samples
- Withdrawal of consent
- Reconsent at the age of maturity
- Information policy regarding clinically relevant results.
- The centralised collection and storage of data and samples in a biobank
- Risk and benefits

A total of 23 questions were asked, answers were collected using 5-point-Likert scales. A sample of sufficient size of patients and parents with chronic illnesses and parents of healthy children was examined during a four-week time interval at the University Children's Hospital Tübingen. (see Figure 5)

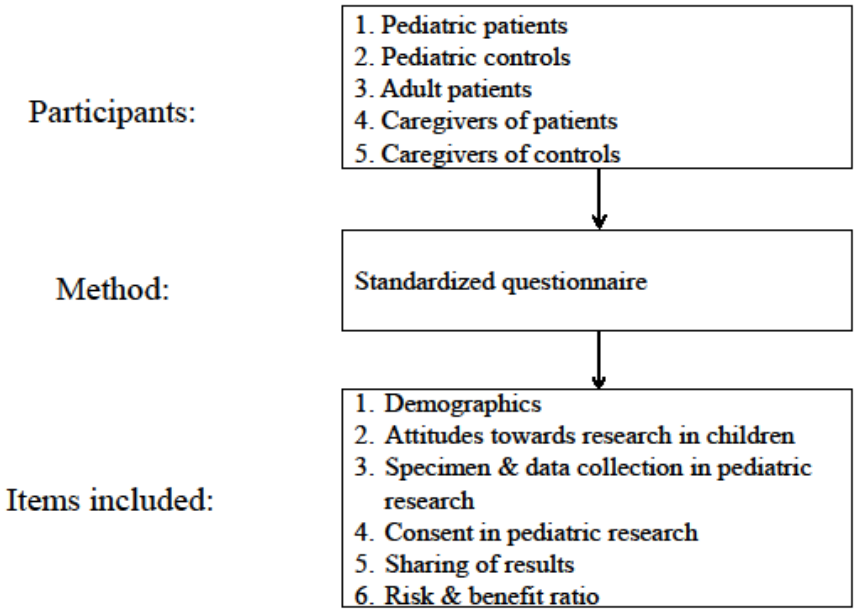


**Figure 5 Methods: Patient and parent perspective questionnaire on pediatric collaborative research**

**Legend:** Pediatric patients with rare diseases, their healthy siblings and their parents were included to answer the questionnaire regarding research in children. 23 questions were asked concerning the following topics: the importance of pediatric research, the subject of subsidiarity, data and sample protection, the circumstances under which samples can be obtained, the inclusion of parents and especially children in the consent process, the scope of consent regarding future use of data and samples, withdrawal of consent, reconsent at the age of maturity, information policy regarding clinically relevant results, the centralised collection and storage of data and samples in a biobank, risk and benefits, standardisation of ethical requirements and REB structures.

## 2.4 Research ethics board perspective

We conducted an interview with the University research ethics boards in Germany. The goal was to investigate the following three topics:

1. Timetable of review process
2. Financial requirements
3. Organizational structure of the research ethics board

In several meetings of the SHARE working group general questions were formulated addressing the challenges of writing an ethics proposal. These questions were identified using nominal group technique and were based on the findings of the systematic literature review.

The questions referred to the timeframe and the evaluation of an ethics proposal, the financial requirements of an ethics proposal and the composition of a research ethics board.

- Review process, Expenditure of time – What is the mean response time?
- Financial requirements – Can a possible financial burden be minimized?
- REB (members) – Is there a pediatrician on the REB?

These 3 topics resulted in a total of eight questions which were sent to the REBs. (see Figure 6)

The 32 German University REBs were contacted. The REBs were called via telephone. In analogy to the real-life clinical work setting of investigators a timeframe to reach the REBs was set. The interviews were performed after the regular working hours of a clinician to mirror real-life. At the beginning of each interview the participants were told that we planned to perform a pediatric observational study at the respective University. The participants' identity was not recorded. The questions were formulated as open questions and the answers organized in categories during the analysis of the findings.

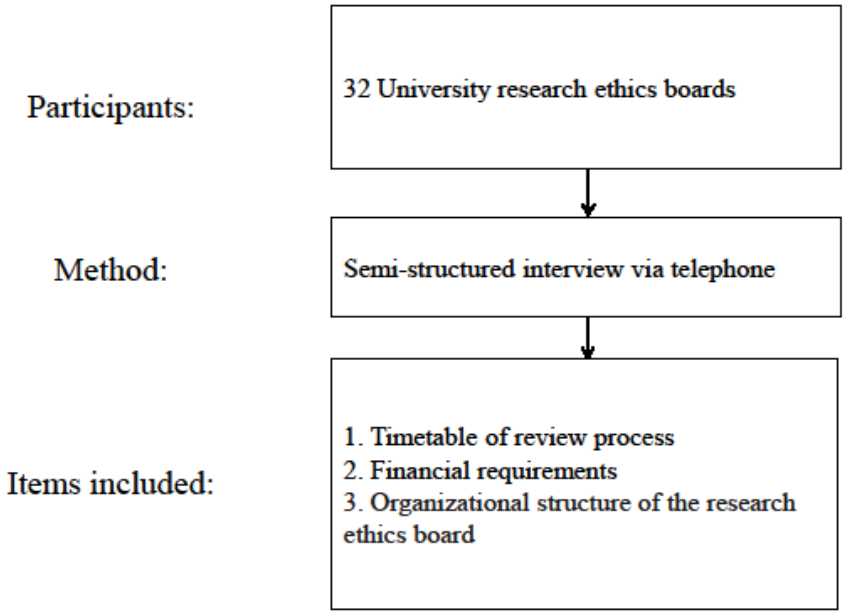


**Figure 6 Methods: REB perspectives on pediatric collaborative research**

**Legend:** We conducted semi-structured interviews with 32 German University research ethics boards. No personal data was recorded. The interviews were performed after the regular working hours of a clinician to mirror real-life.

## 2.5 Ethics proposal

We decided to take a real-life approach. In several meetings of the SHARE working group an ethics proposal was developed and sent to different research ethics boards in Germany and selected European countries participating in the SHARE project. The responses of the REBs were recorded and analysed and barriers within the process of gaining ethical consent were identified. (see Figure 7) We chose an ethics proposal on Behcet's disease as it is a rare disease which can affect children as well as adults. The goal was to facilitate the work of the scientist engaged in the project.

The ethics proposal was developed based on the findings of the systematic literature review and based on the University of Tübingen research ethics board's audit plan as a support to orientation. The ethics proposal was subdivided into 20 paragraphs. Certain paragraphs were designed to be ethically controversial. As an example, we defined only two exclusion criteria for possible participants and proposed indefinite storage of data and samples in a central repository. We have listed the paragraphs in which we included possible pitfalls to evaluate different approaches from the REBs.

Paragraph 2.1: Commercial use of data and samples by other scientists as well as pharmaceutical companies was allowed under the condition that all results must be published or at least made available on a central web site.
Paragraph 2.2: We proposed a multi-centre approach. The number of participating centres was not specified ("as many as possible")
Paragraph 2.2.2 - 2.2.4: Only two exclusion criteria were defined in the ethics proposal. In the study only patients' refusal of consent and adult patients unable to give consent (for example due to mental incapacity) represented an exclusion criterion. Apart from these two criteria we set no restrictions to the participation in the study. Since the goal was to identify predisposing factors typical for BD, especially younger patients aged under 16 showing possible symptoms of BD were of interest, but due to the small overall numbers we planned to include adult patients, patients' parents and healthy siblings as possible HLA-B positive members of the family and asking for permission to collect a blood sample.
In Paragraph 2.2.6: We stated that the identification data should be stored and processed

in a central facility in Tübingen instead of being stored in the respective participating centre.
In Paragraph 2.2.7: We stated that samples and data would be stored for an indefinite amount of time.
In Paragraph 3.2: We explained why the risk of participating in the study is no more than minimal for minors. However, we did not further explain the risk benefit ratio for healthy siblings. We stated that they would benefit from a possible early diagnosis leading to earlier and better treatment resulting in a more favourable outcome.
Paragraph 4: We clearly stated that medically relevant results would have to be communicated to the participants regardless of what the parents/caretakers want, thus overriding the right not to know. Furthermore, the topic of access to the data and samples by researchers and companies was addressed. We stated that data and samples could be shipped and processed for research purposes.
In Paragraph 5.1.2: We stated that notification of donors was planned only if new scientifically relevant questions arise or if there is new health-relevant information concerning the donor. No information about who (parents or participants) would be informed was included.
As participating centres, we included the European partners at the SHARE Project (see Figure 8) and REBs located at the University of collaborating scientists in Germany. (see Figure 9)

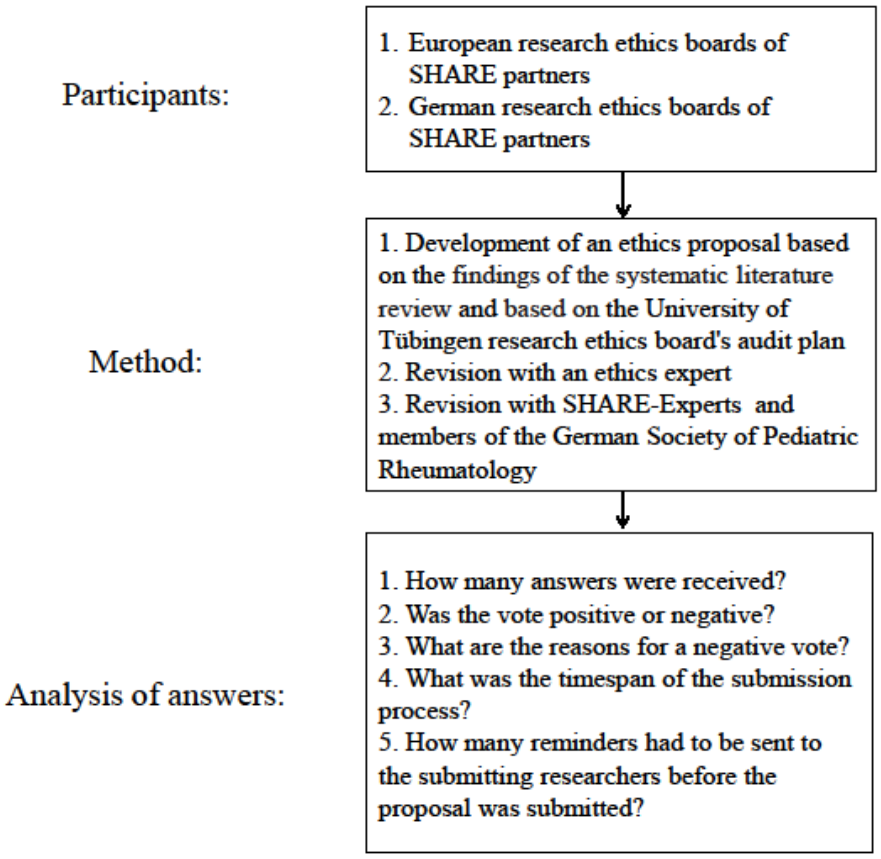


**Figure 7 Methods: Development of the Ethics proposal**

**Legend:** We decided to take a real-life approach. In several meetings of the SHARE working group an ethics proposal was developed and sent to different research ethics boards in selected European countries and Germany. The responses of the REBs were recorded and analysed and barriers within the process of gaining ethical consent were identified.


**Figure 8 Methods: Participating centres in Europe**

**Legend:** As participating centres we included the European partners at the SHARE Project and research ethics boards located at the University of collaborating scientists in Germany.


**Figure 9 Methods: Participating centres in Germany**

**Legend:** As participating centres we included the European partners at the SHARE Project and research ethics boards located at the University of collaborating scientists in Germany

The first draft of the ethics proposal was reviewed with an ethics expert. After revision the proposal was amended and, prior to submission, the final version of the ethics proposal was presented to the SHARE investigators and to the members of the German Society of Pediatric Rheumatology (Gesellschaft für Kinder- und Jugend Rheumatology) for feedback. All investigators agreed to submit the ethics proposal to their institutional ethics board and received the exact same copy of the ethics proposal that was first submitted and approved by the REB in Tübingen and forwarded this copy to their local REB. We provided a copy written in English or French. Whenever needed, the local research partner performed a translation into their national language.
The proposal was sent to collaborating scientists in Berlin, Bremen, Dresden, Freiburg, Gießen, Hamburg, Hannover, Heidelberg, Köln, München, Münster, St. Augustin (Bonn), Ulm and Austria, Belgium, the Czech Republic, Finland, France, Italy, the Netherlands, Slovenia, Spain, Sweden, Turkey and the United Kingdom and Canada.

The answers to the surveys were collected and analysed. The answers to the questionnaire were analysed according to the following items:

1. Total number of responses
2. Responses to the questions applying an optical scale, a nominal scale and a 5-point-Likert-scale
3. Analysis of the free-text responses

The answers to the questionnaires were collected and analysed according to the following items:

1. How many answers were received?
2. Was the vote positive or negative?
3. What are the reasons for a negative vote?
4. What was the response time?
5. How many reminders had to be sent to the submitting researchers before the proposal was submitted?

### 2.6 Barriers

The answers to our surveys and the ethics proposal were summarised in several meetings of the work group and a meeting with an ethics expert. Crucial items that were discussed repeatedly in the literature dealing with pediatric research and real-life barriers in the process of gaining consent for a scientific project when minors are involved were identified. The goal of these surveys was to identify the different kinds of barriers that investigators as well as patients and parents have to face when engaged in pediatric collaborative research. Through in-depth discussion and a profound, iterative review process of the studies an evidence synthesis was performed leading to the development of the draft recommendations.

### 2.7 Recommendations

As a result of the evidence found in the literature, the questionnaires and the ethics proposal we developed draft recommendations to facilitate the implementation of a study involving minors. The recommendations were grouped into the following topics: guiding principles, ethics, pediatric principles, consent to pediatric research and pediatric data- and biobanks (operational principles, sharing of data and samples, commercialization and third-party access).[25]

Several consensus meetings, continuous in-depth discussion with REB staff members as well as experts in pediatric ethics (KH) and international law (DS) followed. This led to several reviews and adjustments of the recommendations. Additional domains were developed including public opinion on pediatric research, guidelines and jurisdiction. As a next step an online survey with the draft version of the recommendations was sent to all participating members of the SHARE initiative for review and revision. All suggestions were integrated and additional recommendations were drafted; the revised documents were re-distributed to the experts for review and evaluation of agreement.[25]

The final draft of the recommendations was then discussed in depth with nominal group technique at a face-to-face consensus meeting between all members of the SHARE expert committee and patient representatives in Rome. (see Table 1) Recommendations were accepted by reaching agreement above 80%.

**Table 1 Methods: SHARE experts participating in the final consensus meeting in Rome**

| | |
|---|---|
| Jasmin B Kuemmerle-Deschner | Division of Rheumatology, Department of Pediatrics, University Hospital Tuebingen, Tübingen, Germany |
| Nico M Wulffraat | Pediatric Rheumatology, Wilhelmina Children's Hospital, University Medical Center Utrecht, The Netherlands |
| Sebastiaan J Vastert | Pediatric Rheumatology, Wilhelmina Children's Hospital, University Medical Center Utrecht, The Netherlands |
| Jordi Anton | Pediatric Rheumatology, Hospital Sant Joan de Déu, Barcelona, Spain |
| Tadej Avcin | Departments of Allergy, Rheumatology and Clinical Immunology, University Children's Hospital, University Medical Centre |
| Alberto Martini | Department of Pediatrics, University of Genoa, Gaslini Children's Hospital, G. Gaslini Research Institute, Genoa, Italy |
| Isabelle Koné-Paut | Department of Pediatric Rheumatology and Haematology, CEREMAI, GHU Paris-Sud - Hôpital de Bicetre, APHP, Le Kremlin-Bicetre, France |
| Yosef Uziel | Pediatric Rheumatology Unit, Department of Pediatrics, Meir Medical Center, Kfar-Saba, Kfar Saba, Israel<br><br>Sackler Faculty of Medicine, Tel-Aviv University, Tel Aviv, Israel |
| Angelo Ravelli | Department of Pediatrics, University of Genoa, Gaslini Children's Hospital, G. Gaslini Research Institute, Genoa, Italy |
| Carine Wouters | Department of Microbiology and Immunology, Laboratory Pediatric Immunology, UZ Leuven Hospital, Leuven, Belgium |
| Seza Özen | Department of Pediatrics, Hacettepe University, Ankara, Turkey |

| | |
|---|---|
| Berent J Prakken | Pediatric Rheumatology, Wilhelmina Children's Hospital, University Medical Center, Utrecht, The Netherlands |
| Nicolino Ruperto | Department of Pediatrics, University of Genoa, Gaslini Children's Hospital, G. Gaslini Research Institute, Genoa, Italy |
| Gerd Horneff | Department of General Pediatrics, Asklepios Clinic Sankt Augustin, Sankt Augustin, Germany |
| Tamas Constantin | Reumatológia, Immunológia, Gyermekgyógyászati Klinika, Budapest, Hungary |
| Michael W Beresford | Department of Pediatric Rheumatology, Institute for Translational Medicine, University of Liverpool, Alder Hey Children's NHS Foundation Trust, Liverpool, UK |
| Marijn Sikken | JIA Patient Council, Department of Pediatric Rheumatology, University Medical Center Utrecht, Wilhelmina Children's Hospital, Utrecht, The Netherlands |
| Helen E Foster | Department of Pediatric Rheumatology, Great North Children's Hospital, Institute of Cellular Medicine Musculoskeletal Research Group, Newcastle University, Newcastle upon Tyne, UK |
| Susanne M Benseler | Division of Rheumatology, Department of Pediatrics, University Hospital Tuebingen, Tübingen, Germany<br>Alberta Children's Hospital Research Institute, Calgary, Alberta, Canada |

**Legend:** The final draft of the recommendations was then discussed in depth with nominal group technique at a face-to-face consensus meeting between all members of the SHARE expert committee and patient representatives in Rome. Recommendations were accepted by reaching agreement above 80%.

## 3 Results

### 3.1 Systematic literature review

The literature search in the databases mentioned above resulted in 1319 papers that were imported into a reference manager. These papers' titles, abstracts and full texts were analysed to meet the inclusion criteria leading to the exclusion of 1096 papers.

Two members of the working group performed a full text screening of 223 papers resulting in the exclusion of another 161 papers. The references of the remaining 62 papers were handsearched for additional literature relevant to our study leading to the inclusion of 23 papers. As a result of this process 85 papers were scored. A full text review of 22 normative documents resulted in the addition of 16 relevant documents including three international declarations, five guidelines, four European legislative documents and four recommendations. (see Figure 10)

Of the 85 retained publications three publications were systematic reviews, defined as evidence level IIa (none IIb) 15 were non-systematic reviews (evidence level III), 24 cross-sectional studies, 16 narrative reviews and 27 expert opinions (evidence level IV b). All 16 normative documents were found to be evidence level I.

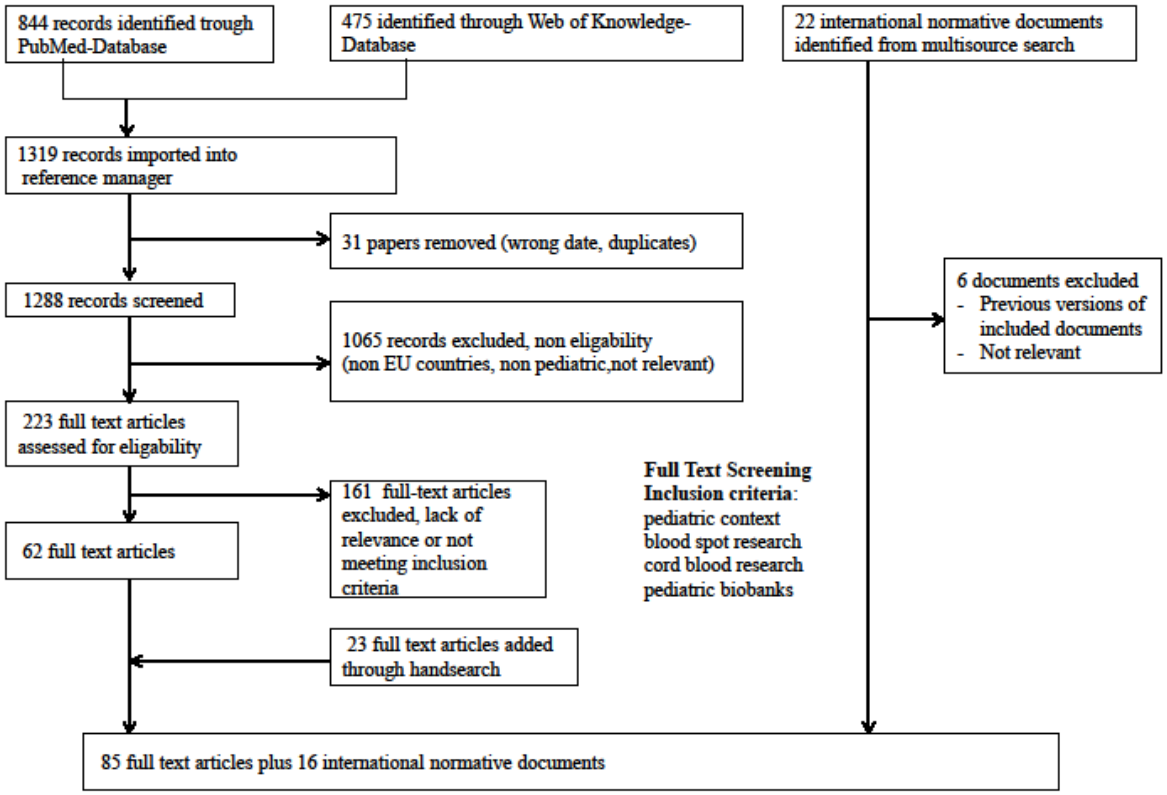


**Figure 10 Results: Systematic literature review**

**Legend:** The literature search resulted in 1319 papers that were imported into a reference manager. These papers' titles, abstracts and full texts were analysed to meet the inclusion criteria leading to the exclusion of 1096 papers. Two members of the working group performed a full text screening of 223 papers resulting in the exclusion of another 161 papers. The references of the remaining 62 papers were handsearched for additional literature relevant to our study leading to the inclusion of 23 papers. As a result of this process 85 papers were scored. A full text review of 22 normative documents resulted in the addition of 16 relevant documents including three international declarations, five guidelines, four European legislative documents and four recommendations.

The topics that were discussed in the literature included informed consent, subsidiarity, return of results as well as risk and benefit for the patients. As an example, the risk for a child, participating in pediatric research should be no more than minimal. Minimal risk is defined as the risk that a child would encounter in everyday live. Furthermore, the principle of subsidiarity, meaning that research should only be done on children, if the same study performed on adults could not obtain the same results, is discussed.
Hens et al. state e.g. that as principle for good practice the principle of subsidiarity should be applied and the risk and burden of sampling should be minimized for children.[10]

In the same study Hens et al. offer a possible solution to the question of whether clinically important results should be returned and to whom. They state that "in the rare case that information about a preventable or treatable early-onset disease is found" the parents should be notified regardless of their wishes to know or not to know.[10]

### 3.2 Investigator perspective

27 questionnaires were sent to participating scientists, 22 were returned which represents a response rate of 81%. (see Figure 11 and Table 2)
91% of the clinicians have participated in the writing of five or more ethics proposals. Every researcher that was addressed has written at least one application on his own or being the principle responsible. On the other hand, 46% of the participants feel that they are only 0-50% familiar with the current jurisdiction concerning pediatric ethics proposals. Another 27% of researchers feel only about 50-75% familiar.
77% of clinicians reported that they have a pediatrician as a member of the REB to consult if necessary. More than 50% of clinicians receive various kinds of support such as administrative support, financial support, support from experts, or specific training. In one case there is a coordinator supporting the writing of an ethical application.
A broad consent for more support and further assistance exists. This was stated by more than 80 % of participants. When given the opportunity to define what kind of support would be most helpful (multiple answers were possible), there was no clear tendency towards a specific form of support.

Two participants do not use specific age-appropriate forms to inform children about a study, although all of the participants who participated in the study are pediatricians. 40% of clinicians (9 of 22) do not seek renewed consent once the participant has reached the legal age of majority.

One third of clinicians does not feel that writing an ethics proposal represents a burden. In general, 50% of clinicians need 10 to 20 consultations before completing an application. 72% of clinicians manage to write an ethics application within 3 days. 31% of researchers stated that the entire completion of an ethics proposal would take one week or less while for 51% of the researchers the completion of an ethics proposal takes between one week and 3 months.

In most cases the head of department (15) or the head of the clinic (13) needs to be informed about an application. In six cases colleagues, in two cases clinical research institutions and in two cases external institutions need to be informed. Again in this case multiple answers could be given.

86% of researchers have to provide up to ten copies. The patient information comprises two or more pages in 96% of the cases.

After submission of the ethics proposal in 70% of all cases two or more queries have to be answered. It takes 32% of researchers between one and three weeks and another 32% more than three weeks to respond to these queries. The period until there is a final verdict varies between two up to ten weeks, but in 46% of the cases a verdict is communicated within five weeks. (see Table 2)

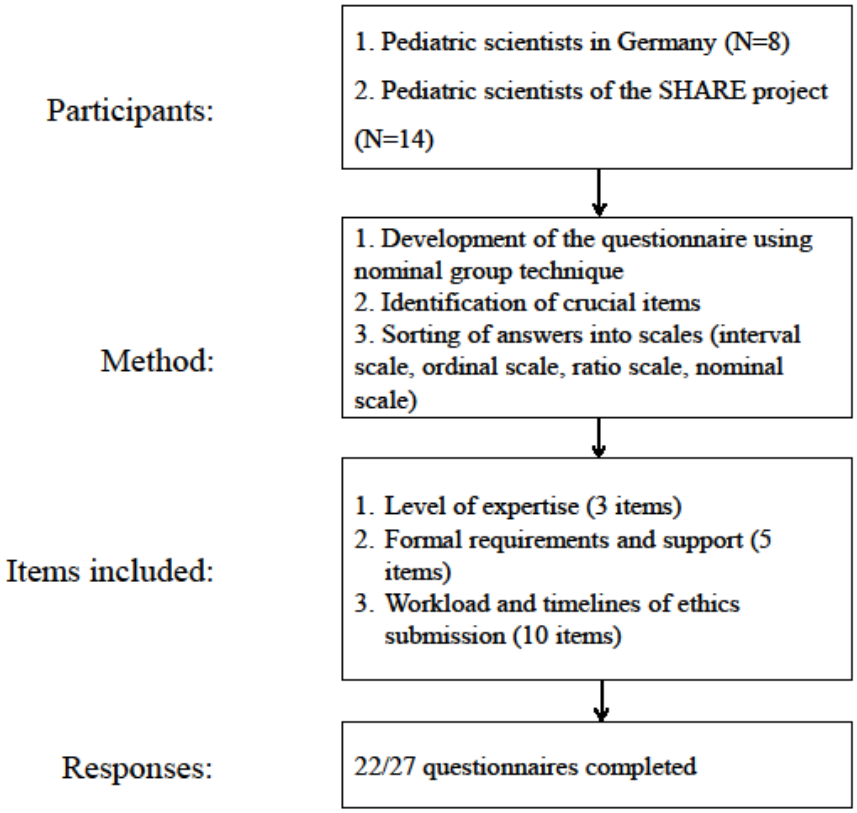


**Figure 11 Results: Investigator perspective questionnaires on pediatric collaborative research**

**Legend:** 27 questionnaires were sent to participating scientists, 22 were returned which represents a response rate of 81%.

**Table 2 Results: Investigator perspective questionnaires on pediatric collaborative research**

| **Question** | | **Pediatric Rheumatology investigators 22/27 (81%)** |
|---|---|---|
| | | • German 8<br>• European 13<br>• Canada 1 |
| **Expertise** | | |
| How many ethics applications have been completed in collaboration with you? | Number of previously completed ethics application<br>• <5<br>• 5-10<br>• 10-20<br>• >20 | <br>• 2 (9%)<br>• 9 (41%)<br>• 4 (18%)<br>• 7 (32%) |
| Have you written at least one application by yourself? | Submission of at least one application | • 22 (100%) |
| How familiar are you with current jurisdiction concerning pediatric ethics applications? | Familiarity with current jurisdiction regarding research ethics<br>• 0-25%<br>• 26-50% | <br>• 1 (5%)<br>• 9 (41%) |

| | | |
|---|---|---|
| | • 51-75%<br>• 76-100% | • 6 (27%)<br>• 6 (27%) |
| **Formal requirements and support** | | |
| Is there a pediatric expert in your local research ethics board you might consult? | Availability of pediatric ethics consultant at your center | • 17 (77%) |
| Do you receive any kind of support while writing an application?<br><br>What kind of support? | Availability of ethics submission support at your center<br><br>Type of available institutional ethics submission support:<br>• Administrative<br>• Experts<br>• Training<br>• Financial<br>• Coordinators | • 12 (55%)<br><br>• 8 (n.a)<br>• 5 (n.a)<br>• 2 (n.a)<br>• 2 (n.a)<br>• 1 (n.a) |
| Would you appreciate further support?<br><br>What kind of support? | Request for additional ethics submission support<br><br>Type of additional further support:<br>• Administrative<br>• Experts | • 18 (82%)<br><br>• 6 (n.a.)<br>• 6 (n.a) |

| | | |
|---|---|---|
| | • Training<br>• Financial | • 5 (n.a)<br>• 7 (n.a) |
| Do you have access to forms taking the age of the child into consideration? | Age appropriate pediatric specific ethics form at your center | • 20 (91%) |
| Do you seek renewed approval once the patient reaches legal age of consent? | Mandatory re-consenting when reaching legal age? | • 13 (59%) |
| **Workload and timelines of ethics submission** | | |
| To which amount do you feel hampered by the duty of writing ethics applications? | Amount<br>• 0-25%<br>• 26-50%<br>• 51-75%<br>• 76-100%<br>• not applicable | <br>• 7 (32%)<br>• 2 (9%)<br>• 9 (41%)<br>• 2 (9%)<br>• 2 (9%) |
| How many times do you have to consult colleagues, superiors, the research ethics board in order to complete an application? | Number of consultations prior to completion of an ethics submission<br>• <10<br>• 10-20<br>• >20 | <br>• 11 (50%)<br>• 11 (50%)<br>• 0 |

| | | |
|---|---|---|
| How long does writing an application take you? | Estimated timeframe of writing the ethic proposal<br>• <1 day<br>• 1-3 days<br>• 4-7 days<br>• >1 week<br>• not applicable | • 5 (23%)<br>• 3 (14%)<br>• 8 (36%)<br>• 2 (9%)<br>• 4 (18%) |
| How much time do you usually allow for the entire completion of an application including planning, writing and settling possible queries? | Estimated timeframe to completion of pre-submission ethic process<br>• <1 day<br>• 1-7 days<br>• 1-4 weeks<br>• 1-2 months<br>• 3 months<br>• not applicable | • 2 (9%)<br>• 5 (23%)<br>• 6 (27%)<br>• 4 (18%)<br>• 1 (5%)<br>• 4 (18%) |

| | | |
|---|---|---|
| Who do you have to inform about the application? | Mandatory information and signatures on ethics submission<br>• Head of Department<br>• Head of Hospital<br>• Colleagues<br>• Clinical research institution<br>• External institution | <br>• 15 (n.a)<br>• 10 (n.a)<br>• 5 (n.a)<br>• 2 (n.a)<br>• 2 (n.a) |
| How many application copies do you have to provide? | Number of copies<br>• 1-4<br>• 5-10<br>• >10<br>• not applicable | <br>• 14 (63.5%)<br>• 5 (23%)<br>• 2 (9%)<br>• 1 (4.5%) |
| How many pages does the patient information comprise? | Number of pages<br>• 1<br>• 2<br>• >2 | <br>• 1 (4.5%)<br>• 6 (27%)<br>• 15 (68.5%) |
| How many research ethics board-queries regarding the application do you usually have to answer? | Average number of ethics queries per application<br>• 0-1 | <br>• 7 (32%) |

| | | |
|---|---|---|
| | • 2<br>• 3<br>• >5 | • 7 (32%)<br>• 6 (27%)<br>• 2 (9%) |
| How much time does it take to answer these queries? | Average time to completion of ethics board queries<br>• < 1 day<br>• 1-7 days<br>• 1-3 weeks<br>• > 3 weeks<br>• not applicable | <br>• 3 (14%)<br>• 7 (32%)<br>• 6 (27%)<br>• 1 (5%)<br>• 5 (23%) |
| How much time passes before you receive the research ethics board´s verdict? | Estimated average time to approval<br>• 1-2-weeks<br>• 3-5 weeks<br>• 6-10 weeks<br>• 10 weeks<br>• not applicable | <br>• 3 (14%)<br>• 7 (32%)<br>• 7 (32%)<br>• 3 (14%)<br>• 2 (8%) |

**Legend:** 22 of 27 researchers answered the questionnaire. For questions 5, 6 and 13 multiple answers could be given, therefore no percentage distribution is provided in these cases.

### 3.3 Patient and parent perspective

15 patients with a mean age of 15,4 (8-18) and 13 parents of patients participated in filling out the questionnaire. Additional 12 healthy children with a mean age of 14.9 years (11-18) and 17 parents of healthy children as well as 7 adult patients with a mean age of 23 years (19-48) participated. All 64 participants completed the questionnaire. This represents a response rate of 100%. (see Figure 12 and Table 3)

About 50% of the responders had some experience with clinical studies. All healthy children and parents and more than 90% of the patients and parents indicated their willingness to participate in research. 98% of participants think that research on pediatric diseases is important.

Only the group of patients' parents with 23% agreement does not support the concept of subsidiarity. This concept in pediatric research specifies that a study that is likely to produce generalizable results among all age groups should preferably be performed with adult participants instead of children.

There is broad agreement of 88-100% that pediatric biospecimen need special protection. Between 46 and 94 % support leftover sampling only, which means that genetic material cannot be collected for the sole purpose of using it for a research project. Instead only genetic material that has been collected for diagnostic or clinical reasons and is no longer needed for these primary purposes may be used for research projects. Between 69 and 100% support non-invasive sampling of urine and saliva and between 65 and 83% support invasive blood sampling for research purposes.

There is broad agreement of between 87 to 100% that parental consent should be obtained, a child's dissent should be respected, the information should be age-appropriate and that appropriate time to make the decision should be given. Patients and parents prefer to give consent for a limited scope rather than giving broad consent for future studies. 80% or more would give consent for a specific study while only between 12 and 31% of caregivers would agree to a broad consent model.

Furthermore between 87 and 100% of the minor participants think that upon reaching the age of maturity they should be asked to reconsent.

100% of the participants of the study want to be informed about clinically relevant results.

59% of all participants of the study think that research will help either to promote the progress of science and even more (84%) think that research will help to improve the treatment of future patients. Only 29% of the patients and parents thinks that the focus of today's research projects is the treatment of themselves.

81% of the participants think that samples should be stored in a biobank and reused in order to reduce the need to collect new samples. About 50% of all participants see their privacy at risk, when participating in pediatric research entailing collection and storage of data and samples. Only 14% see a risk of stigmatization in this context. (see Table 3)

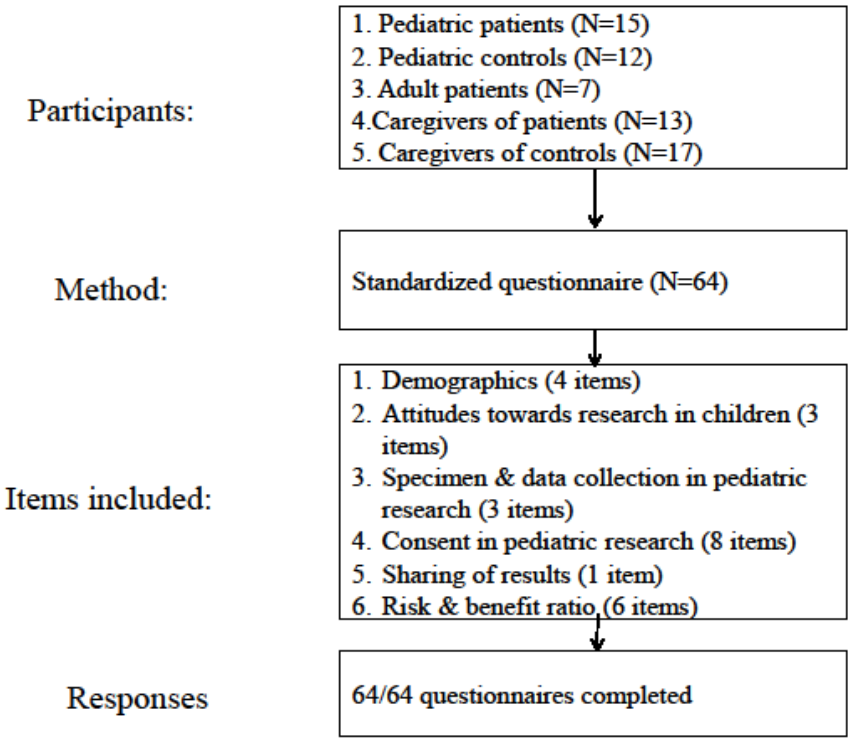


**Figure 12 Results: Patient and parent perspective questionnaires on pediatric collaborative research**

**Legend:** A total of 64 questionnaires were handed out, the response rate of the questionnaire was 100%. 15 pediatric patients, 12 healthy pediatric controls, 7 adult patients and 13 caregivers of patients as well as 17 caregivers of healthy pediatric controls submitted the completed questionnaire.

**Table 3 Results: Patient and parent questionnaires on pediatric collaborative research**

| | **pediatric patients N= 15** | **pediatric controls N=12** | **adult patients N=7** | **caregivers of patients N=13** | **caregivers of controls N=17** |
|---|---|---|---|---|---|
| **Demographics** | | | | | |
| Median age (range) in years | 15.4 (8-18) | 14.9 (11-18) | 23.0 (19-48) | n.a. | n.a. |
| Gender male: female | 8:7 | 6:6 | 4:3 | 4:9 | 7:10 |
| | | | | | |
| Do you have any experience with clinical studies? | 6 (40%) | 6 (50%) | 4 (57%) | 6 (46%) | 10 (59%) |
| In general, are you yourself willing to participate or let your child participate in clinical studies? | 14 (93%) | 12 (100%) | 6 (85%) | 12 (92%) | 17 (100%) |
| | | | | | |

| | | | | | |
|---|---|---|---|---|---|
| **Attitudes towards research in children** | | | | | |
| Research of pediatric diseases is important | 15 (100%) | 12 (100%) | 6 (85%) | 13 (100%) | 17 (100%) |
| Subsidiarity: Specific research should only be conducted in children, if it can't be conducted in adults | 8 (62%) | 7 (58%) | 4 (57%) | 3 (23%) | 13 (76%) |
| Research data and biospecimens of children require a special protection | 15 (100%) | 12 (100%) | 7 (100%) | 13 (100%) | 15 (88%) |
| | | | | | |
| **Specimen collection in pediatric research** | | | | | |
| Leftover sampling only | 11 (73%) | 9 (75%) | 6 (85%) | 6 (46%) | 16 (94%) |
| Non-invasive sampling for research only (urine, saliva) | 13 (87%) | 11 (92%) | 7 (100%) | 9 (69%) | 16 (94%) |
| Invasive blood sampling for research only | 11 (73%) | 10 (83%) | 5 (71%) | 10 (77%) | 11 (65%) |

| | | | | | |
|---|---|---|---|---|---|
| **Consent/assent in pediatric research** | | | | | |
| Research in children only possible after obtaining parental consent | 13 (87%) | 12 (100%) | 7 (100%) | 13 (100%) | 17 (100%) |
| Child´s reject/dissent on study participation should be considered | 13 (87%) | 12 (100%) | 7 (100%) | 13 (100%) | 17 (100%) |
| Consent/assent should be age appropriate | 15 (100%) | 12 (100%) | 7 (100%) | 12 (92%) | 17 (100%) |
| Appropriate time for decision making when consenting | 14 (93%) | 12 (100%) | 7 (100%) | 13 (100%) | 17 (100%) |
| Scope of consent/assent limited to specific study | 12 (80%) | 11 (92%) | 7 (100%) | 12 (92%) | 16 (94%) |
| Support for broad scope of consent/assent | 4 (27%) | 2 (17%) | 0 (0%) | 4 (31%) | 2 (12%) |
| Renewed consent is needed when stored samples are to be used again for research. | 14 (93%) | 12 (100%) | 3 (43%) | 11 (85%) | 16 (94%) |

| | | | | | |
|---|---|---|---|---|---|
| Re-consenting at legal age should be mandatory | 13 (87%) | 12 (100%) | 5 (71%) | 13 (100%) | 14 (82%) |
| | | | | | |
| **Sharing of results** | | | | | |
| Clinically relevant results should be communicated so that a treatment can be initiated. | 15 (100%) | 12 (100%) | 7 (100%) | 13 (100%) | 17 (100%) |
| | | | | | |
| **Risk/Benefit ratio** | | | | | |
| Research is performed mainly to promote/serve Science. | 11 (73%) | 8 (67%) | 2 (29%) | 9 (69%) | 8 (47%) |
| Research is performed mainly to improve the treatment of patients suffering from the same disease | 15 (100%) | 10 (83%) | 5 (71%) | 12 (92%) | 12 (71%) |
| Research is performed mainly to improve the treatment of patients themselves. | 7 (47%) | 2 (17%) | 2 (29%) | 4 (31%) | 1 (6%) |

| | | | | | |
|---|---|---|---|---|---|
| Storage of data & samples after obtaining consent is useful to reduce the need of future sampling of other/the same patients. | 13 (87%) | 9 (75%) | 6 (85%) | 10 (77%) | 14 (82%) |
| The risks entailed in research are mainly privacy risks. | 6 (40%) | 6 (50%) | 2 (29%) | 7 (54%) | 10 (59%) |
| The risks entailed in research are mainly risks of stigmatization. | 3 (20%) | 3 (25%) | 0 (0%) | 1 (8%) | 2 (12%) |

**Legend:** All 64 participants of the patient and parent perspective study completed the questionnaire.

### 3.4 Research ethics board perspective

32 University research ethics boards (REBs) were called for interviews. Within our timeframe we managed to reach 30 of 32 ethics boards selected. In order to maintain the real-life character of our studies, the interviews were only conducted after the regular working hours of a clinician. Due to the limited timeframe we were unable perform the interview with two REBs. These REBs were thus excluded from the survey. This represents a response rate of 94%. (see Figure 13and Table 4)

In 70% of the cases the application needs to be handed in two to three weeks before the next REB meeting. As not all REBs meet on a regular basis it is not always possible to define a fixed deadline for the submission. In 80% of the cases the REBs meet once a month or even more often. One REB however does not meet on a regular basis, but rather "on demand".

The REB meets and discusses every proposal that has been submitted. In more than 50% of the cases a detailed verdict in written form can be expected within 3 weeks after the meeting if no queries need to be resolved, but it can also take up to 6 weeks before researchers receive a detailed answer. 73% of REBs do not charge a fee for the scrutiny of an ethics proposal if the study is not sponsored. If the REB does charge a fee, a reduction of this fee can be requested in 13,5% of the cases.

The composition of the REB varies greatly between universities, there are between 5 and 39 members, usually every member can be replaced, for example in case of illness. 10% of REB's maintain more than one task force, but it is much more common that there is only one task force per REB.

Members can be exchanged after a certain time, in most cases after four years. 60% of the research ethics boards include a pediatrician as a permanent member; another 37% can ensure the presence of one, if needed.

The question of whether or not research ethics boards ask for renewed consent when study participants reach the legal age of majority could not be categorized and scaled like the others. The research ethics boards stated that as long as a certain plan of action for this specific case is described in the ethics proposal and approved by the REB in charge, this verdict is valid for the duration of the study. Thus there is no definitive plan

of action when the participant reaches the age of majority. Asking for renewed consent may or may not be mandatory. (see Table 4)

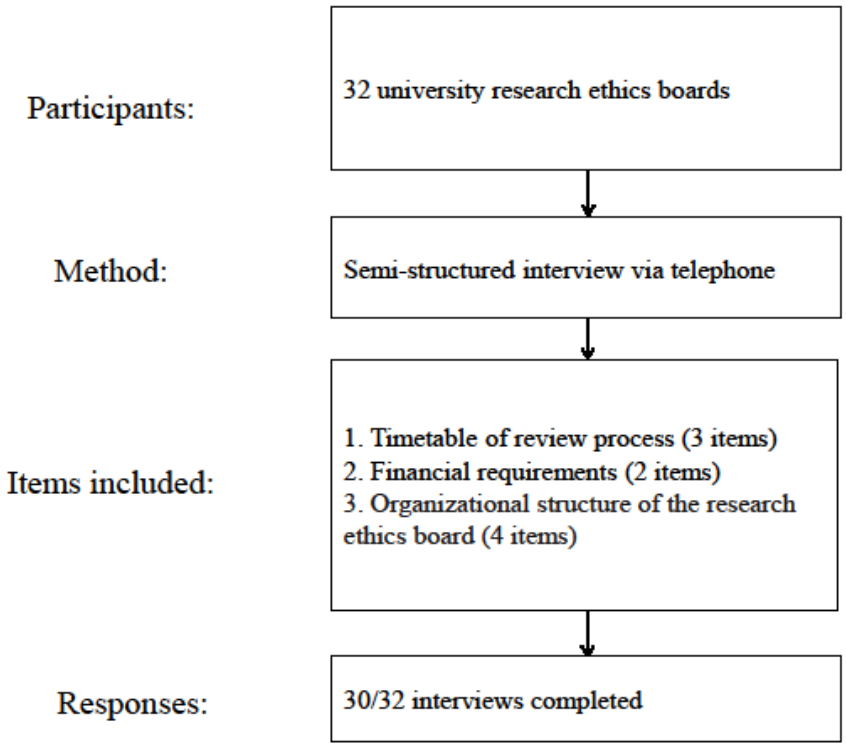


**Figure 13 Results: Research ethics board perspective interview**

**Legend:** Within our timeframe we managed to reach 30 of 32 ethics boards selected. In order to maintain the real-life character of our studies, the interviews were only conducted after the regular working hours of a clinician. Within the set timeframe we did not manage to perform the interview with two REBs. These REBs were thus excluded from the survey. This represents a response rate of over 90 %.

**Table 4 Results: Research ethics board perspective interview**

| | | **German Ethics Board Interviews** |
|---|---|---|
| **Participation in telephone interview** | | 30/32 (94%) |
| **Process** | | |
| Mandatory pre-meeting submission timeline of application<br>• < 14 workdays<br>• 14-21 days<br>• > 3 weeks<br>• no fixed time<br>• no precise answer | How far in advance do applications need to be submitted? | <br>• 1 (3%)<br>• 21 (70%)<br>• 3 (10%)<br>• 1 (3%)<br>• 4 (14%) |
| Meeting schedule times<br>• 1/month<br>• 3/month<br>• Weekly<br>• On demand | How often does the EB meet to discuss applications? | <br>• 24 (80%)<br>• 3 (10%)<br>• 2 (7%)<br>• 1 (3%) |
| | | |

| | | |
|---|---|---|
| Post-meeting response timeline:<br>• No statement<br>• < 1 week<br>• 1-2 weeks<br>• 2-3 weeks<br>• 3-4 weeks<br>• 4-6 weeks | How much time passes before a response is submitted? | • 1 (3%)<br>• 1 (3%)<br>• 3 (10%)<br>• 17 (57%)<br>• 3 (10%)<br>• 5 (17%) |
| **Fees** | | |
| • Fees between 100-200 Euro<br>• Fee reduction on request<br>• No fee charged if there is no sponsoring | Does the EB charge a fee for processing an application? | • 4 (13.5%)<br>• 4 (13.5%)<br>• 22 (73%) |
| **Membership** | | |
| Number of ethics board members | | • 5-39 |
| Work groups per ethics board<br>• 1<br>• Up to 3<br>• Up to 9 | How many work groups are there? | • 27 (90%)<br>• 2 (7%)<br>• 1 (3%) |
| Duration of term per board member: 4 years | At what intervals are members of the EB replaced? | |

| | | |
|---|---|---|
| • Every 4 years<br>• Every 3 years<br>• Every 2 years<br>• Depending on the faculty board´s term of office | | • 25 (84%)<br>• 1 (3%)<br>• 3 (10%)<br>• 1 (3%) |
| Designated pediatric member of ethics board?<br>• permanent<br>• On demand<br>• No | Is there a pediatrician in the EB staff applicants may contact? | • 18 (60%)<br>• 11 (37%)<br>• 1 (3%) |

**Legend:** The REBs were called via telephone. We asked questions about the process of submitting an ethics proposal, about the costs involved in the submission and about the personnel structure of a REB.

### 3.5 Ethics proposal

The ethics proposal was sent to 13 European SHARE research partners, six ethics proposals were submitted. We received five answers from our collaborators, which represents a responsive rate of 39%. (see Figure 14 and Table 5)

The informed consent protocol had to be translated by research partners into their national language of the respective country. Seven of the ethics proposals were not submitted to the local REB. We recontacted them to find out the reason why, but in four cases no further contact could be established regarding the proposal.

One of the collaborators did not submit the proposal for lack of personnel and time resources. In two cases the ethics proposal was not submitted because of the costs involved and no further contact could be established. One ethics proposal was submitted but we did receive no feedback from the REB involved nor from the research partner that submitted the proposal.

Until April 2014 we received 5 responses from the European partners, which represents a responsive rate of 39%. One research ethics board approved the ethics proposal without raising any queries. One REB stated that the study in question did not fall into their area of responsibility. Three research ethics boards objected to the proposal because of different reasons. One REB requested another copy of the abstract protocol in the national language. In this case no verdict was communicated. Another REB criticised the lack of clear rules for protection of the privacy of data and samples and one REB criticised the inclusion of healthy siblings in the study protocol.

In Germany the ethics proposal was sent to 14 collaborating scientists. Of those 14 ethics proposals 10 were not submitted to the local research ethics board. This represents a responsive rate of 29%.

One partner did not agree to submit the ethics proposal to the REB. Five ethics proposals were not submitted due to the fees included, two ethics proposals were not submitted because there was not enough personnel, i.e. the associated time commitment was too high and two ethics proposals were not submitted due to unknown reasons.

Apart from the ethics proposal submission in Tübingen, in Germany, three ethics proposals were submitted to the local REB for review. Until April 2014 the collaborating researchers forwarded us three responses from the research ethics boards. Two REBs, including Tübingen, approved the ethics proposal. Two REBs demanded amendments to be made and rejected the original proposal.

During the submission period of the ethics proposal we were in constant contact with our research partners in Europe and Germany. In an effort to achieve the submission of the ethics proposal by the scientists to the local research ethics board, a total of 159 email queries from our collaborators were answered. Over a period of 13 months between one and fourteen emails were answered per contact. (see Figure 14 and Table 5)

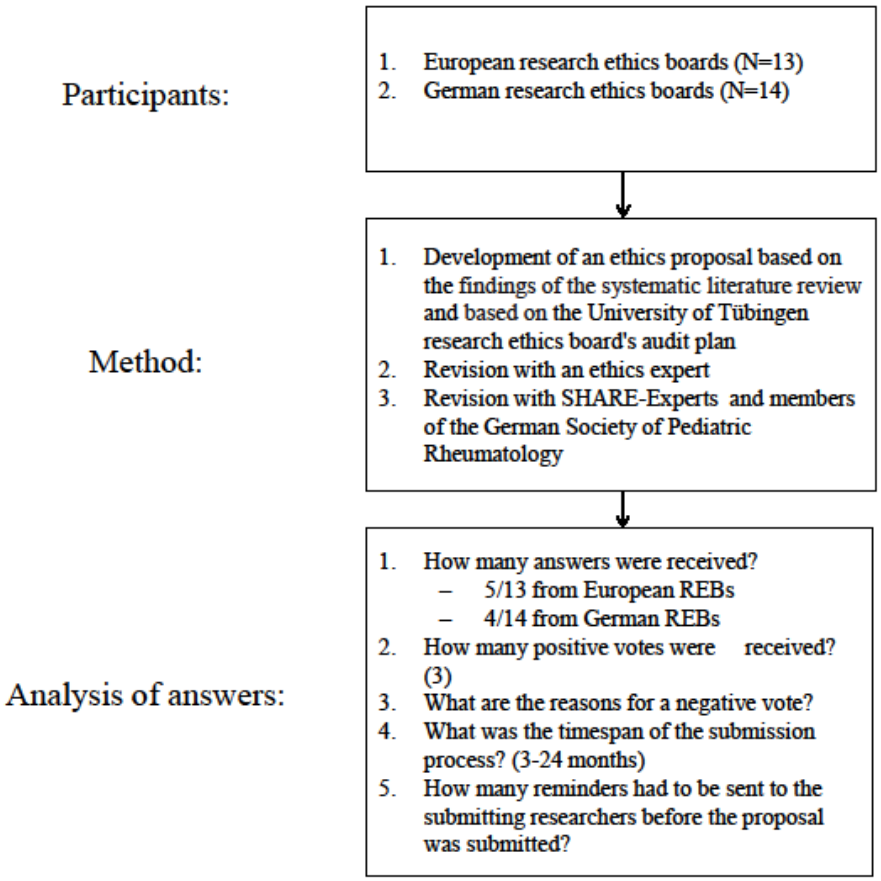


**Figure 14 Results: Ethics proposal**

**Legend:** The ethics proposal was sent to 13 European SHARE research partners. Six ethics proposals were allegedly submitted. We received five answers from our collaborators, which represents a responsive rate of 39%. In Germany the ethics proposal was sent to 14 collaborating scientists. Of those 14 ethics proposals 10 were not submitted to the local research ethics board. This represents a responsive rate of 29%.

**Table 5 Results: Behcet Ethics proposal submission & answers**

| Country or town | Number of email-contacts/ reminders | Translation of consent form | Reason not submitted/no verdict | Proposal submitted | EB answer | Time span in months | verdict | Verdict justification |
|---|---|---|---|---|---|---|---|---|
| Austria | 10 | n.a. | additional formal requirements, no research personal | no | n.a. | n.a. | n.a. | - |
| Belgium | 6 | done | | uncertain | n.a. | n.a. | n.a. | - |
| Czech Republic | 7 | done | | uncertain | n.a. | n.a. | n.a. | - |
| Finnland | 2 | uncertain | | uncertain | n.a. | n.a. | n.a. | - |
| France | 5 | done | submitted, additional formal requirements | yes | yes | 5 | rejected | Formal requirements, translation needed |
| Italy | 5 | done | additional formal requirements | yes | n.a. | n.a. | n.a. | - |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Netherlands | 2 | done | submitted | yes | yes | 4 | rejected | Biobanks do not need a verdict from a REB, no permission required for data collection from clinical routine |
| Sweden | 4 | uncertain | costs | no | n.a. | n.a. | n.a. | - |
| Slovenia | 5 | done | submitted | yes | yes | 15 | rejected | Amendments needed, blood collection from healthy siblings is ethically inappropriate |
| Spain | 3 | done | submitted | yes | yes | 7 | approved | In accordance with statutory provision regarding biomedical examinations |
| Turkey | 11 | done | submitted | yes | yes | 8 | rejected | Collecting data of ethnicity is no local practice, sending samples abroad is losing intellectual property rights |
| UK | 11 | done | funding and sponsorship not con- | no | n.a. | n.a. | n.a. | - |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | firmed | | | | | |
| Canada | 5 | done | contact lost | yes | no | n.a. | n.a. | - |
| | | | | | | | | |
| Berlin | 8 | n.a. | costs, no time | no | n.a. | n.a. | n.a. | - |
| Bremen | 2 | n.a. | | no | n.a. | 5 | n.a. | - |
| Dresden | 4 | n.a. | submitted | yes | yes | 24 | rejected | Complaints in form and content, revision necessary |
| Freiburg | 2 | n.a. | costs | no | n.a. | 3 | n.a. | |
| Giessen | 11 | n.a. | submitted | yes | yes | 5 | approved | Approval with cons-traints |
| Hamburg | 2 | n.a. | | uncertain | n.a. | 10 | n.a. | - |
| Hannover | 6 | n.a. | no research person-al, time commitment | no | n.a. | 24 | n.a. | - |
| Heidelberg | 2 | n.a. | overall large time commitment | no | n.a. | 24 | n.a. | - |
| Köln | 7 | n.a. | costs, internal re-view not submitted to EB | no | n.a. | 24 | n.a. | - |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| München | 1 | n.a. | refusal to submit | no | n.a. | 9 | n.a. | - |
| Münster | 3 | n.a. | costs | no | n.a. | n.a. | n.a. | - |
| St. Augus-tin | 1 | n.a. | costs | no | n.a. | 9 | n.a. | - |
| Tübingen | n.a. | n.a. | submitted | yes | yes | 4 | approved | Approval with cons-traints |
| Ulm | 14 | n.a. | submitted | yes | yes | 2 | rejected | No final decision, complaints in form and content, revision necessary |

**Legend:** The ethics proposal was sent to the research partners from SHARE and participating centres in Germany. When the ethics proposal was submitted, we analysed the answer given by the REB.

The results from the investigator perspective study, the patient and parent perspective study, the research ethics boards study and the ethics proposal study were gathered and thoroughly analysed. During the analysis of the survey results several crucial topics and relevant problems for research on tissue from minors were identified. These topics were discussed in repeated meetings of the work group and a meeting with an ethics expert. They represent crucial items often discussed in the literature that deals with pediatric research. Furthermore these topics emerged as a barrier in the real-life process of gaining consent for a scientific project when minors are involved.

- **Minimal age of inclusion** → at what age should children be included in the study and the consent process? Hens et al. found that children, even at a very young age, prefer to receive some information about a certain procedure. [10] (22 papers discuss this question) This information should match their respective level of understanding. Biobanks should implement consent policies that take the growing autonomy of children into account.[10] In the patient survey no minimal age of inclusion was defined. Patients rather wish the information given about a study to be age appropriate and the assent/dissent of a child to be considered.
- **Random findings, return of results** → which information should be returned (all or only clinically relevant?) and to whom? The CIOMS International ethical guidelines for biomedical research involving human subjects clarifies that life-saving information and information of clinical utility must be made available to study participants. [37] (12 papers discuss this question) All of the patients and their parents agree that clinically relevant results should be communicated, without specifying who should receive the information.
- **Risks and benefits for minors (and healthy siblings) involved in pediatric research (venepuncture, side effects)** → is more than minimal risk acceptable for non-therapeutic research? The 2008 CIOMS International Ethical Guidelines on Epidemiological Studies states that research performed on individuals who are unable to give competent informed consent may only be performed if there is only minimal risk involved. Also, the research must have the potential to benefit the group

represented by these individuals. [30] (12 papers discuss this question.) The patient perspective survey showed that 73% of participants would accept invasive sampling for research purposes.

- **Duration of sample storage** → is indefinite storage ethically justifiable? The European society of human genetics states that study participants should be informed about the duration of the storage of their samples and that the possibility to withdraw from a study should always include the destruction of the stored samples.[53] It does not define the maximum duration of storage. (21 papers discuss this question) In the ethics proposal we proposed an indefinite storage time, which in only one case resulted in a mandatory revision being required by an REB.

- **Goal and extent of the sample collection** → does a specific goal need to be defined? The European Society of Human Genetics states that it is difficult to define all possible future use of samples. Therefore, it might be acceptable to ask for a broader consent. On the other hand, if possible, information on the planned use of samples should be provided.[53] In the ethics proposal we did not define a specific goal of the collection (7 papers discuss this question).

- **Financial barriers** → who should have to pay a fee, if there is no industrial sponsor? This topic was not addressed in the literature, but the ethics proposal and the investigator perspective survey showed that fees (e.g. for REB verdicts) can in fact represent a significant barrier for research projects when no additional funding is provided. Researchers also stated that financial support could help research projects to progress.

- **Data storage, collection and protection** → who should have access to the data and samples and under which circumstances? What kind of protection will be in place, especially in the case of shared samples? The literature discussing this topic broadly agrees that a third-party access on identifiable data (e.g. by insurance companies) would not be acceptable.[37,53]

- **Scope of consent** → is it ethically sound to ask for broad consent meaning that researchers do not necessarily have to ask for renewed consent for the re-use of

samples? In the patient perspective survey 87% of participants agreed that renewed consent is necessary for re-use of stored samples for other research projects. In one case the ethics proposal was rejected due to the lack of a legal paper regulating the collective use and access of samples.

- **Subsidiarity** → Can a study be performed on adults and produce equally relevant results for children? Hens et al. clearly state that as a principle of good practice, genetic research should only be performed on samples from minors, if the same study or a study likely to produce generalizable results, cannot be done with samples from adult study participants.[10] (5 papers discuss this question)
  55% of the all the participants of the study on the patients and parents perspective agree that the concept of subsidiarity should be applied in pediatric research.
- **Informed consent** → who should consent? At what age or from which point onwards should children's assent/dissent be respected and possibly overrule the parents' decision? (5 papers discuss this question) As mentioned above children can and should be included in the consent process as long as the information given is transformed into an age appropriate form.[10] In a systematic review Hens et al. found that most authors addressing this topic agree that it is sufficient if one of the parents gives consent .[9] The patient survey shows a broad agreement for children to be included in the consent process, without defining a fixed age for this course of action.

A detailed outline on the relevant literature will be provided in another thesis written by my co-worker. In this thesis we will focus on the real-life experiences made by researchers, patients, parents and research ethics boards.

### 3.6 Barriers

Through the repeated and continued analysis of the results of the real-life surveys and through the review of the results of the systematic literature review different kinds of barriers that investigators as well as patients and parents have to face when engaged in pediatric collaborative research were identified. These barriers hinder the progress of pediatric multi-centre studies on rare diseases and can be organized into three categories.

First there are **process barriers** that appear when a multi-centre study is started. The study on the REB perspective and the ethics proposal showed how different formal and financial requirements of an REB can be. Furthermore there are different legal frameworks of the participating countries that have to be taken into account.
The study on the investigator perspective showed that clinicians would appreciate more support for the implementation of research projects. The ethics proposal study showed it takes between 3 and 24 months before an ethics proposal is submitted and at least another month before the REB sends a detailed verdict.

Secondly, there are **research partner barriers**. The researchers do not feel well informed about current jurisdiction even though they participate regularly in the writing of pediatric ethics proposals. A clear need for more support can be seen, but the researchers remained undecided about what kind of support is needed the most: financial support in form of funding, in form of more personnel or in the form of time reserved exclusively for the process of writing an ethics proposal.

Thirdly, there are **patient-related barriers**. Many ethical questions remain unresolved. In the patient survey the question of who should give consent and at what point a child's opinion should be taken into consideration are very important to the participants. In the systematic literature review this topic is often discussed, but no clear course of action exists.

### 3.7 Recommendations

The evidence found in the systematic literature review and the four real-life studies, the investigator perspective study, the patient and parent perspective study, the research ethics boards study and the ethics proposal study, were translated into a total of 21 recommendations. These recommendations were grouped into the domains of Guiding Principles (Recommendation 1 - 3), Ethics (Recommendation 4 -7), Pediatric Principles (Recommendation 8 and 9), Consent in Pediatric Research (Recommendation 10 - 14), Pediatric Data- and Biobanks: Operational Principles (Recommendation 15 and 16), Sharing of Data and Samples (Recommendation 17 - 19) and Commercialization and Third-Party Access (Recommendation 20 and 21). (see Table 6)

**Guiding principles – Recommendation 1-3**

**Recommendation 1: Advancing Care and Discovery**

Research in children should be supported including international, multi-centre data collection and banking and transfer of biological specimens. Collaboration enables discovery in pediatric diseases and care advancement for children, in particular for those with rare diseases.

**Recommendation 2: Enabling Support**

Pediatric researchers should be offered research-training opportunities, access to mentorship and guidance, protected time and financial support to conduct pediatric research. Institutional resources for research protocol development, translation services, ethics submission and research conduct should be made available.

**Recommendation 3: Supportive Legislative Framework**

A supportive legislative framework for international collaborating biobanks is lacking. A framework (WHO, ICH, EMA, FDA, other) should be implemented to overcome legal and ethical barriers in international research. An international binding shipment and custom agreement for biological samples should be established.

**Ethics – Recommendation 4-7**

**Recommendation 4: Centralized Ethics**

All international collaborative pediatric research should be reviewed by a central European research ethics boards. All auxiliary studies require additional review and approval. The review has to capture all ethical principles including privacy rights.

**Recommendation 5: Standardization and Transparency**

All collaborative pediatric research applications in the European Community should be filed in a standardized format and be submitted to a central electronic application portal. Following submission, the review process should be transparent and electronically traceable.

**Recommendation 6: Central Competency**

The European Central Ethics Application Board should rapidly assess all multi-centre applications for meeting formal EU-standards. All applications including timelines should be tracked in a central repository. The application should be transferred to the applicant's designated National research ethics board for Pediatric Research and Biobanking and undergo review including compliance with the specific ethical principles. After signing off, the other participating National research ethics boards should rapidly adopt the decision.

**Recommendation 7(1): Membership expertise**

Each National research ethics board for Pediatric Research and Biobanking should operate according to uniform standards.

Membership: Each Committee has to include independent experts in pediatric research, lay members (non-professionals including patient / parent organizations or community advocates) and those with specific content expertise including genetics to review specific applications when appropriate.

**Recommendation 7(2): Support and Clarity**

Ethics application: Each Committee should provide direct assistance, clear instructions and training courses to support the researcher.

Instructions and applications should be written in a simple, universally understood language.

Fees: Administrative fees should exclusively be charged in non-academic research; if charged, they should not constitute an obstacle.

**Pediatric Principles – Recommendation 8+9**

**Recommendation 8: Subsidiarity**

A study that will produce generalizable results across all age groups should preferentially be performed in adults.

**Recommendation 9: Pediatric Rule**

Children should receive special protection when included in data and biobank studies.

**Consent in Pediatric Research – Recommendation 10-14**

**Recommendation 10: Integration of Minors**

Voluntary and age-appropriate informed consent/assent has to be obtained from legal guardians and/or minors as appropriate according to the international guidelines (ICH, WHO, others) before pediatric data and biospecimen can be collected and used for research. Minors should be integrated into the process of consent and those capable of forming an opinion and assessing the information given, should be asked to give assent or consent, as appropriate.

**Recommendation 11: Enabling Informed Consent**

All information given to the child and the legal guardian should be age-appropriate, written and presented by a competent person in the country's official language. Pediatric participants and legal guardians should be granted appropriate time to make and reconsider their decision. Withdrawal of consent should be possible at any time of the study.

**Recommendation 12: Scope of Consent**

The scope of consent should preferably be broad. Broad consent should include future research opportunities, possibility to share samples and data with national and/or international research partners. Broad consent should include the possibility to re-contact participants. Consent forms need to be internationally harmonized to ensure international research projects. Consent forms have to include the possibility for specimen shipment and data transfer. Consenting should include the opportunity to opt out of certain aspects of research.

**Recommendation 13: Re-consenting**

Pediatric participants that have previously only given assent should be re-contacted for consent to an ongoing study when reaching legal age. Researchers should make considerable effort to re-contact participants for further use of data and samples. The research ethics board should evaluate the option of further use of data and sample, if participants are not reachable.

**Recommendation 14**: **Incidental Findings**

Researchers should partner with expert health care providers and inform patients and legal guardians about clinically relevant results. Participant's refusal to be informed about clinically relevant results represents an exclusion criterion.

**Pediatric Data and Biobanks Recommendation 15+16**

**Recommendation 15: Organizational Framework**

The organizational frameworks for collaborative pediatric data- and biobanks must include a governance structure. Terms of transparency, fair access to data and samples including ownership, authorship of research publications, payment and reciprocity of sample sharing should be defined. Principles of interoperability should be followed. Data- and /or material transfer agreements should be elaborated and signed between research partners. Researchers should develop a long-term plan for sustainability. Biobanks should be captured in a central electronic tracking system.

**Recommendation 16: Sampling**

Non-invasive sampling approaches should be preferentially used in children. Standard operating procedures (SOPs) of pediatric sample collection, processing, pre-analytic handling and shipment should be defined and observed to ensure high quality specimen handling.

**Sharing of data and samples – Recommendation 17-19**

**Recommendation 17: Data Harmonization**

Collaborative databanks should build on available instruments of data harmonization, standardized access to data, define measures of high data quality including data dictionaries, and regulate data transfer.

**Recommendation 18**: **Data Protection**

Researchers should implement a state-of-the-art data and sample protection system. Secure coding of data and samples should ensure confidentiality while enabling withdrawal of consent, re-consenting and notification of clinically relevant results. Secure data-sample linkage systems should be established.

**Recommendation 19: Standardization of Transfer**

Specimen transfer should include standardized packaging and labelling, accompanying transfer documentation, customs regulations and sample tracking. The consent form must include the agreement to share data and samples.

**Commercialization and third-party access – Recommendation 20+21**

**Recommendation 20: Fees and Incentives**

Biobanks should enable research to improve medical knowledge. Provision of data and samples should be free; shipment and processing costs should be covered by the requesting research team. Participants or their parents should not receive payment.

**Recommendation 21: Third Parties**

Researchers have to obtain ethics approval before giving patient data or sample access to third parties. Continuous education of the public about biobanks is important to retain public trust in research.

For every recommendation a justification was formulated based on the evidence found in the systematic literature review and the four real-life studies. Every recommendation was reviewed, discussed in depth and adjusted with the help of REB staff members and international experts on pediatric ethics and legislation. The recommendations were then sent to all SHARE experts for review and revision. After all suggestions were integrated and additional recommendations were drafted, we re-distributed the recommendations for review and evaluation of agreement.

In a face-to-face consensus meeting in Rome the SHARE expert committee and patient representatives discussed the final versions of the recommendations. Recommendations were accepted by reaching agreement above 80%. (see Table 6)

**Table 6 Recommendations for data and sample collection in pediatric rheumatic diseases**

| Text of recommendations | Justification | Evidence level I-Vb | Strength of recommendation (A-G) | Level of agreement at SHARE Consenus meeting in Rome |
|---|---|---|---|---|
| | | | | |

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|---|---|---|---|---|
| ***Guiding principles*** | | | | |
| **Recommendation 1: Advancing Care and Discovery**<br><br>Research in children should be supported including international, multi-centre data collection and banking and transfer of biological specimens. Collaboration enables discovery in pediatric diseases and care advancement for children, in particular for those with rare diseases. | Discovery and care advancement in pediatric diseases requires collaborative longitudinal research projects of international scale in order to include sufficient numbers of participants and generate robust scientific data. The international collaborative collection, storage and sharing of human biological material and associated clinical information reduce the overall burden of sampling for patients and researchers enabling sustained, high-quality research[4,9,10,32,98,99]. | I | B | 100% |

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| **Recommendation 2: Enabling Support**<br><br>Pediatric researchers should be offered research-training opportunities, access to mentorship and guidance, protected time and financial support to conduct pediatric research. Institutional resources for research protocol development, translation services, ethics submission and research conduct should be made available. | The complexity of collaborative pediatric diseases research and the heterogeneity of rules, regulations and processes within and across European countries mandate researchers to develop distinct skill sets and content knowledge. Focused, comprehensive training, institutional assistance and guidance partnered with financial and other support will enable researchers to overcome the disproportionally challenging barriers towards successful multi-national pediatric diseases research requiring sample and data collection [22,24,90,98,100,101]. | I | B | 100% |

| | | | | |
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| **Recommendation 3: Supportive Legislative Framework**<br><br>A supportive legislative framework for international collaborating biobanks is lacking. A framework (WHO, ICH, EMA, FDA, other) should be implemented to overcome legal and ethical barriers in international research. An international binding shipment and custom agreement for biological samples should be established. | The regulatory requirements for pediatric biobanking vary significantly between European countries. This dramatically complicates the implementing of international pediatric diseases biobanks. A unified European framework should be developed and implemented in order to facilitate the international sharing of precious pediatric biospecimen and enable life-saving discoveries [4,21,22,26,38,54,84,102]. | II | B | 100% |

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| ***Ethics*** | | | | |
| **Recommendation 4: Centralized Ethics**<br><br>All international collaborative pediatric research should be reviewed by a central European research ethics boards. All auxiliary studies require additional review and approval. The review has to capture all ethical principles including privacy rights. | Designated and highly qualified, independent and centralized research ethics boards should serve as Competent Authority for pediatric research. Subsequent, auxiliary studies should be reviewed by the same ethics board. The resulting single ethics vote captures the highest ethical principles and privacy standards. Subsequently National research ethics board reviews are solely tasked with evaluating cultural appropriateness [4,26,30,101,103-107]. | I | B | 94% |

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| **Recommendation 5: Standardization and Transparency**<br><br>All collaborative pediatric research applications in the European Community should be filed in a standardized format and be submitted to a central electronic application portal. Following submission, the review process should be transparent and electronically traceable. | The current necessity of multiple ethics applications, the large variability in the submitting formats and the lack of transparency of the reviewing process hinder collaborative pediatric research within the EU. A standardized submission and approval process through a central application portal as implemented in the EU portal for all clinical trials will overcome this barrier and facilitate research and care advancement [30]. | I | B | 100% |
| **Recommendation 6: Central Competency**<br><br>The European Central Ethics Application Board should rapidly assess all multi-centre applications for meeting formal EU-standards. All applications including timelines should be tracked in a central repository. The application should be transferred to the applicant's designated National research ethics board for Pediatric Research and Biobank- | The standardization of application requirements and a unified primary, central review process overcomes barriers by simplifying the process while increasing the quality in accordance to the European regulation on clinical trials on medicinal products for human use (Clinical Trials Regulation)[30,58]. | I | B | 100% |

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| ing and undergo review including compliance with the specific ethical principles. After signing off, the other participating National research ethics boards should rapidly adopt the decision. | | | | |
| **Recommendation 7(1):**<br><br>**Membership expertise**<br><br>Each National research ethics board for Pediatric Research and Biobanking should operate according to uniform standards.<br><br>Membership: Each Committee has to include independent experts in pediatric research, lay members (non-professionals including patient / parent organizations or community advocates) and those with specific content expertise including genetics to review specific applications when appropriate. | The research ethics board review of collaborative pediatric research studies and biobanking requires specific expertise reflected in its membership: Pediatricians should provide advice on clinical, ethical and psychosocial aspects of research in minors. Lay members should offer support evaluating individual and societal impact of the proposed research. The review of genetic studies mandates an additional content expert for guidance<br><br>[28-30,58,101,104]. | I | A | 94% |

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| **Recommendation 7(2):**<br><br>**Support and Clarity**<br><br>Ethics application: Each Committee should provide direct assistance, clear instructions and training courses to support the researcher.<br><br>Instructions and applications should be written in a simple, universally understood language.<br><br>Fees: Administrative fees should exclusively be charged in non-academic research; if charged, they should not constitute an obstacle. | Administrative support, training opportunities and transparent, simple instructions will help facilitate the pediatric research ethics application. For investigator initiated, non-commercial studies fees should not constitute a barrier to research. Fees should be set solely on the basis of cost recovery principles and be reduced or waived when appropriate [30,57,100,101]. | I | A | 100% |

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| ***Pediatric Principles*** | | | | |
| **Recommendation 8: Subsidiarity**<br><br>A study that will produce generalizable results across all age groups should preferentially be performed in adults. | Adults should be primarily included in research studies, since they are capable of giving truly informed consent. Children are a vulnerable population and need protection. Generalizable research has to be conducted in adults capable to consent [4,10,26,58,84,101,104-106]. | I | A | 88% |
| **Recommendation 9: Pediatric Rule**<br><br>Children should receive special protection when included in data and biobank studies. | Children are a vulnerable population. The potential risks including privacy risks related to genetic information, physical and emotional harms and disrespect of values should be minimized during sample collection and the duration of the research study. | I | A | 100% |

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| | Justification is required when inviting vulnerable individuals to serve as research subjects, the risk should be minimal and the means of protecting rights and welfare must be strictly applied [4,10,12,28,84,101,103-106]. | | | |

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|---|---|---|---|---|
| ***Consent in Pediatric Research*** | | | | |
| **Recommendation 10: Integration of Minors**<br><br>Voluntary and age-appropriate informed consent/assent has to be obtained from legal guardians and/or minors as appropriate according to the international guidelines (ICH, WHO, others) before pediatric data and biospecimen can be collected and used for research. Minors should be integrated into the process of consent and those capable of forming an opinion and assessing the information given, should be asked to give assent or consent, as appropriate. | Children have the right to be included in research and benefit from research discoveries. All research mandates voluntary, informed consent given by a competent individual, who has received the necessary information and has adequately understood the information. The decision to participate has to be reached without coercion, undue influence or intimidation. Informed consent embodies the individual's freedom of choice and respects the individual's autonomy. Legal guardians may serve as proxies for minors, who do not have full capacity, in the consent process; children should be integrated in the consent process and their opinion and views have to be respected [4,10,13,15,29,40,68,69,71,101,103-108]. | I | A | 100% |

| | | | | |
|---|---|---|---|---|
| **Recommendation 11: Enabling Informed Consent**<br><br>All information given to the child and the legal guardian should be age-appropriate, written and presented by a competent person in the country's official language. Pediatric participants and legal guardians should be granted appropriate time to make and reconsider their decision. Withdrawal of consent should be possible at any time of the study. | The process of consenting must not be simply a ritual recitation of the contents of a written document. The information must be conveyed in language that suits the individual's level of understanding. Parents/legal guardians and children must be given time and opportunity for discussion to make the decision without any pressure to consent. Participants should be informed that consent/assent can be withdrawn at any time. Exercising the right to withdraw cannot entail consequences in medical care services [10,12,13,29,69,76,101,103-107]. | I | B | 100% |
| **Recommendation 12: Scope of Consent**<br><br>The scope of consent should preferably be broad. Broad consent should include future research opportunities, possibility to share samples and data with national and/or international research partners. Broad consent should | Broad consent reduces the burden for participants as it avoids the need for re-sampling of biospecimen and re-collection of data in addition to the need for re-consenting. Broad consent avoids the need to re-contact and re-consent participants, | I | B | 100% |

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| include the possibility to re-contact participants. Consent forms need to be internationally harmonized to ensure international research projects. Consent forms have to include the possibility for specimen shipment and data transfer. Consenting should include the opportunity to opt out of certain aspects of research. | which may represent a significant barrier to conducting research. It allows for novel research to be conducted that had not been conceptualized at the time of the initial study. Permission for data and specimen transfer should be included in the harmonized consent forms. A governance specification and an opt-out option have to be included enabling participants to limit the use of their specimens and data to distinct research questions [6,10,12,22,28,61,103,106,107,109,110]. | | | |
| **Recommendation 13: Re-consenting**<br><br>Pediatric participants that have previously only given assent should be re-contacted for consent to an ongoing study when reaching legal age. Researchers should make considerable effort to re-contact participants for further use of data and samples. The research ethics board should evaluate the option of | At time of reaching legal age the formal legal status of the participant changes. This mandates obtaining re-consent since the initial consent was not obtained from the minor and therefore has limited temporal scope. Allowing the competent child a right to withdraw materials given into the biobank by proxy consent is consistent with the idea of a child's "right to an open fu- | I | A | 88% |

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| further use of data and sample, if participants are not reachable. | ture", which states that choices made for a child when being a minor should not preclude the right to make decisions when reaching legal age. The former minor has now full autonomy and is now able to oversee the dimension of the research and can give informed consent for ongoing research generated from databases and biobanks. In case the participant cannot be reached, the researcher should seek advice from the research ethics board for further use of data and samples [9,10,12,14,30,106,107,111]. | | | |
| **Recommendation 14**: **Incidental Findings**<br><br>Researchers should partner with expert health care providers and inform patients and legal guardians about clinically relevant results. | In adults the principle of autonomy and the individual right "to know or not to know" defines the extent to which researchers should inform participants including children and their legal guardians about clinically relevant results detected in research studies. In pediatric studies, the proxy con- | I | B | 100% |

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| Participant's refusal to be informed about clinically relevant results represents an exclusion criterion. | sent does not cover this decision. Here, researchers have a moral duty to inform minor participants and their legal guardians about clinically relevant results that mandate action including research result and incidental findings. Findings should be communicated by an expert clinician [4,10,36,60,84,100,101,103-106]. | | | |

| *Pediatric Data and Biobanks: Operational Principles* | | | | |
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| **Recommendation 15: Organizational Framework**<br><br>The organizational frameworks for collaborative pediatric data- and biobanks must include a governance structure. Terms of transparency, fair access to data and samples including ownership, authorship of research publications, payment and reciprocity of sample sharing should be defined. Principles of interoperability should be followed. Data- and /or material transfer agreements should be elaborated and signed between research partners. Researchers should develop a long-term plan for sustainability. Biobanks should be captured in a central electronic tracking system. | An organizational framework prevents ethical and legal conflicts and enables long-term collaborations between participating researchers. The development and endorsement of standards enables higher research interoperability. Transparency of the framework and its policies is necessary for biobanks in all levels. Standardized design and harmonization of data fields enables interoperability between biobanks. A governance structure and a long-term sustainability plan will ensure public trust and long benefits. A central registry for European biobanks will not only reduce the burden of repeated sample collection but also helps to use existing resources in the most efficient way [4,22,30,100,102,103,106,107,109,112]. | I | B | 100% |

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| **Recommendation 16: Sampling**<br><br>Non-invasive sampling approaches should be preferentially used in children. Standard operating procedures (SOPs) of pediatric sample collection, processing, pre-analytic handling and shipment should be defined and observed to ensure high quality specimen handling. | The Pediatric Rule mandates minimal invasive sampling, which may result in small quantities of biospecimen and may require designated, harmonized SOPs. Processing of pediatric biospecimen and capture of pediatric data samples should include necessary measures to ensure the accuracy, reliability, quality and security [3,26,29,100,101,104,106,109,112]. | I | B | 100%) |

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| ***Sharing of Data and Samples*** | | | | |
| **Recommendation 17: Data Harmonization**<br><br>Collaborative databanks should build on available instruments of data harmonization, standardized access to data, define measures of high data quality including data dictionaries, and regulate data transfer. | Harmonization of data fosters the interoperability of systems and facilitates the exchange of scientific data. High quality standards enable the possibility of international collaborative research with health-related benefits for future generations. Quality assurance measures should be implemented, including conditions to ensure appropriate security and confidentiality during establishment of the collection, storage, use and, where appropriate, transfer of data and materials [4,42,100,102,106,107,109,110,112]. | I | A | 100% |
| **Recommendation 18**: **Data Protection**<br><br>Researchers should implement a state-of-the-art data and sample protection system. Secure coding of data and samples should ensure confidentiality while enabling withdrawal of | Researchers are custodians of personal data and biospecimen. They are responsible for establishing a system of secure safeguards for privacy, confidentiality and legitimate access. While using anonymous data and | I | A | 100% |

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| consent, re-consenting and notification of clinically relevant results. Secure data-sample linkage systems should be established. | samples is the best way to protect personal information, it is not feasible in pediatric research as it limits the researchers' ability to act on withdrawal of consent, the need for re-consenting and the detection and notification of clinically relevant results. All data handling has to follow the standards of the EU General Data Protection Regulation [4,22,29,42,101,106,107,109,110,112]. | | | |

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| **Recommendation 19: Standardization of Transfer**<br><br>Specimen transfer should include standardized packaging and labelling, accompanying transfer documentation, customs regulations and sample tracking. The consent form must include the agreement to share data and samples. | Standardization of shipment in accordance with international regulations and laws including all accompanying documents ensures a safe and confidential transfer of biological materials across borders. A documented agreement between the sender of the biological materials and the recipient should be signed. The patient's agreement of data and specimen transfer has to be obtained and shared [22,32,100,106,107]. | I | B | 100% |

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| ***Commercialization and Third-Party Access*** | | | | |
| **Recommendation 20: Fees and Incentives**<br><br>Biobanks should enable research to improve medical knowledge. Provision of data and samples should be free; shipment and processing costs should be covered by the requesting research team. Participants or their parents should not receive payment. | Responsible sharing of biospecimen and data should be guided by the principle of the "Universal Declaration of Human Rights, 1948", which grants every individual the right to „share in scientific advancement and its benefits". In fact, the Council of Europe states that sharing of all knowledge and distribution of materials will be obligatory. Collaborative pediatric research aims to maximize discoveries by sharing of resources, data and samples. Financial incentives should be avoided. The operators of data and biobanks must ensure that any stratified access or fee policies are fair, transparent and do not inhibit research [4,21,22,50,100,101,104,107,112,113]. | I | A | 100% |

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| **Recommendation 21: Third Parties**<br><br>Researchers have to obtain ethics approval before giving patient data or sample access to third parties. Continuous education of the public about biobanks is important to retain public trust in research. | The autonomy principle mandates that a patient has to give consent to any sharing of data and biospecimen. A researcher therefore should not share any data or specimens with third parties unless the patient permits such submission and an ethics approval was obtained. The most important prerequisite for successful biobank related research is ensuring the public trust. This can be achieved through continuous education of people and protection of privacy [4,9,21,28,101,103,104,107,110]. | I | A | 100% |

**Legend:** In an effort to overcome these barriers and facilitate the work of scientists engaged in pediatric research we have developed twenty-one recommendations to support the establishment of a European legislative framework including data and sample sharing across borders. These recommendations have been evaluated and discussed in depth by all members of the SHARE project and (after careful revision) finally approved by the SHARE Consensus meeting in Rome.
Level of evidence; I, International normative document; IIa, Systematic review, IIb randomized controlled study, III, Non systematic review, observational study, IV, cross-sectional study, Va, Narrative review, Vb, Expert opinion; Strength of recommendation; A, based on level 1 evidence; B, based on level 2 or extrapolated from level 1;
Agreement: Level of agreement at SHARE Consensus meeting in Rome.

# 4 Discussion

In the process of the systematic literature review, the study on the investigator perspective, the study on the patient perspective, the interview on the research ethics board perspective, and the ethics proposal three types of barriers were identified.
The SHARE initiative developed the first European recommendations for collaborative, pediatric research including biobanking for children with rheumatic diseases.

## 4.1 Systematic literature review

By performing a comprehensive systematic literature review, which included European legislative documents, we wanted to find the best practices for ethical consent in pediatric research and best practices for the organization and exchange of data and samples throughout Europe as well as ethical issues on this topic. The selection process of the references comprised full-text screening by two members of the SHARE working group, continuous discussion and a repeated consensus process by all SHARE working group members. Furthermore, we evaluated the existing regulations and guidelines written by the European Union and the Council for International Organizations of Medical Science.
In an effort to gain insight into the real-life implications of the various existing legal environments and documents as well as the scientific literature we sought input from the key stakeholders including European pediatric rheumatology researchers, patients with rare diseases as well as their families, REB members and the REB as a responder to an ethics proposal.

## 4.2 Investigator perspective

The investigators' perspective on the challenges and barriers that they meet in the implementation of a study including minors have been analysed. We have gained insight into the level of expertise and time load of researchers working in the field of pediatric rheumatology and handling these applications.

During this process we were in constant contact with the participating researchers. To the best of our knowledge, no study investigating the researchers' point of view on this issue exists. A study from Hens et al. focusses on the researchers' point of view on the use of tissue samples for genetic research originating from minors[23], but it does not examine day-to-day challenges that researchers encounter.

This study showed a considerable gap between the fact that 91% of investigators have written at least five or more ethics proposals, at least one being the main responsible, while on the other hand almost a fourth of them does not feel more than 80% sure about the current jurisdiction concerning pediatric ethics proposals. 46% of them even feel that they are less than 50% familiar with the laws in question.

Another striking issue is that writing an ethics proposal is done within a week at most by 90% of the researchers while the entire completion of the proposal takes up to three months.

In summary the high response rate of 81% indicates that investigators have a high interest in improving the current situation. A great need for more support was shown. One study on the views of researchers engaged in clinical care of pediatric patients showed that the difficulties of managing the process and problems of maintaining a paper trail are among the main problems they have to face[24].

Further investigation on this topic is necessary in order to evaluate what kind of support would be most helpful to the researchers.

### 4.3 Patient and parent perspective

Furthermore, we evaluated the opinions and perceptions of the patients and their families who are directly or indirectly affected by a rare disease. We were able to identify issues and concerns that are of particular interest and importance to the patients and their families. It is perhaps the most notable issue that the concept of subsidiarity is of rather low importance for caregivers of pediatric patients. Only 23% agreed that research should be conducted with adult patients if generalizable results can be derived from it. On the one hand this can be interpreted as the parents wish for progress and improvement of their children's situa-

tion. On the other hand the concept of subsidiarity has been acknowledged by all important guidelines including EU-Regulation 536/2014 Art. 32 1 e).[51] Furthermore the literature shows broad consensus on this topic and is in favour of applying this concept.[10,28,40,52-55] These issues will be discussed in-depth in another thesis written by my WP7 colleague.

### 4.4 Research ethics board perspective

Additionally, we performed a study on the research ethics boards' perspective with 30 German REBs investigating three major topics. The timetable of the review process, the financial requirements of an application and the structure of the REBs that we contacted have been discussed. Through the practical studies we have gained insight into the formal and financial requirements for writing and submitting an ethics proposal.

The findings of the study on the REB perspective and the findings from our ethics proposal study showed a rather high discrepancy. On the one hand we found that 73% of REBs do not charge a fee for the scrutiny of an ethics proposal that has no sponsoring, but on the other hand 50% of the failed ethics proposal submissions were explained with the fees that were involved. This is in contrast to the submission process on the European scale. Only two of these ethics proposals were not submitted due to the costs involved, but in the cases were we received no further answer to our queries a fee might have been part of the problem. EU-Regulation 536/2014 does not provide a strong guidance on this issue as it states that fees might be levied but might also be waived in the case of non-commercial studies. [51] A study focussing on the REB perspective on the European scale can provide further insight concerning this issue.

### 4.5 Ethics proposal

As a final step an ethics proposal was sent to the research partners from SHARE and collaborating researchers all over Germany and Europe. The intention was to submit the same ethics proposal to multiple independent REBs and analyse their reaction and possible differences in the evaluation of the application.

There is a high discrepancy between the theoretical time expenditure and the predicted workload caused by the application process when setting up a pediatric multicentre study. Of the 26 ethics proposals that were sent to the researchers, only nine were submitted and evaluated by the REBs, which represents a submission rate of 35%. In Europe the main reason for this was loss of contact with the research partner (four cases), in Germany, the main reason was the fees that were involved (five cases).
In 23% of the cases we could not maintain contact with our partners, eight per cent could not finish the submission process due to lack of time, one of our partners refused to submit the proposal and in 27% of the cases (a total of seven applications, five of which in Germany) the submission was associated with additional costs which led to non-submission of the ethics proposal. Additionally, there were different terms and conditions for the submission to the various REBs (Which part of the proposal needs to be translated? How many copies need to be provided? Are there specific formal criteria that the proposal must meet?).
This was supported by the findings from the study on the REB perspective, which showed that the structure of research ethics boards around the country varies considerably as far as REB staff, time schedules and costs involved are concerned.

The problems that we encountered during the submission process were to some extent in accordance with the results of the study on the investigator perspective. It showed that researchers involved in pediatric research require more support. In Europe 55% of investigators receive support consisting of financial help, help from experts/administrators and/or extra time awarded for handling an application and possible queries. On the other hand, 82% would appreciate further support. In Germany the need for more support especially urgent as only two investigators receive any kind of support.
The questionnaire also revealed a lack of up-to-date legal expertise even among researchers experienced in handling applications for pediatric studies. On the other hand, it is highly important that the process itself is simplified. This is especially important in the case of international studies since these studies are in themselves more complicated to perform.

Apart from the fact that translations are needed in international projects, for every country participating there are different legal, ethical and societal issues and regulations to consider for each country.

In summary, researchers often lack the time and legal expertise to effectively organize and coordinate scientific projects. Further support in the form of legal experts and free time slots used exclusively for scientific projects is needed to ensure the effective progress of clinical studies.
The process of submitting an ethics proposal and receiving a verdict should be standardised across Europe to facilitate the work of researchers.

In the study on the research ethics board perspective we found that a REB charges a fee in less than 10% of the cases if there is no sponsoring for the study. The ethics proposal study on the other hand showed that in 27% of the cases the costs involved represent a considerable obstacle in carrying out a study without funding. A closer examination of the European situation shows that only 15% of researchers did not submit the proposal due to the fees involved and 7,5% of researchers did not submit the proposal due to lack of time and research personnel. In Germany 38% of the ethics proposals were not submitted because of financial reasons. Birmingham et al. state that the costs of an extended ethical review process need to be considered when carrying out longitudinal studies[8]. Apart from that the issue of costs involved in the ethical review process is not discussed in the literature.

In summary, the financial requirements of an ethics proposal vary from country to country and even within the same country when an application is submitted to multiple REBs. This may result in studies not being performed due to lack of funding which, especially in research on rare pediatric diseases represents a significant barrier for the progress of these studies.

Overall only two of the REBs approved the proposal (one without any amendments to be made) while six proposals were rejected. In one case we did not receive a final verdict. The reasons for disapproval were very heterogeneous. In one case formal requirements were not met and one REB stated that biobank related research did not fall into their area of responsibility. The remaining REBs required a mandatory revision of the proposal.
One research ethics board for example was concerned about the risk of losing intellectual property through the sharing of data and samples as well as the collection of data about the ethnicity of study participants. A topic the participants of the patient study were less concerned with was privacy: only about 48% worried about it and even fewer participants (9%) worried about a risk of stigmatization.
Since the patient survey was not performed in the country from which we received this rejection of the ethics proposal, we cannot be sure if the REB's opinion adequately reflects the public opinion of the country in question.

Another issue that led to the rejection of the proposal was the participation of healthy siblings in the proposed study and the fact that blood samples would be collected for the research projects. Again, the patient perspective study showed much less concern among the participants. All healthy siblings and all caregivers of healthy siblings would participate i.e. let their children participate in a study, even though the kids themselves were not affected by the disease in question. 83% and 65% respectively would also agree to invasive blood sampling for research purposes only.
This lack of consistency is to some extent in agreement with the findings of Hens et al.[26] They found that there is no existing standardised list of issues to be taken into consideration in pediatric research[26]. Furthermore, the European Union states that an REB is an independent body acting in accordance with the law of the respective member state. The members of a research ethics board need not be appointed according to a fixed quota regulation.[27]
Birmingham et al. recommend that (depending on the focus of the conducted study) members should have specialized knowledge, such as pediatricians in the case of studies involv-

ing children.[8] While Hens et al. mention the need for a pediatrician as a member of the research ethics board[12,28] Merlo et al. found that their composition varies considerably even within one country.[29] These findings were supported by the study on the research ethics board perspective.
As far as European legislation is concerned both Decision 1901/2006 and Regulation 536/2014 of the Council state that pediatric expertise is needed in the field of research involving minors[21, 30], but it is not clearly stated that a pediatrician has to be a permanent member of a research ethics board reviewing pediatric studies. This explains to some extent why some of the research ethics boards that have been interviewed include a pediatrician permanently while others have "on demand" pediatrician expertise.

In summary, the personnel structure, the bureaucratic requirements of an application and the legal framework upon which an REB decision is based should be standardised across Europe to ensure comparability and consistency. This will make the ethical review process more transparent and reduce the work of research ethics boards by making sure that all the applications they receive meet the same technical and formal requirements.

**4.6 Barriers**

As mentioned above during the course of the studies on the stakeholders' perspectives we identified three types of barriers that hinder the progress of pediatric multicentre studies on rare diseases.

First there are **process barriers** that appear when a multi-centre study is started. As we showed with the study on the REB perspective and the ethics proposal, a proposal needs to be evaluated by REBs that have varying staff members, different formal and financial requirements and which are restricted by different legal frameworks. With the study on the investigator perspective and, again, in the process of the ethics proposal we showed that there is a big difference between expectations and reality. 69% of researchers estimated that the entire completion of the application, including answering and settling queries, would

not take more than 4 weeks. The ethics proposal study showed that even with a prefabricated application it takes several months before the application is submitted and at least another month before the REB sends a detailed verdict. As far as the actual consent process is concerned Pawlikowski et al. have found a surprisingly high variability in the implementation of consent standards in Polish biobanks across the country.[82]

Secondly, there are **research partner barriers**. 45% of researchers do not feel well informed about current jurisdiction concerning pediatric ethics proposal. There is a need for more support, either in the form of funding, of more personnel or in the form of time reserved exclusively for the process of writing an ethics proposal. In Germany in particular, there is a discrepancy between 63% of ethics proposals not being submitted for lack of funding and the study on the REB perspective showing that 73% of research ethics boards work free of charge.[31]
A study on the views of researchers engaged in clinical care of pediatric patients showed that the problems they have to face are mainly related to timing of the approach to families, the availability of suitable staff, the sensitivity of the issues, difficulties of managing the process and problems of maintaining a paper trail.[24]

Thirdly, there are **patient-related barriers**. In the patient survey it became clear that the question of who should give consent and at what point a child's opinion should be taken into consideration are very important to the participants. The systematic literature review showed that no clear course of action for this topic exists in Europe and countries have regulations that vary greatly from one country to another.[31] As a result, recommendations have been developed, refined and agreed on by expert clinicians in childhood disease, methodologists, pediatric researchers and content experts of pediatric ethics and legislation, partnered with patient representatives.

### 4.7 Recommendations

In an effort to overcome these barriers and facilitate the work of scientists engaged in pediatric research we have developed twenty-one recommendations to support the establishment of a European legislative framework including data and sample sharing across borders.

These recommendations have been evaluated and discussed in depth by all members of the SHARE project and (after careful revision) finally approved by the SHARE Consensus meeting in Rome. (see Table 6)

### Guiding principles – Recommendation 1-3

With the first three recommendations we tackle research partner barriers. We recommend international collaboration, extended training and support for scientists and an EU-wide standardisation of the legislative framework in pediatric research.

(see Table 6 Recommendation 1-3).

When we started sending ethics proposals to researchers across Europe, they showed great willingness to support the project and improve pediatric research in Europe. This is in accordance with several studies that show that rare disease research needs a multi-centre-approach to accumulate patient numbers that are sufficient to produce reliable results.[10,32,33]

In the following months it became more and more apparent that international collaboration is difficult to achieve when ethical and administrational standards are not unified across Europe. The researchers had to translate the patient information, modify the proposal form to fit their respective REB requirements and find the time to submit the proposal parallel to their clinical work. Four applications were not submitted due to lack of time and in six cases the reason is unknown. Whereas all the clinicians we contacted receive some kind of support, the extent and the nature of that support vary greatly. The ethics proposal study shows that if the submission of the ethics proposal to research ethics boards failed, that failure was due to different reasons. In seven cases the submission failed because of the fees involved because financial support was missing.

In four other cases scientists simply could not find the time to finish the application process (for example providing a translation, modify the proposal form to fit their respective REB requirements and find the time to submit the proposal parallel to their clinical work) although they had been provided with a prefabricated application.
Additionally, there were deadlines for the submission of the ethics proposal. With a simpler application process demanding less time, many more of the applications would have probably been submitted leading to a more reliable result of the survey.

The literature dealing with this issue also concluded that multi-national pediatric diseases research which requires sample and data collection is particularly challenging.[34]

The study on the investigator perspective shows that only 27% of scientists feel well informed with regard to current European jurisdiction concerning pediatric studies. It also shows broad consensus (82%) for more support in writing and submitting an ethics proposal. While in the practical approach we addressed mainly human related barriers, the legislative side with its varying and often imprecise regulations represents another barrier. The lack of a unified international legislative framework has been addressed as an obstacle by many different authors[4,21,26,29,34-46], but only few of them propose a specific plan of action for one of the issues under discussion, for instance the issue of children's privacy. Hens et al. state that biobank research is associated with the risk of a breach of privacy and that this risk needs to be addressed by legislation. At the same time sufficient data protection policies must be implemented by the biobanks.[29]
The European Union has recognized and addressed the issue of varying levels of data protection across the European Union in the EU-Regulation 2016/679 in order to provide uniform rules and legal certainty throughout the EU.
Hansson et al. acknowledge that there is "a need to harmonize the ethical requirements in order to prevent countries from competing for research by underbidding in terms of consent procedures, privacy requirements, or security arrangements" [39] but they also state "the advancement should not be hindered by privacy issues".[5]

Meanwhile the public is less concerned about the risk of a privacy breach. Only 48% see their privacy at risk and only 14% fear a stigmatization if data and samples are stored in biobanks.

The public opinion on who should be in charge of regulating and governing biobanks is divided between those who think, that a biobank should be self-regulated by doctors, researchers and/or public institutions (universities/hospitals) and those who prefer an external governance structure such as an research ethics board[47], although we found that in some countries, research ethics boards are not even in charge of dealing with biobank related research projects.

In summary we recommend international collaboration to ensure that sample numbers are sufficient to generate robust data. For this collaboration the sharing of data and samples is an important factor since it would reduce the burden of sampling for each affected child. Furthermore, a unification of regulations surrounding biobanks in Europe would facilitate the task of researchers and enable the sharing of samples across international borders. Finally, researchers need additional training to face the challenging tasks implied in pediatric research on rare diseases.

**Ethics – Recommendation 4-7**

The process of the ethics application needs to be simplified and unified.
A single centralized research ethics board should be in charge of the first evaluation of a proposed study. A pediatrician as an expert on questions concerning minors as participants should always be part of the REB staff. Financial issues should not represent a barrier for research projects without financial support (see Table 6 Recommendation 4-7).

The systematic literature review as well as the studies on the investigator perspective, the study on the patient and parent perspective and the study on the research ethics board perspective show that no single standard on organizational and ethical issues exists, e.g. the

structure of an REB. In Germany research ethics boards differ a great deal from one another as their composition varies considerably. Whereas in some countries such as England only one central research ethics board is in charge of reviewing applications, the situation in other European countries is the same as in Germany.

Additionally, the ethics proposal showed that the same application, reviewed by German and European research ethics boards sometimes provokes completely different reactions. In one case the REB stated that biobank research was not their field of responsibility, another stated that the application was in accordance with the statutory provisions of the respective country while six REBs rejected the application demanding mandatory revisions of various parts of the proposal.
While this may be understandable with regards to the highly variable historic developments in the countries involved there is broad consensus that REB guidelines need to be unified on a European scale since according to Eriksson et al. the existing guidelines „are intrinsically vague“.[21,26,29,38,41,48,49]
Furthermore McHale et al. state that a decentralized approach in which local research ethics boards and biobanks „develop their own ethics and governance structures independently“ would lead to uncertainty followed by distrust from the public side.[48]
Public trust however is a fundamental factor for the success of pediatric biobank research.

As multinational surveys become more and more common, there is an obvious need for the harmonisation of REB practices.[29] One step towards this goal will be the implementation of a central electronic application portal as promoted by the Clinical-trials-Regulation EU 536/2014.[27] We also recommend all trials and biobanks to be registered before they start. The process of designing, conducting, performing, monitoring, auditing, recording, analysing and reporting studies will be streamlined and thus simplified. This project has already been started by the EU with the implementation of the BBMRI-ERIC (Biobanking and BioMolecular Resources Research Infrastructure-European Research Infrastructure Consortium).

With regard to membership expertise both CIOMS guidelines and the Clinical-trials-Regulation EU 536/2014 as well as the preceding Directive 2001/20/EC analysed by Pinxten et al. state that an research ethics board with pediatric expertise is needed in the evaluation of research involving minors.[36] Accordingly Merlo et al. found the inclusion of a pediatrician in the evaluation process to be mandatory.[50]

In the study on the REB perspective we found that most of the research ethics boards include a pediatrician either as a mandatory or optional member of the board. This is in accordance with Merlo et al. as well as international guidelines which state that pediatric expertise is needed in research including minors.[27,29,51]

According to the Clinical-trials -Regulation EU 536/2014 personnel involved in pediatric research should "be suitably qualified by education, training and experience".[27]

This in accordance with a study of the views of researchers showing that the sensitivity of the issues is seen as one of the main barriers by researchers for gaining consent.[24]

It is debatable whether training and instructing people involved in pediatric research or, rather, a simplification of the rules would be sufficient.

While Rushforth et al. support offering training opportunities to scientists[34] Jackson et al. stated that while scientists do support the idea of receiving specific training, "highly formalized prescriptive rules might not be helpful in this area".[24]

In conclusion we recommend a centralized, specialized ethics proposal portal to ensure the same standard in the evaluation of an application while at the same time dramatically reduce the workload for researchers in charge through standardized application steps. While a pediatrician offers the necessary clinical expertise, lay members of the research ethics board offer a different, yet important point of view on the perspective of patients, participants and society. The fees entailed need to be reduced to a minimum or waived altogether to avoid financial bias favouring well-funded projects.

**Pediatric Principles – Recommendation 8+9**

We recommend that studies that are likely to produce results that are valid across all age groups should be performed in adults. Children should receive special protection. (see Table 6 Recommendation 8+9).

The concept of subsidiarity has been acknowledged by all important guidelines including EU-Regulation 536/2014 Art. 32 1 e).[51] When given the choice between a study on adults or on children every aspect of the study is easier when working with adults.
The literature shows broad consensus on this topic.[10,28,40,52-55]
Public opinion however is rather undecided, with only 55% of participants approving the concept of subsidiarity and only 23% of the patients' caregivers.
Some authors point out that there are situations when the principle of subsidiarity also demands pediatric research to be performed.[28,56] In fact, 92% of participants of the study about the stakeholders' perspective showed a great willingness to let children participate in studies and 98% point out the importance of pediatric research.

With regard to the vulnerability of children the literature broadly acknowledges the need for special protection measures. Risks should not be taken if they can be avoided.[4,14,28,29,40,51-53,55,57-59]

The concept of minimal risk is still a matter of debate. Hens et al. analysed that there is not yet a clear definition of what "minimal risk" really is.[60] Some define a risk as "minimal" if, for instance, a single blood sample is taken during the study.[58] Minimal risk, however, in non-interventional, non-therapeutic research, cannot be defined only by the degree of the physical risk a child faces.[61]
The risk of privacy breaches and stigmatization needs to be taken into account as well. As scientific resources evolve and become more sophisticated, it becomes easier to attribute samples to individuals. While very small children do not mind that, the need for privacy grows as they grow older.[40] In order to avoid ethical pitfalls of sharing data and samples of

minors it has been suggested to postpone sharing them until a minor comes of age. Other authors argued that this would slow down research so much that a whole generation of patients could not benefit from scientific progress.[4]
Westra et al. argue that too strict a policy on minimal risk would slow down progress of pediatric studies and that the degree of risk taken for a specific study should be assessed on a case-by-case basis.[62] In fact, in the study about the public opinion the participants turned out to be significantly less concerned. Only about 50% see their privacy at risk, when participating in pediatric research entailing the collection and storage of data and samples and only about 14% see a risk of stigmatization in this context.

In summary even though the public might not be as concerned about the risks of genetic research on pediatric samples as the scientific community we still recommend every precaution to be taken when they are included in research. A strong justification is needed when research is performed on a vulnerable group such as children. We recommend including children as much as possible in the consent process and to inform them in a language they can truly understand. True informed consent, given without coercion is the cornerstone of every ethically sound research.

**Consent in Pediatric Research – Recommendation 10-14**

The recommendations state that children should be included in the process of consenting with age-appropriate information. The scope of consent should be broad, but both reconsent at the age of maturity and the possibility to withdraw consent are paramount. Clinically relevant results should always be forwarded. Refusal on the children's side to receive these results represents an exclusion criterion (see Table 6 Recommendation 10-14).

Ever since the introduction of the Nuremberg Code - supported by documents like the Declaration of Helsinki, the Charter of Fundamental Rights of the European Union, EU Regulation 536/2014 and the CIOMS guidelines of 2002 and 2008 - a scientific experiment involving human beings requires voluntary and - preferably - written consent.
While every author agrees with this basic principle it is much more difficult to be applied when children are involved. In the study about the stakeholder's perspective 97% feel that children should be included in the consent process in general and their opinion should be considered, but numerous studies discuss the question of when children become mature enough to decide for themselves if they want to be enrolled in a study and when they are actually able to give informed consent.

Proposed ages range from seven[63], over eight to ten[64] to fourteen years, which, for example, is also where Portugal puts the threshold.[9]

- 3 countries include the child in the consent process when he/she is 18
- 4 countries include the child in the consent process at a fixed age
- 2 countries decide on a case-by-case basis
- 1 country has a fixed age and case-by-case-system

In most cases there simply is no fixed age threshold, the guidelines are vague and children's opinions should be "taken into consideration".[4,14,15,24,29,49,50,52-54,58,60,65-68]
Stultiens and colleagues analysed the adoption of Article 6 of the European Convention on Human Rights and Biomedicine of the Council of Europe stating that "The opinion of the minor shall be taken into consideration as an increasingly determining factor in proportion to his or her age and degree of maturity".[31]

A study about the public opinion on this topic shows a similar uncertainty.[9]
The patient survey showed great support for asking children for consent and taking the child's wishes into consideration (97%). However, we did not evaluate if people had an opinion on when exactly the right moment to include children in the consent process and let them actually decide has come.

In the ethics proposal we suggested to give age-appropriate information and to ask for written consent when the children reach the age of fourteen. Furthermore, we suggested asking for renewed consent at the age of majority.
Waligora et al. propose a similar approach. They propose to include children in the consent process when they reach school age stating that this precise threshold would serve children better than flexible and therefore vague recommendations simply because it would be more likely to be applied.[69]
When it comes to the issue of how to inform children authors agree that children should be informed in a way that enables them to truly understand the goal of the scientific project and the risks and benefits thereof. A withdrawal of consent should be possible at any given moment[27] of the study and should not result in diminished medical care or any negative consequence for that matter.[4,8,9,11,13,14,29,37,41,49,50,52,55,57,60,70-80]
Helgesson et al. state that, according to the public opinion, asking children to consent "is a way to show respect to children participating in scientific studies".

Hofmann et al., while agreeing with the idea of withdrawal in general, argue that in times of international multi-centre studies a complete withdrawal might be impossible to achieve since it might be impossible to completely delete all individual information.

The scope of consent is another issue that is discussed in depth in literature. While international guidelines do not specify "scope of consent" as an individual topic, they do give advice on how to inform study the participants of a study on the possible future use of their samples and under what circumstances (previous approval of an research ethics board) this may take place.[27,51,59]
Authors agree that the approval of an research ethics board is a "conditio sine qua non" for the future use of stored samples and data[3-6,22,27,51,65,71,81,82] sometimes with an opt-out model for future research.[44,83] This is in agreement with the patient survey. 97% of participants wish to be asked for consent before data and samples can be used for research purposes.

Hens et al. argue that consent in childhood research is proxy consent by the parents and that proxy consent can never be a consent for all possible future research purposes, thus has limited temporal scope.[40,53,60,84] This is in accordance with the patient questionnaire, which showed that 89% feel that children should be asked to reconsent upon reaching the legal age of majority. On the other hand, the study on the investigator perspective showed that no more than 59% of researchers actually do seek renewed consent when participants come of age. The analysis of the literature dealing with the public opinion shows a tendency of supporting broad consent.[6,9,35]
Sometimes the public is in favour of broad consent under REB control.[6]
Sometimes they are in favour of a consent in general provided jurisdiction has taken care of the issue [9]. This in contrast to the patient study which showed a clear tendency to a limited consent model. Only 18% support a broad consent model, while 90% are in favour of only giving consent for a specific study. The practical implementation of gaining consent in biobanks is seldom assessed. One study, however, shows that in one of the countries included

in the study a surprising 29% of biobanks do not ask for consent to possible future uses of samples.[82]

When minors reach the legal age of majority the question arises whether they should be asked to reconsent to the future use of their samples and data. The study on the investigator perspective shows that the course of action varies between different research centres. This is in accordance with the findings of the study on the REB perspective that showed that as long as a certain plan of action is described and approved in the ethics proposal, both courses of action are possible. Obtaining a renewed consent may or may not be mandatory. In the literature some authors argue that this is not mandatory if confidentiality of the data and/or ethical oversight is secured.[4,22,74] Sometimes the task of contacting participants to reconsent is described as too costly.[85,86] Numerous authors strongly support the idea of reconsenting upon reaching the age of maturity, since the minor should be able to withdraw a consent which was given as proxy consent by the legal guardian and does not necessarily reflect the minor's wishes.[14,26,28,29,35,45,60,79,87,88]

Reconsent is also supported by international guidelines, but there is no specific reason given for that.[27,89]

The EU-Regulations reviewed do not provide instructions on how to handle incidental findings and clinically relevant results in children. Public opinion on how scientists and researchers should handle incidental findings and clinically relevant results is ambiguous. Some say that they want to be informed about every result, others are indifferent and some only want to be informed if the result shows a contagious disease.[10,12,15]

The literature shows a broad consensus that clinically relevant results or clinically relevant incidental findings should be communicated to children and their parents that have agreed to enrol in a study.[4,11,15,55,83] Some authors even state that refusal to be informed should result in the exclusion from the study.[55,65,90] In the case of non-clinical results the question remains unsolved.[60] Another topic that is discussed is who should give that information to the participants.[36,83] Hansson et al. state that "Communicating genetic information implies

skills in genetic counselling and the information may be of direct concern to genetic relatives who also must be informed “. International guidelines do not provide clear advice on who should inform a patient of results or incidental findings.[36]

In summary we recommend including children in the consent process because ethically sound research mandates voluntary consent given by the participants. Furthermore, we must really make participants understand what they are consenting to, no matter what their level of understanding is. The recommendation for broad consent is based on the consideration that this course of action reduces the burden of sampling. For researchers this also reduces the burden of recontacting participants in the case of a new study and makes it possible to conduct research projects that had not been conceptualized at the time of sampling. When participants reach the legal age of maturity asking for reconsent is mandatory in our opinion since this protects the children’s right to an open future. In pediatric research the participants right not to know does not apply since in the case of proxy consent this decision is not made by the participants themselves.

**Pediatric Data and Biobanks – Recommendation 15+16**

The recommendations state that the organizational framework of biobanks needs to ensure inter-operability, well-regulated and fair sharing of samples and data and electronically traceable information of every European biobank. Sampling needs to be non-invasive whenever possible and should follow SOP's of the highest standards to ensure long-term usability of samples and data. (see Table 6 Recommendation 15+16)

In the ethics proposal survey one REB denied the application for fear of losing intellectual property by sharing data and samples. Other research ethics boards showed no such preoccupation.

Concerns of this kind hinder scientific progress and the improvement of pediatric treatment. Authors dealing with the possibilities of standardizing and unifying the governance structures and access to pediatric biobanks in order to enable international collaboration and interoperability between these biobanks broadly agree that there is an urgent need to install an organizational framework for all European biobanks.[4,7,21,32,35,37,41,46,50,55,91]

Pawlikowski et al. have found a surprisingly high variability in the implementation of consent standards in Polish biobanks across the country.[82] Hansson et al. mention a lack of rules or guidelines that regulate important issues such as ownership of human tissue collections, their transfer across borders and access to collections that already exist.[39]

Although some guidelines mention safety measures that need to be installed and standard procedures that should be followed, these guidelines are described as too vague to provide true guidance.[38,92]

This lack of guidelines, laws and unified standards enabling pediatric biobanks to ensure inter-operability and long-term sustainability is pointed out by several authors.[39,41,82,88] As a possible solution Godard et al. propose to commission an organization which could monitor sample and data flows across borders.[21] A study evaluating the safety measures that have already been implemented in real life and evaluating the views of researchers in charge of biobank data protection could provide valuable insight into this topic.

As far as the collection of samples from minors is concerned, authors agree that it should entail only minimal risks and the smallest possible trauma.[4,29,40,55]
In accordance to this study among patient stakeholders showed a preference towards leftover sampling or non-invasive sampling (75% and 87% respectively). At the same 73% would also agree to a blood sample being taken for research purposes only.
Smaller samples equal smaller trauma, but also less material to be used in the future. Consequently, it is of vital importance that small sample quantities can still be used for a maximum of possible research projects. Authors agree that standard operating procedures should be used when collecting and storing samples from minors in order to ensure high accuracy, reliability and quality of the sampling process.[3,32,61,70,93-95]
The implementation of SOPs furthermore ensures the inter-centre comparability of results and findings in multi-centre studies.[51,96]
Petrini et al. mention that although there is a common framework, there is still a great variety of procedures and regulations used in different biobanks across Europe.[91]
One possible way of ensuring that SOPs are honoured could be certification of biobanks and regular inspections by an accreditation authority as it is performed in Denmark.[44]

In summary we recommend the unification of the organizational framework surrounding pediatric biobank research and the mandatory implementation of SOPs in order to advance the pressing simplification of international collaborative research regulations. This will ensure inter-operability of data and samples and ensure public trust through transparency.

Minimal invasive sampling is demanded by the Pediatric Rule and in turn this demands for SOPs ensuring optimal usage of the samples available.

**Sharing of data and samples – Recommendation 17-19**

Data needs to be stored and encrypted in a way that is secure and at the same time enables researchers to access the data for reconsent, informing participants of clinically relevant results and possible withdrawal of consent. Transfer procedures need to be standardized to ensure a safe and confidential transfer of samples across borders. The possibility to share data and samples across borders needs to be included in the consent form.
(see Table 6 Recommendation 17-19).

In pediatric research, especially in the field of rare diseases, international collaboration including data sharing is important to generate patient numbers that are large enough to produce reliable results.[8] Many authors agree that data sharing, with the provision that this data is thoroughly protected, should be based upon uniform standards of data sampling and data protection.[4,7,8,37,42,70] This is in accordance with the EU-Decision 2013/701/EU on setting up the Biobanks and Biomolecular Resources Research Infrastructure Consortium (BBMRI-ERIC) as a European Research Infrastructure Consortium.

While researchers that address this issue generally agree that sharing represents a risk to data privacy, they also state that this risk should not hinder
the advancement of research.[4,81]
In the patient survey the participants showed less concern about these issues. Only 48% of participants see their privacy at risk and only 14% see a risk of stigmatization.
A study evaluating the perceptions of the research ethics boards could further examine legal, ethical and organizational issues surrounding this topic.

An issue that is discussed in depth is anonymization of date and samples.
While complete anonymization would seem to be the safest way of handling and sharing data, there is broad consensus among researchers that this would impede important features of ethically sound research such as the possibility of withdrawal of consent[4,14] and hinder the return of clinically relevant information.[51,96]

Complete anonymization is even deemed unethical by some authors.[5,11]
Additionally, Hoffman et al. [73] argue that ultimate safety in biobank research can never be achieved. Merlo et al. argue that one way of ensuring data safety would be to code that data and minimize the number of people with access to the coding key.[50]
As a possible way of restricting access, Birmingham et al. propose a centralized data access hub, a structure that would automatically reduce the number of people that have access to the coding key.[8]
In this context it has been stressed that while a central data repository with the possibility of accessing a set of anonymised core data "encourages many further collaborations", this core data needs to be chosen very carefully in order not to endanger the privacy of study participants.[8] On the other hand Godard et al. state that it is indeed standardization of ethical requirements that would facilitate the protection of individuals.[21]
While securing the personal information of participants is an important issue, meaningful research on rare diseases can only progress, if sharing of data and samples across international borders is possible. The public opinion on this topic is rather open-minded. A study among the European public showed that most people would not mind providing blood and tissue samples as well as a genetic profile and/or medical records to support a biobank.[47] This in accordance with the patient survey that shows that 74% of the participants support the idea of invasive blood sampling even if the blood is taken for research purposes only.
The international guidelines agree that the possibility of sample transfer across national borders needs to be mentioned (as broader consent) in the consent form and that appropriate safety measures should be in place.[89,97] Lochmüller et al. describe a method enabling researchers to store, preserve and share samples for many years including training opportunities for receiving institutions.[32]

Garcia-Merino et al. state that ethical, legal and social differences in different countries need to be addressed and that SOP's concerning sample quality and data formats are need-

ed.[70] There is general agreement that the process of the sharing of samples is beneficial and needs to be unified.[22,32,37,39,55,70]

While unification and simplification are desirable Hansson et al. point out that this should not lead to countries "competing for research by underbidding in terms of consent procedures, privacy requirements, or security arrangements." [39]

In summary international collaborative research is only possible the collection and storage of data is standardized and if the data is comparable. We recommend not to completely anonymize the data and samples as this would impede the possibility to withdraw consent for participants as well as impeding the researchers' possibility to ask for reconsent and to notify participants of clinically relevant results. Cross border sharing needs to be simplified and standardized to ensure that researchers can collect large quantities of samples needed for rare disease research with a reasonable effort.

**Commercialization and third-party access – Rec. 20+21**

Biobanks should not charge a fee for providing data and samples. Costs for shipment and processing should be covered by the requesting institution. Third-party access always needs to be under REB scrutiny to promote and ensure public trust.
(see Table 6 Recommendation 20 + 21)

In some cases, the submission of the ethics proposal was not completed due to the costs involved. This finding was in part in accordance with the information derived from the telephone survey, which found that in some cases the research ethics board charges a fee, whether the study in question was funded in general, funded by pharmaceutical companies or not funded at all. While these fees represented a barrier for the ethics proposal survey, the CIOMS guidelines on Epidemiological Studies state that charging a fee for ethical review does not necessarily represent a conflict of interest as long as the fee is related to the

actual costs of performing the review and as long as the members of the REB are not involved in the negotiation.[51]

However, many questions regarding financial issues in biobank research remain unanswered. Authors state that there is urgent need for a discussion regarding financial benefits of companies derived from free sample donations.[4,21,22] Authors dealing with the issue of financial benefits for participants agree that participants of a study should not be paid.[9,54,86,87] In fact, Godard et al. state that "most international, regional and national bodies prohibit payment".[21]

One of the most important issues to be discussed is public trust. Without broad acceptance and public trust biobanks cannot exist.[4] On the other hand, without the possibility to share data and samples, biobanks will not exploit their full potential.
One of the fundamental questions of (pediatric) biobanking is whether the samples can be shared and forwarded to third parties.
In the ethics proposal and the consent form we mentioned the possibility of sharing samples with research partners such as scientists as well as pharmaceutical companies but ruled out the possibility of these research partners further sharing the samples with third parties such as employers or insurance companies.

Hens et al. found that public opinion on this topic is quite controversial. On the one hand people do not want insurers and employers to have access to their data and samples, on the other hand they do not regard researchers having access to and sharing the data and samples as a problem.[12] Hens et al. acknowledge the risk that the information gathered from pediatric biobank research may be misused by employers and insurance companies, but also state that this "does not warrant the exclusion of children from biobank research".[28]
Other authors agree that third-party access needs to be inhibited if there is danger of misuse by employers and insurance companies.[4,81] Some scientists are quite optimistic that the protection of privacy will be ensured by coding [6,10] while others argue that in the case of pedi-

atric research this issue deserves special consideration and is not defined precisely enough by existing international guidelines.[26]
This opinion is supported by EU-Regulation 2016/679 stating that there is a fragmentation of data protection policies across the European Union leading to the public perception that personal data may not be adequately protected.

Much of the discussion revolves around the question of whether companies that intend to benefit commercially should be allowed access to the samples. While according to Balaguer et al. commercialization implies the risk of losing public trust and support[2], parts of the public see pharmaceutical companies as valuable partner.[12] Some authors argue that the chance of promoting scientific progress justifies this access.[21,81] while other organizations and authors disagree and oppose access by commercial parties.[87,93]
Finally Pinxten et al. state that, while an EU-regulation may provide prolonged market exclusivity for companies engaged in pediatric research, there is still little risk of companies only seeking financial profit because patient numbers generated are too small.[58]

Every individual has the fundamental right to benefit from new findings. In summary, we recommend that the fees for receiving data and samples for research projects should be reduced to a minimum to ensure that the costs involved do not represent a barrier for research projects. Furthermore, access to the samples by third parties needs to be carefully monitored to ensure the protection of participants privacy. Finally, the autonomy principle demands that participants are asked for consent before their samples are shared.

The most important thing is to ensure public trust, because without public trust no kind of biobank can continue to exist and help find solutions and cures to diseases that affect millions of patients in Europe and the rest of the world.

# 5 Limitations

There are several limitations to the study and its results.
One general limitation was that only the views of researchers engaged in pediatric rare diseases research were asked to participate which leads to results that seem to be more generalizable than they are. The study does not include a comparison of the views of pediatricians in general, those pediatricians enrolled in rare diseases research and researchers treating and dealing mainly with adult diseases was not performed.

## 5.1 Investigator perspective

Another limitation is the relatively low number of scientists that filled out the questionnaire.The percentage response rate was quite high, the total number of questionnaires sent out though was relatively low compared to the number of scientists engaged in pediatric research across Europe.

## 5.2 Patient and parent perspective

The views, perceptions, feelings and needs of patients and their families from other European countries and consequently from another cultural context are not evaluated. Furthermore, this study is limited to rheumatic childhood diseases in Europe. In order to increase the generalizability patients and families with a spectrum of other conditions and in other cultural context such as North or South America as well as Asia including common and rare, acute and chronic illnesses would need to be part of the process.

## 5.3 Research ethics board perspective

For the study on the REB perspective we called only research ethics boards based in Germany. It would have added considerable information to the European approach to evaluate the situation in different EU-countries thus putting the findings and results on a broader base.

## 5.4 Ethics proposal

While the response rate to the ethics proposal of the research ethics boards involved was quite good, the absolute number of ethic applications that were submitted for evaluation was low. The small number of responses makes it difficult to interpret the results.
It is difficult to determine whether the ethics proposal would have been accepted or would have needed major or minor amendments before receiving a positive response. With the small number of answers the analysis tends to go to extremes rather than representing a precise reflection of REB opinion.
It also remains unclear if a standardized composition of REB personnel would have led to a more consistent ruling concerning the ethics proposal. Another question that remains is which problems led to non-submission of the TP. Was it because the collaborating researchers knew they were actually dealing with a TP? While this remains a possibility, the researchers involved were asked for permission before receiving the TP and agreed to submit it to their local REB.

Whenever we received no response, we tried to analyse the problem that led to the non-submission of the ethics proposal. We established that in some cases the ethics proposal was not forwarded for further assessment by the research ethics board and analysed the reasons for that. In many cases the costs involved represented a barrier that could have been overcome with more funding. On the other hand, this is how we identified the costs as a possible barrier for research projects.
Furthermore, it was difficult to maintain contact and resolve queries coming from the participating scientist. In many cases after multiple attempts to resolve queries and sending reminders the applications were ultimately not submitted for various reasons.
Sending the application directly from Tübingen would have been easier, but at the same time this would have resulted in higher costs and would have conflicted with the idea to evaluate the REB response from the local scientist's point of view. Furthermore, it would have been difficult to provide a translation of the patient information and the consent form in the national language of the various research ethics boards.

### 5.5 Key limitation and Outlook

The poor generalizability across and beyond Europe represents perhaps the key limitation to the study. Another cultural context, such as North America or Asia has to be explored. This context would pose new questions due to differences in clinic and REB structures as well as significant differences in medical legislation and public perception. As mentioned above neither the Nuremberg Code nor the Declaration of Helsinki have any binding legal force and may or may not be considered in medical legislature in the respective country. Another issue that will have to be explored in more depth is third-party access and under which circumstances it may or may not be allowed.

Legislation will have to find a way of ensuring participants' privacy and prevent patient groups from being disadvantaged because of a certain genetic attribute they possess.

At the same time these regulations and rules should not impede scientific progress. Nor should they leave patients suffering from rare diseases behind as "therapeutic orphans".

In addition, the study showed that researchers highly underestimate the actual expenditure caused by the submission of an ethics proposal and the formal requirements surrounding it. While we mention that scientists need more support in the second recommendation, we cannot make any statement whether more support in form of money, more personnel or more free time for scientific work would make a difference. Further studies evaluating what kind of support makes the biggest difference is needed.

The suggestion is to perform a study comparing the process of submitting an ethics proposal with and without the help of specifically trained personnel responsible for the submission.

## 6.1 Summary

Rare pediatric diseases have incidences as low as 1/million, but the entire sum of all various those rare diseases still affects thousands, if not millions of young patients across Europe. Scientists in every country have made substantial contributions to improve treatment strategies with the goal of developing early-onset therapies preventing irreversible organ damage and improving long-term prognosis.
International collaboration can foster progress, but still many scientists struggle with the immense variety of ethical requirements, the regulations for data and sample sharing and biobanking structures. A unified, standardized framework applicable for all member states of the European Union is still missing.
In order to design recommendations for this urgently needed standardization of the research process, we performed a systematic literature review and several real-life studies with the aim of identifying the best practices of and barriers to transnational pediatric research.

An ethics proposal was designed to evaluate the real-life work of research ethics boards across Europe.
A study on the investigator perspective was sent to multiple research partners to evaluate their level of experience and ideas to improve the current ways of conducting pediatric research. A study on the REB perspective was performed with REBs across Germany to examine their structural and procedural differences. With these practical approaches, accompanied by a comprehensive literature review, barriers for pediatric research have been identified. Recommendations to overcome these barriers have been drafted, revised, and finalized with the help of research ethics board members and European experts for ethical and legal aspects of pediatric research.

The results of the ethics proposal showed the greatest possible variety. Some research ethics boards have denied the proposal while others have approved it. The study on the inves-

tigator perspective has shown a great need for more support of pediatricians involved in research projects. The study on the REB perspective supported the wide variety of findings of the ethics proposal with personnel composition and organizational characteristics differing greatly. These findings have been analysed and led to a total of 21 recommendations. The issues that were addressed include 1) general principles, 2) ethics, 3) pediatric principles, 4) consent to pediatric research, 5) pediatric data and biobanks, 6) sharing of data and samples and 7) commercialization and third parties.

The process of the evidence synthesis and the resulting recommendations were published in our study:
"Recommendations for collaborative paediatric research including biobanking in Europe: a Single Hub and Access point for paediatric Rheumatology in Europe (SHARE) initiative." [25]

These recommendations for collaborative pediatric research on a European scale including data- and sample-biobanking and sharing across borders are the first of their kind and show the urgent need for a unified European legislative framework and evidence-based guidance for its implementation.
Children with rheumatic conditions and the many others suffering from rare diseases should no longer be left behind when life-changing research discoveries can be made.

## 6.2 Zusammenfassung

Seltene pädiatrische Erkrankungen haben zum Teil eine Inzidenz von 1/1.000.000, aber die absolute Zahl der Patienten innerhalb Europas geht aufgrund der Gesamtanzahl von seltenen Erkrankungen in die Millionen.
Wissenschaftler aus verschiedenen Ländern haben wichtige Beiträge zur Verbesserung von Behandlungsstrategien geleistet, um Therapien zu entwickeln, die frühestmöglich irreversible Organschäden verhindern und die Langzeitprognose verbessern.
Fortschritte im Bereich der pädiatrischen Forschung können durch intensive internationale Zusammenarbeit erleichtert werden, viele Wissenschaftler scheitern jedoch an der großen Bandbreite an ethischen Richtlinien und Bestimmungen für die Sammlung und Speicherung von Daten und Proben. Es ist festzuhalten, dass einheitliche, standardisierte Rahmenbedingungen, die für alle Mitgliedsstaaten der EU gelten, nach wie vor nicht definiert sind.

Um Empfehlungen für die Vereinheitlichung dieser Rahmenbedingungen erstellen zu können, führten wir eine systematische Literaturanalyse sowie praxisorientierte Studien durch. In diesen wurden die verschiedenen Interessensgruppen (Patienten und Angehörige, Forscher und Ethikkommissionen) befragt und deren Sicht- und Arbeitsweisen dokumentiert. Dies hatte zum Ziel, optimale Vorgehensweisen und typische Hindernisse bei der Durchführung internationaler pädiatrischer Forschungen im klinischen Alltag zu identifizieren.

Wir formulierten einen Ethikantrag um die Arbeitsweisen der verschiedenen Ethikkommissionen in Deutschland und Europa kennen zu lernen. Wir versendeten einen Fragebogen an in der pädiatrischen Forschung tätige Kliniker, um den Erfahrungsgrad der Forscher und ihre Ideen zur Verbesserung und Erleichterung pädiatrischer Studien zu erfassen.
Ergänzend wurde ein Interview mit Ethikkommissionen in ganz Deutschland durchgeführt, um die strukturellen Unterschiede und die unterschiedlichen Arbeitsweisen der Ethikkommissionen zu analysieren. Schließlich wurden die Patienten selbst und ihre Angehörigen

befragt, um herauszufinden, welche Wünsche, Sorgen und Ideen sie zu diesem Thema beschäftigen.
Mit Hilfe dieser Studien, kombiniert mit der Literaturanalyse, wurden Barrieren für pädiatrische Forschung identifiziert und Empfehlungen für die Überwindung dieser Barrieren entwickelt, überarbeitet und mit Hilfe von Ethikkommissionsmitgliedern sowie Experten für ethische und legale Aspekte im europäischen Rahmen fertig gestellt.
Die Antworten auf den Ethikantrag unterschieden sich deutlich voneinander. Einige Ethikkommissionen lehnten den Antrag ab, während andere ihn ohne weitere Änderungswünsche annahmen. Die Klinikerumfrage zeigte einen großen Bedarf für mehr Unterstützung für Pädiater, die in Forschungsprojekten engagiert sind. Durch die Telefon-Interviews wurde deutlich, dass große strukturelle Unterschiede zwischen den einzelnen Ethikkommissionen bestehen. Diese strukturellen Unterschiede erklären zum Teil die große Bandbreite an Reaktionen.
Mit Hilfe der Erkenntnisse, die wir aus diesen Untersuchungen gewonnen haben, wurden insgesamt 21 Empfehlungen entwickelt und in die folgenden Themengebiete unterteilt:

1) Allgemeine Prinzipien
2) Ethik
3) Pädiatrische Prinzipien
4) Einverständnis in pädiatrische Studien
5) Pädiatrische Daten und Biobanken
6) Versand von Daten und Proben
7) Kommerzialisierung und Zugriff durch Dritte

Diese Empfehlungen für Europa-weite Forschungsprojekte unter Einbeziehung von Daten- und Probenaustausch über Landesgrenzen hinweg sind die ersten ihrer Art und zeigen die

Notwendigkeit einheitlicher legaler und ethischer Rahmenbedingungen und eine evidenz-basierte Anleitung für ihre Implementierung.

Kinder mit rheumatischen oder seltenen Erkrankungen sollten viel stärker beachtet werden, wenn innovative lebensverändernde Entdeckungen gemacht werden können.

## 7 Literature


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## 8 Erklärung zum Eigenanteil der Dissertationsschrift

Die Arbeit wurde in der Universitätsklinik für Kinder- und Jugendmedizin, Allgemeine Pädiatrie, Hämatologie/Onkologie Abteilung Rheumatologie

unter Betreuung von

Frau Professor Dr. med. Jasmin Kümmerle-Deschner durchgeführt.

Die Konzeption der Studie erfolgte durch Prof. Kümmerle-Deschner in Zusammenarbeit mit Frau Dr. med. Sandra Hansmann, Betreuerin und Prof. Dr. med. Susanne Benseler, Betreuerin.

Die Studien, die in den Abbildungen 2, 4, 6 und 7 dargestellt sind, wurde mit Unterstützung durch Frau Dr. Sandra Hansmann durchgeführt. Die entsprechenden Ergebnisse der Studien wurden von mir in Zusammenarbeit mit Frau Dr. Hansmann ausgewertet.

An der Studie sowie an der Auswertung der Studie die in Abbildung 5 dargestellt ist, war ich als Teil der Arbeitsgruppe SHARE WP7 beteiligt. Die Daten zu der in Abbildung 5 dargestellten Studie wurden von Dr. Sandra Hansmann zur Verfügung gestellt.

Die statistische Auswertung erfolgte eigenständig durch mich.

Im Rahmen der Dissertation erfolgte eine Veröffentlichung unter dem Titel:

„Recommendations for collaborative paediatric research including biobanking in Europe: a Single Hub and Access point for paediatric Rheumatologyin Europe (SHARE) initiative.“

Die Veröffentlichung wurde als Erstautoren durch Professor Dr. med. Kümmerle-Deschner und Professor Dr. med. Susanne Benseler verfasst.

Ich versichere, das Manuskript selbständig nach Anleitung durch Frau Dr. Hansmann sowie Frau Professor Kümmerle-Deschner verfasst zu haben und keine weiteren als die von mir angegebenen Quellen verwendet zu haben.

Tübingen, den 12.03.2019

## 9 List of Figures

# 10 Appendix

## 10.1 Investigator perspective (English)

General Questions

How many ethics applications have been completed in collaboration with you?

<5 ☐ 5-9 ☐ 10-19 ☐ >20 ☐

Have you written at least one application by yourself?

Yes ☐ No ☐

Legal Matters

How familiar are you with current jurisdiction concerning pediatric ethics applications?

0% ——————————————— 100%

Is there a pediatric expert in your local ethics committee you might consult?

Yes ☐ No ☐

Do you receive any kind of support while writing an application?

financial ☐ administrative ☐ training ☐

experts ☐ other (see below) ☐

Would you appreciate further support?

Yes ☐ No ☐

If so, please specify:

Do you have access to forms taking the age of the child into consideration?

Yes ☐ No ☐

Do you seek renewed approval once the patient reaches the age of consent?

Yes ☐ No ☐

Procedural Difficulties

To which amount do you feel hampered by writing ethics applications?

0% 100%

How much time do you usually allow for the entire completion of an application including planning, writing and settling possible queries?

days/weeks (please mark where applicable)

How many times do you have to consult colleagues, superiors, the ethics committee (by e-mail/on the telephone) in order to complete an application?

<10 ☐ 10 to 20 ☐ >20 ☐

Who do you have to inform about the application? (e.g. superiors)

head of department ☐ head of clinic ☐

colleagues ☐ other(see below ☐

How long does writing an application take you?

___ hours (please mark where applicable)

How many copies do you have to provide?

1-4 ☐ 5-10 ☐ >10 ☐

How many pages does the patient information comprise?

1 ☐ 2 ☐ >2 ☐

Postapplication Queries

How many ethics-committee-queries (by telephone/written) regarding the application do you usually have to answer?

between____ and ____ by telephone between ____ and ____ written

How much time passes before you receive the ethics-committee's verdict?

_____ weeks (please mark where applicable)

How long does it take you to answer these queries?

_____ hours (please mark where applicable)

**10.2 Investigator perspective (German)**

Allgemeines

An welcher Anzahl von Ethikanträgen waren Sie beteiligt?

<5 ☐ 5-10 ☐ 10-20 ☐ >20 ☐

Haben Sie mindestens einen Antrag selbst erstellt?

Ja ☐ Nein ☐

Gesetze

Wie gut kennen Sie sich mit den aktuellen Gesetzen zu Ethikanträgen in der Pädiatrie aus?

0% 100%

Gibt es bei Ihnen einen pädiatrischen Experten als Ansprechpartner in der Ethikkommission?

Ja ☐ Nein ☐

Erhalten Sie Unterstützung bei der Erstellung der Ethikanträge?

finanziell ☐ administrativ ☐

Experten ☐ Fortbildungen ☐

sonstiges (siehe Feld unten) ☐

Würden Sie sich zusätzliche Unterstützung wünschen?

Ja ☐ Nein ☐

Wenn ja, welche?

Stehen Ihnen den Altersklassen entsprechende Aufklärungsbögen zur Verfügung?

Ja ☐ Nein ☐

Holen Sie bei Erreichen der Volljährigkeit der Patienten eine neue Einverständniserklärung ein?

Ja ☐ Nein ☐

Durchführung

Wie sehr fühlen Sie sich durch das Erstellen von Ethikanträgen belastet?

0% 100%

Wie viel Zeit müssen Sie im Schnitt für die vollständige Erstellung eines Ethikantrages (inklusive Planung, Erstellung, Klärung eventueller Rückfragen) einplanen?

_____ Stunden/Tage/Wochen (Zutreffendes bitte unterstreichen)

Wie viele Mail- bzw. Telefonkontakte (Rückfragen der Ethikkommission, Rücksprache mit Vorgesetzten, Kollegen) sind für die Antragstellung im Durchschnitt nötig?

<10 ☐ 10 bis 20 ☐ >20 ☐

Wen müssen Sie zusätzlich über die Antragsstellung informieren? (z.B. Vorgesetzte)

Abteilungsleitung ☐ Klinikleitung ☐

Kollegen ☐ Sonstiges ☐

Wie groß ist der Zeitaufwand für das Schreiben des Antrags?

_____ Minuten/Stunden/Tage (Zutreffendes bitte unterstreichen)

Wie viele Ausfertigungen des Antrags werden benötigt?

1-4 ☐ 5-10 ☐ >10 ☐

Wie viele Seite umfasst dabei die Patientenaufklärung im Anhang?

1 ☐ 2 ☐ >2 ☐

Bearbeitung

Wie viele Rückfragen (telefonisch/schriftlich) gibt es von Seiten der Ethikkommission nach Einreichen des Antrages im Schnitt?

_____ schriftlich _____ telefonisch

Wie viel Zeit vergeht von der Antragsstellung bis zum Erhalt des Ethikvotums?

_____ Tage/Wochen (Zutreffendes bitte unterstreichen)

Wie lange dauert die Bearbeitung der Rückfragen der Ethikkommission Ihrerseits?

_____ Stunden/Tage/Wochen (Zutreffendes bitte unterstreichen)

### 10.3 Patient perspective

Umfrage zu den Schwierigkeiten bei der Erforschung von seltenen Erkrankungen am Kind

Lieber Teilnehmer,

Es gibt 6000 bis 8000 unterschiedliche seltene Erkrankungen, in Europa sind etwa 30 Millionen Menschen von einer dieser Erkrankung betroffen. Aufgrund der Seltenheit jeder einzelner dieser Erkrankungen wäre es wünschenswert, Daten von Patienten auch aus anderen Ländern auswerten zu können, um sowohl Diagnostik als auch mögliche Therapieoptionen weiter zu entwickeln.

Dies ist momentan schwierig, da es in den verschiedenen Ländern unterschiedliche Gesetze und Regularien gibt. Daher gilt es bei der praktischen Umsetzung immer wieder Barrieren und Hindernisse zu überwinden. Gewünscht ist eine Zusammenarbeit, die nicht durch formelle oder bürokratische Barrieren erschwert oder gar blockiert wird.

Gemeinsame Richtlinien sollten eine länderübergreifende Zusammenarbeit erleichtern. In einem von der EU geförderten Projekt sollen diese Richtlinien erstellt werden, an denen sich die Forscher orientieren können. Experten zu den unterschiedlichen seltenen Erkrankungen haben Netzwerke entwickelt, um gemeinsame Fragestellungen und Probleme zu bearbeiten. Ziel dieser Initiative ist es, internationale Richtlinien zu verabschieden, die sowohl Patienten als auch ihre Familien schützen. Diese Richtlinien sollen aber auch multizentrische internationale Untersuchungen ermöglichen, um damit weitere Erkenntnisse zu gewinnen und diese den Patienten und Familien zu Gute kommen zu lassen.

Unsere mehrköpfige Arbeitsgruppe steht unter der Leitung von Priv. Doz. Dr. Jasmin Kümmerle-Deschner und würde gerne mehr über den Standpunkt von betroffenen und gesunden Kindern und deren Eltern erfahren.

Wir wären daher sehr dankbar, wenn Sie sich ein paar Minuten für die Beantwortung der folgenden Fragen Zeit nehmen könnten.

Ihre Arbeitsgruppe

| | | | |
|---|---|---|---|
| ***Demographische*** | *Bitte beantworten Sie folgende Fragen!* | | |
| | In welchem Jahr sind Sie geboren? | | |
| | Sind Sie männlich oder weiblich? | männlich<br><br>O | weiblich<br><br>O |

| | | | |
|---|---|---|---|
| | Haben Sie Kinder? | Ja<br>O | Nein<br>O |
| | Haben Sie bereits Erfahrung mit klinischen Studien (z.B. bereits teilgenommen) | Ja<br>O | Nein<br>O |
| | Wären Sie grundsätzlich bereit an einer Studie teilzunehmen bzw. Ihr Kind teilnehmen zu lassen? | Ja<br>O | Nein<br>O |
| | Leiden Sie selbst unter einer chronischen/seltenen Erkrankung? | Ja<br>O | Nein<br>O |
| | Leidet ihr Kind unter einer chronischen/seltenen Erkrankung? | Ja<br>O | Nein<br>O |
| | Leidet jemand anderes in ihrer Familie unter einer chronischen/seltenen Erkrankung? | Ja<br>O | Nein<br>O |

| | *Passendes bitte ankreuzen!* | **Trifft zu** | **Trifft meistens zu** | **Trifft teilweise zu** | **Trifft meistens nicht zu** | **Trifft nicht zu** | **Keine Angabe möglich** |
|---|---|---|---|---|---|---|---|
| ***Generelle Fragen*** | Erforschung von Erkrankungen im Kindesalter ist wichtig. | O | O | O | O | O | O |
| | Forschung an Kindern soll nur dann durchgeführt werden, wenn diese nicht auch am Erwachsenen durchführbar ist. | O | O | O | O | O | O |
| | Kindliche Proben und Daten sollen besonders und angemessen geschützt werden. | O | O | O | O | O | O |
| | **An folgenden Proben darf ihrer Meinung nach geforscht werden:** | | | | | | |
| | Nur zu Forschungszwecken entnommene ge- | O | O | O | O | O | O |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | websverletzende Proben (z.B. Biopsien) | | | | | | |
| | Nicht invasiv (nicht gewebsverletzend) entnommene Proben (z.B. Urin Speichel, Haare, Nägel,…). | O | O | O | O | O | O |
| | Nur zu Forschungszwecken entnommene Blutproben. | O | O | O | O | O | O |

Um bei einer Studie teilzunehmen, muss der Studienteilnehmer (Proband) zuerst über diese Studie aufgeklärt werden (z.B. über Ziel der Studie, Risiken für den Probanden, Umgang mit Daten,…). Nach der Aufklärung darf der Studienteilnehmer entscheiden, ob er an dieser Studie mitmachen will oder nicht. Bei Studien an Kinder müssen auch die Eltern informiert werden, die dann letztendlich über die Teilnahme entscheiden.

Wie bewerten Sie hinsichtlich dieses informierten Einverständnisses folgende Aussagen?

| | *Passendes bitte ankreuzen!* | **Trifft zu** | **Trifft meistens zu** | **Trifft teilweise zu** | **Trifft meistens nicht zu** | **Trifft nicht zu** | **Keine Angabe möglich** |
|---|---|---|---|---|---|---|---|
| ***Wer und wie wird aufgeklärt*** | Forschung am Kind soll nur nach vorherigem Einverständnis der Erziehungsberechtigten möglich sein. | O | O | O | O | O | O |
| | Sollte das Kind die Teilnahme in einer Studie ablehnen, soll dies von den Eltern und dem Forscher beachtet werden. | O | O | O | O | O | O |
| | Die Aufklärung soll altersgerecht erfolgen. | O | O | O | O | O | O |
| ***Auf-*** | Den Eltern und dem Kind soll Zeit gegeben werden, ihre Entscheidung zur Studienteil- | O | O | O | O | O | O |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | nahme zu überdenken. | | | | | | |
| | Die Zustimmung sollte sich nur auf diese eine Studie beziehen. | O | O | O | O | O | O |
| | Es ist sinnvoll auch die Zustimmung für zukünftige noch nicht bekannte Studien zu geben. | O | O | O | O | O | O |
| ***Reconsent und Rekontakt*** | Sollte an den gelagerten Proben/Daten weitere Forschung möglich sein, muss ein erneutes Einverständnis des Probanden eingeholt werden. | O | O | O | O | O | O |
| | Die Einverständniserklärung sollte direkt vom Kind bei Volljährigkeit erneut eingeholt werden. | O | O | O | O | O | O |
| ***Weitergabe*** | Klinisch relevante Ergebnisse sollen an den Probanden bzw. seine Eltern weitergegeben werden, um eine Therapie einleiten zu können. | O | O | O | O | O | O |

Bereits entnommenes menschliches Gewebe wird häufig in sogenannten Biobanken gelagert. Diese Lagerung macht es möglich, dass weitere Forscher Zugriff auf das anonymisierte (personenbezogene Daten werden unkenntlich gemacht) Gewebe haben können und somit nicht überflüssiges Gewebe verworfen werden muss.

Wie bewerten Sie folgende Aussagen?

| | *Passendes bitte ankreuzen!* | **Trifft zu** | **Trifft meistens zu** | **Trifft teilweise zu** | **Trifft meistens nicht zu** | **Trifft nicht zu** | **Keine Angabe möglich** |
|---|---|---|---|---|---|---|---|

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| ***Sammlung*** | Eine Lagerung von Proben/Daten ist nach vorherigem Einverständnis sinnvoll, da keine weiteren Studienteilnehmer rekrutiert werden müssen. | O | O | O | O | O | O |
| ***Nutzen*** | Forschung wird vor allem zum Dienst der Wissenschaft gemacht. | O | O | O | O | O | O |
| | Forschung wird vor allem zum Nutzen weiterer Kinder (mit derselben Erkrankung,…) durchgeführt. | O | O | O | O | O | O |
| | Forschung wird vor allem zum Nutzen des Probanden durchgeführt. | O | O | O | O | O | O |
| ***Risiken*** | Die Risiken bei der Forschung am Menschen liegen v.a. beim Datenschutz (Privates Risiko). | O | O | O | O | O | O |
| | Die Risiken bei der Forschung am Menschen liegen v.a. bei einer Stigmatisierung (einen Menschen aus bestimmten Gründen benachteiligen und herabsetzen, indem man ihn schlechter als andere Menschen behandelt.) | O | O | O | O | O | O |

Vielen Dank für Ihre Teilnahme an der Umfrage!

### 10.4 Research ethics board perspective

**Zeit**

Wie häufig kommt die EK zusammen, um Anträge zu bearbeiten?

Wie weit im Vorraus müssen Anträge eingereicht werden?

Ist es möglich, dass vor Erhalt des eigentlichen Votums telefonische Rückfragen erfolgen?

Wieviel Zeit wird im Schnitt für die Bearbeitung eines Antrages verwendet?

Wieviel Zeit vergeht, bis man eine Rückmeldung bzw. eine ausführliche Antwort erhält?

**Geld**

Wird von der Ethikkommission eine Gebühr für ihr Votum erhoben?

Wird diese Gebühr auch erhoben, wenn keine Pharma- oder Drittmittelfinanzierung für das Projekt besteht?

Wie hoch ist diese Gebühr?

Wie errechnet sich diese Gebühr?

**Allgemeines**

Wieviele Mitarbeiter zählt die Ethikkommission?

Gibt es mehrere Arbeitsgruppen oder nur eine?

In welchem Turnus werden die Mitarbeiter ggf. ausgetauscht?

Gibt es bei Ihnen einen pädiatrischen Experten als Ansprechpartner in der Ethikkommission?

Was passiert mit dem Ethikvotum wenn die Studienteilnehmer volljährig werden? Muss in diesem Fall ein neuer Antrag gestellt werden?

## 10.5 Ethics proposal

### Table of contents

# 1 Abbreviations

- BD = Behçet's Disease
- IDAT =identification data
- MDAT= medical data
- arcT = Autoinflammation Reference Center Tübingen
- HLA = Human Leukocyte Antigen

## 1.1 Morbus Behçet, establishment of a biobank to improve diagnosis and treatment of Behçet's disease in minors

Behçet's disease (BD) is a severe illness defined by systemic vasculitis of unknown origin affecting arteries and veins causing thrombosis and/or aneurysm. Various organs can be involved such as the central nervous system, kidneys, lungs, joints and frequently ocular involvement (Uveitis). It is extremely rare in northern Europe and even in countries like Japan, the Far and Middle East as well as countries bordering on the Mediterranean where BD is more common prevalence does not exceed 15-300/100000.

In children aged under 16 it is even less frequent, but takes a more severe course than in adults. Since the initial disease phase can show only one symptom or even atypical signs, the numbers of patients are believed to be highly underestimated. A study performed by I. Koné-Paut et al. showed a mean delay of 3.5 years between the first symptoms and satisfying international BD criteria.

It is difficult to diagnose BD early enough in these young patients to begin treatment and prevent consequential organ damage.

There are important differences between patients with early BD and adults with BD:

- the occurring Uveitis is less common, but more damaging

- the clinical course is worse in young male patients aged 15 to 25

- 10% of all cases showed higher prevalence in some families pointing towards a genetic precondition [1]

Although being identified as a clinical entity consisting of buccal-genital aphtae and ocular inflammation as early as 1937 by Huluçi Behçet, clinical symptoms are highly diverse. Considering the mostly unspecific symptoms and the lack of specific bio-pathological markers[2], diagnosis remains to be problematic. One of the major genetic risk factors of early-onset Behcet's Disease is a specific form of chromosome 6 in the Human Leukocyte Antigen region (HLA-B*51)[3]. A positive status for HLA B51 combined with clinical symptoms points to the diagnosis of BD.

Differentiating between BD and other inflammatory diseases is difficult. Some physicians still believe BD to be a syndrome sharing symptoms with various other inflammatory diseases.

The clinical presentation is marked by unpredictable phases of high inflammatory activity followed by remission of symptoms affecting mainly young adults at the age of 30. The diagnosis is generally based on the combination of clinical symptoms and is often delayed, leaving patients with severe consequential organ damage, especially in younger patients often presenting with a more severe disease course.

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[1] http://dx.doi.org/10.1016/S0022-3476(99)70333-1

[2] http://dx.doi.org/10.1038/ng.2551

[3] Close association of HLA-B51 with Behçet's disease. Arch Ophthalmol. 1982,100:1455-1458

Internationally valid criteria have been defined and published by an expert committee in 1990. In the absence of other clinical explanations, patients must present with:

1. Recurrent oral ulceration (aphtous or herpetiform) observed by the physician or patient recurring at least three times in a 12-month period;

and two of the following:

2. Recurrent genital ulceration
3. Eye lesions; anterior uveitis, posterior uveitis, cells in the vitreous by slit lamp examination or retinal vasculitis observed by an ophthalmologist.
4. Skin lesions: erythema nodosum, pseudofolliculitis, papulopustular lesions, acneiform nodules in postadolescent patients not on corticosteroids.
5. Pathergy, read by a physician at 24-48 hours

In practice, however, these criteria lack sensitivity and specificity since they have only been tested on adults predominantly originating from the Middle East. [4]

On the basis of this situation a biobank analysing clinical and genetic parameters to define predispositioning factors can only be effective by recruiting large numbers of mainly minor patients from all over the European Union.

[4] http://www.behcets.com/site/pp.asp?c=bhJIJSOCJrH&b=260549

The International Study Group for Behçet's disease. Br J Rheumatol. 1992;31:299-308

## 2.1 Objectives of the application and reasons for the establishment of a biobank

This application aims at initiating the establishment of a biobank and database, storing samples of human tissue and corresponding data.

The proposed biobank serves as a resource for scientific research. Therefore, defining a close range of possible fields of use is not possible. Due to rapid scientific development continuous progress in the field of finding new illness-related genes, gene products or metabolites is to be expected. It must be considered future-oriented to establish a biobank containing specimen that have been collected following a structured, standardised, high-quality assembly process. Today, any analysis of relevant aspects of diseases, e.g. diagnostic markers or possible therapeutic approaches is, to an increasing extent, based upon genetic research performed on human tissue samples. As a consequence this biobank should be open to local research teams as well as international research partners or third parties, thus allowing and encouraging different scientific groups to cooperate.

With regard to our topic the examination of a stored sample in association with the clinical presentation of a donor patient may lead to a profounder understanding of the pathological significance of a newly found gene, protein or metabolite, thereby allowing an earlier diagnosis of BD. A biobank would enable us to find answers to scientific problems arising without the necessity of recruiting patients again and again, thereby linking non-therapeutic basic research and applied medicine.

## 2.2 Patient pool, multicentre approach

A study performed by I. Koné-Paut in 2002[5] highlighted the importance of carrying out a genetic linkage study in order to further examine the genetic component of the Behçet

[5] *doi:10.1136/ard.61.7.655*

Disease. We will include as many hospitals and rheumatology centres as possible especially from countries showing higher prevalence of BD.

### 2.2.1 Founding

Financial support for the Biobank resource is being provided by the Autoinflammation Reference Center Tübingen (arcT) research grant. In the process of recruiting more participating centres and continuously expansion of the biobank we will apply for additional founding by the European Union.

### 2.2.2 Definition of potential research subjects

Behçet's Disease mainly presents itself in patients aged between 20 and 35, with a geographic distribution characterised by greatest prevalence in Turkey, Iran and Japan. The sex distribution is 1:1 with more severe courses in male patients.

Since it is our aim to identify predispositioning factors typical for BD, especially younger patients aged under 16 showing possible symptoms of BD are of interest, but due to the small overall numbers we will add adult patients as well. Also patients' parents and siblings as possible HLA-B positive members of the family will be asked for permission to collect a blood sample.

### 2.2.3 Qualifying criteria

- every patient showing signs of expected BD (i.e. inflammation of unknown origin, joint pain, recurring oral/genital aphtosis) until diagnosed otherwise
- the first diagnostic step in patients' siblings with only vague symptoms should be restricted to giving blood samples
- siblings of patients diagnosed with BD, even when they appear to be healthy, should also be included in the study since they would benefit directly from an early diagnosis.
- Parents of patients with BD
- according to the respective weight (rather than age) only a certain amount of blood will be taken from the patient:

| Weight range category (kg) | Maximum Allowable Blood Volume Drawn/Visit (mL) | Maximum Allowable Blood Volume Drawn/ 4 Week Period (mL) |
|---|---|---|
| 7-10 | 5,6 | 16,8 |
| ➢ 10-12 | 8,0 | 24,0 |
| ➢ 12-14 | 9,6 | 28,8 |
| ➢ 14-26 | 11,2 | 33,6 |
| ➢ 26-38 | 20,8 | 62,4 |
| ➢ 38 | 30,4 | 91,2 |

### 2.2.4 Disqualification criteria

- patients' refusal of consent
- adult patients unable to give consent (e.g. due to mental incapacity)

### 2.2.5 Recruitment of potential research subjects and gaining consent from minors

The local attending physician will refer the patient to the local biobank Assessment Centre.

Children that have not yet reached the legal age of majority will be included in the process of seeking consent. They will receive age-appropriate information about the collection, storage and use of their samples. From children aged 14 and older a signed consent form has to be obtained. Children will have the opportunity to contact researchers and withdraw their consent, once they are mature enough or once they have reached adulthood. Also they will be recontacted on our part to discuss the further approach regarding their stored samples and data.

### 2.2.6 Site of Research

The biobank will be based in Tübingen. We will store samples and data arriving from local study Assessment Centres participating in the project (see 2.2.1)

### 2.2.7 Sample size and projected timetable

A limitation of the sample size is not intended, we plan to include patients of all age groups. The goal of this application is to initiate the founding of a biobank and database storing samples of human tissue and corresponding data for an indefinite period of time.

## 3.1 Interventions, sampling-related procedures

All samples will be gathered as part of the clinical routine or in the process of finding the correct diagnosis. Only after the diagnostic process is completed, one part of the sample will be added to the biobank. The other part will remain at the pathology lab in case other diagnostic procedures need to be performed. Apart from a supplementary blood vial only residual material will be used, NO ADDITIONAL biopsies or samples will be removed from the patient.

## 3.2 Risk benefit relation

Minors: Since all samples added to the biobank will be taken during the process of finding the correct diagnosis and only an additional tube of blood will be collected during the regular venipuncture, no further risk arises from these procedures.

Adults: Adults will face only the risks arising from the additional venipuncture.

Risks associated with having blood drawn are slight but may include:

1. Excessive bleeding
2. Fainting or feeling light-headed
3. Hematoma (blood accumulating under the skin)
4. Infection (a slight risk any time the skin is broken)

## 4 Who will benefit from our research?

Samples will be collected both for our own research and cooperation schemes. Transmission of samples to researchers or companies will only be permitted after reversible anonymisation (see 5.1). Use of the biological samples will be carefully coordinated and controlled since they are limited and depletable.

We would propose to grant non-exclusive use for both non-profit and commercial purposes.

Pharmaceutical companies will not be granted the right to pass on any of the samples to a third party. Further detail, especially the prohibition on passing on samples to third parties, will be regulated by another agreement designed by the UKT legal department, which will have to be signed for each individual case. Only if there is a positive verdict from both the legal department and the applicant's local ethics committee, will the material be transferred to the company, agreeing to apply good scientific practice when using them.

Patients will benefit directly from new findings or developments concerning BD therapy. In order to further augment the value of the resource and ensure that the greatest potential benefit for participants may be realised from it, all research users will be required to put results from all analyses made on participants' data and samples as well as any relevant supporting information in the biobank database so that they are available to all scientific researchers approved to access the biobank database.

# 5 Processing of data and samples

### 5.1.1 Data registration, storage and encryption

Patient data gathered in the process of sampling will include: Name, date of birth, date of sampling (identification-data, IDAT) as well as clinical data including diagnosis, duration of illness, medication (medical-data, MDAT). Samples and data will be coded (reversible anonymisation), so that the identity of the donor is not available to the researcher using the sample.

All identifying information will be held centrally by the Biobank in a restricted access database that is controlled by Biobank staff. It is necessary to retain this link with identifying information, to allow follow-up of participants' health, health relevant developments in patient's habits and to observe the familial course of the disease. All Biobank staff will be required to sign confidentiality agreements as part of their contracts empowering them to refuse to testify in court or in front of other federal authorities. Only a few people will have access to the "key" to the code for re-linking the participants' identifying information with their data and samples (i.e. "reversible anonymisation") and to find specific data or samples if participants withdraw.

All samples and MDAT will be brought to the lab and processed following a given protocol by biobank employees. The samples will be stored in Eppendorf-tubes and marked with an ID (at first manually, later the tubes will be marked automatically e.g. with a Barcode).

### 5.1.2 Who will have access to which data?

| | |
|---|---|
| - technical staff: | MDAT & ID |
| - head of the department/deputy, IT-administrator: | IDAT, MDAT, &ID |
| - clinical employees gathering samples: | IDAT, MDAT |
| - partners, scientists receiving a sample: | certain MDAT plus ID |

### 5.1.3 Notification of donors and the ethics committee in case of new findings

At this point we intend to notify donors only if new scientifically relevant questions arise or if there is new health-relevant information concerning the donor. This will only be done if the donor has signed the corresponding section in his consent form allowing the researchers to contact him in this particular case.

Following the German ethics committee statement („Humanbiobanken für die Forschung“, Berlin 2010) it is planned to:

- document all data- or sample-related processes

- publish the following information

(E.g. on a restricted access biobank website, accessible only to researcher, donors and their parents)

- Department in charge of data protection
- Administrator of data protection
- Contact data for further information
- Areas of responsibility within the biobank
- Lay term explanation of rules concerning collection, use and transmission of samples
- Biobank activities including quality management

### 5.1.4 Withdrawal of consent and data deletion

Withdrawal may be declared by signing a corresponding form or verbally.

Patients will be informed that they may withdraw consent to data or sample storage without cause and without penalty. In this case we would provide information about the following options for withdrawal:

- "No further contact": the Biobank would no longer contact the participant directly, but would still have their permission to use information and samples provided previously and to obtain further information from their health-relevant records.
- "No further access": the Biobank would no longer contact the participant or obtain further information, but would still have their permission to use the information and samples provided previously.
- "No further use": All patient-related data (gender, age, diagnosis) and samples stored in the biobank will be deleted. Anonymised samples that have already been sent to research partners cannot be destroyed; research results without any personal reference or results that have already been published will not be deleted.

## 5.2 Biobank confidentiality

Biobank confidentiality applies as soon as sampling has been carried out and remains valid as long as the samples exist. It will limit data processing and sample dispatch to the purpose of scientific research. Furthermore it will ensure the inaccessibility of data and samples towards all third parties not involved in such scientific research (private authorities such as insurance companies or employers). Anonymised Data and samples shall be used only as intended by the applicants and will only be transferred if this use has been approved and is secure.

Finally it guarantees that no action is taken to identify the donor by non-biobank staff.

# 6 Informed consent protocol

- see Appendix

## 10.6 Curriculum vitae