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| Clinical information sheetEhlers-Danlos & Cutis Laxa syndromes |  |
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| Centrum Medische Genetica UZ Gent  |  |

Patient information

|  |  |
| --- | --- |
| Name: |  |
| First name(s): |  |
| Sex:  | [ ]  Male  [ ]  Female |
| Date of Birth: |  |
| Address: |  |
|  |  |
| Referring physician:  |  |
| Referring center:  |  |

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| SAMPLE: | [ ]  EDTA blood | [ ]  DNA | [ ]  Skin biopsy | [ ]  Chorionic villi |
|  | [ ]  Heparin blood | [ ]  RNA | [ ]  Aortic biopsy  | [ ]  Amniocytes |
|  | [ ]  Buccal swab  | [ ]  Fibroblasts  | [ ]  Paraffin embedded material |
|  | [ ]  Other: |  |  |  |

|  |  |
| --- | --- |
| **Date:** |  |
| **Sample arrived:** |  |

Suspected diagnosis

|  |  |
| --- | --- |
| [ ]  Classic type of EDS (type I/II)  | [ ]  Autosomal dominant Cutis Laxa |
| [ ]  Hypermobile type of EDS (type III)  | [ ]  Autosomal recessive Cutis Laxa type I |
|  | [ ]  Urban Rifkin Davies syndrome |
| [ ]  Vascular type of EDS (type IV)  | [ ]  Autosomal recessive Cutis Laxa type II |
| [ ]  Kyphoscoliosis type of EDS (type VIA)  | [ ]  Wrinkly Skin syndrome |
| [ ]  Musculocontractural type of EDS (type VIB)  | [ ]  Occipital horn syndrome |
| [ ]  Arthrochalasis type of EDS (type VIIA/B)  | [ ]  De Barsy syndrome |
| [ ]  Dermatosparaxis type of EDS (type VIIC)  | [ ]  RIN2 syndrome |
| [ ]  Other:  |  |  |

The differential diagnosis in patients referred for additional genetic testing with a clinical presentation of Ehlers-Danlos syndrome or cutis laxa syndrome is extensive. Please indicate which diagnosis you suspect in your patient and make sure to fill out the check-list as complete as possible so that we can set up the appropriate genetic testing.

Clinical summary

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Pedigree

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# Systemic clinical check-list

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| --- | --- | --- |
| **Suspected clinical diagnosis:**  |  |  |
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| Height: |  | Weight: |  | Head circumference: |  |
| Armspan: |  | Lower segment: |  |  |  |
|  |

|  |  |  |
| --- | --- | --- |
| **SKIN** (PLEASE PROVIDE CLINICAL PICTURES if possible) | **Yes** | **No** |
| Hyperextensible skin | [ ]  | [ ]  |
| Smooth velvety skin | [ ]  | [ ]  |
| Thin, transparent skin | [ ]  | [ ]  |
| Widened, atrophic scars  | [ ]  | [ ]  |
| Acrogeria | [ ]  | [ ]  |
| Easy bruising | [ ]  | [ ]  |
| Cutis laxa:  | [ ]  | [ ]  |
| Age of onset |  |  |
| Localisation (please specify): |  |  |
|  |  |  |
| Progressive |  |  |
| Hernia:  | [ ]  | [ ]  |
| Recurrent:  |  |  |
| Localisation (please specify): |  |  |
|  |  |  |
| Other (please specify): | [ ]  | [ ]  |
| **MUSCULOSKELETAL** | **Yes** | **No** |
| Beighton score for joint hypermobility \*  | /9 |
| Congenital hip dislocation  |  |  |
| Unilateral | [ ]  | [ ]  |
| Bilateral | [ ]  | [ ]  |
| Recurrent dislocation/subluxations: | [ ]  | [ ]  |
| Frequence: |  |  |
| Localisation (please specify): |  |  |
|  |  |  |
| Club feet | [ ]  | [ ]  |
| Delayed closure of the fontanels | [ ]  | [ ]  |
| Muscle hypotonia | [ ]  | [ ]  |
| Tendon rupture: | [ ]  | [ ]  |
| Muscle rupture: | [ ]  | [ ]  |

|  |  |  |
| --- | --- | --- |
|  | **Yes** | **No** |
| Fractures:  | [ ]  | [ ]  |
| Number: |  |  |
| Localisation: |  |  |
| Osteoporosis on BMD: | [ ]  | [ ]  |
|  |  |  |
| Scoliosis | [ ]  | [ ]  |
| Age at onset: |  |  |
| Degree: |  |  |
| Progressive: |  |  |
| **CARDIOVASCULAR** | **Yes** | **No** |
| Arterial rupture/dissection  | [ ]  | [ ]  |
| Localisation (please specify): |  |  |
|  |  |  |
| Cardiac-valvular abnormality: | [ ]  | [ ]  |
| Localisation (please specify): |  |  |
|  |  |  |
| Severity: |  |  |
| Arterial Tortuosity | [ ]  | [ ]  |
| Localisation (please specify): |  |  |
|  |  |  |
| Other vascular problems (please specify): |
|  |
|  |
| **OTHER SYSTEMIC FEATURES** (please specify): |
| Ocular: |
| Central Nervous: |
| Gastro-intestinal: |
| Genito-Urinary: |
| Pulmonary:  |

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| **\*Beighton's Criteria for Joint Hypermobility**  |
| **Joint/Finding** | **Negative** | **Unilateral** | **Bilateral** |
| Passive dorsiflexion of the 5th finger >90° | 0 | 1 | 2 |
| Passive flexion of thumbs to the forearm | 0 | 1 | 2 |
| Hyperextension of the elbows beyond 10° | 0 | 1 | 2 |
| Hyperextension of the knees beyond 10° | 0 | 1 | 2 |
| Forward flexion of the trunk with knees fully extended and palms resting on the floor | 0 | Present=1 |

A total score of at least 5 defines hypermobility.

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| Informed consentfor patients willing to participate in diagnostic and scientific studies concerning heritable connective tissue and blood vessel disorders |
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| Centrum Medische Genetica UZ Gent  |
| Diensthoofdprof. dr. B. PoppeKlinische Geneticaprof. dr. J. De Backerprof. dr. A. De Paepeprof. dr. B. Dermautprof. dr. B. Leroy | prof. dr. F. Malfaitprof. dr. O. Vanakkerprof. dr. B. Callewaertdr. S. Janssensdr. R. De Putter | Psychologische begeleidingS. HellemansA. Van Tongerloo | Genetische counselingV. SzymczakA. Van MullemL. Wildero-Van WouweKwaliteitsbeheerLic. G. Van der Cruyssen | DNA Laboratoriumprof. dr. K. Claesprof. dr. E. De BaereBindweefsellaboratoriumprof. dr. P. Couckedr. S. Symoens | Laboratorium Cytogeneticaprof. dr. B. Mentenprof. dr. F. Spelemanprof. dr. N. Van Roydr. A. Dheedene |

Subject of the study

Genetic diagnostics of heritable connective tissue- and blood vessel disorders

General information and objectives of this study

Connective tissue disorders comprise a heterogeneous group of disorders, characterized by abnormalities involving the skin, eyes, cardiovascular system, the lungs, the skeleton and joints. These disorders are often caused by specific genetic defects and are in these cases heritable. Connective tissue plays various important roles in the body such as providing strength to the different organs and tissues and enabling communication between tissues, required for their growth and normal functioning.

Connective tissue diseases can present in very different ways (according to the system(s) that is (are) mainly affected). E.g. problems of connective tissue of the bone and skeleton can result in an increased risk of fractures and bone deformities. These are important characteristics of osteogenesis imperfecta or brittle bone disease. Other heritable connective tissue disorders, such as the Ehlers-Danlos syndromes, are mainly characterized by weakness of the soft connective tissue and are associated with symptoms such as hyperelasticity and fragility of the skin, abnormal and delayed wound healing and joint hypermobility. The latter finding often leads to recurrent joint dislocations and chronic joint pain. Other types of connective tissue disorders such as Marfan syndrome are associated with dilatation and/or fragility of blood vessels.

Because your (child’s) condition can be heritable, it is useful to perform genetic analysis first to confirm the diagnosis and second to perform further screening of family members.

Genetic analysis is mostly performed on blood and in some cases it can be useful to investigate other tissues (see below).

1. The aim of this study is to identify the genetic defect(s) (mutation(s)) that is (are) causing or influencing your (child’s) health problems or those in (one of) your family members. This knowledge can be of importance for the treatment and management of your (child’s) disease. The identification of a mutation also enables exclusion or confirmation of the diagnosis in family members who are at risk of having this condition or who have already developed symptoms. Prenatal genetic diagnostics (the genetic diagnosis of congenital or heritable disorders in the future/unborn child) can be performed when there is a significant risk for future or unborn children.

It is possible that the underlying genetic defect can not be found at short term. When in the future new scientific insights permit to find the genetic defect responsible for your (child’s) condition, this (these) analysis (analyses) can be performed on your (child’s) sample and/or data received by analysis of your (child’s) sample. However, this analysis will not automatically be performed. At any time you can inquire about further diagnostic and/or research modalities.

It is possible that with this genetic analysis (a) genetic variant(s) is (are) found from which is it not clear whether this (these) variant(s) is (are) responsible for your (child’s) condition. In that case the options to further explore this (these) variant(s) will be discussed with you.

2. Besides analysis of the genetic defect(s) related to your disease, further studies aimed at exploring the underlying pathogenic mechanisms of this disorder can be performed on the prelevated anonymized material (see below). These studies lead to a better understanding of the mechanisms, inheritance and evolution of connective tissue disorders. This knowledge may be important for you (your child) and your family and also enables better management, treatment and care for all patients affected by this disorder.

3. These investigations can be performed on the following material that has been taken from you (your child) (check the appropriate boxes):

[ ]  **Blood sample**

These will only be used for the study of connective tissue disorders. From this blood sample, we can extract and preserve DNA and/or generate a lymphoblast cell line (white blood cell line). The lymphoblast cell line can be preserved to extract DNA at a later time.

[ ]  **Skin biopsy**

This biopsy is used for culturing fibroblasts (connective tissue cells). The fibroblast culture can be stored and used at a later time. Fibroblast cells can be used to study the extracellular matrix proteins they produce and can be used to extract DNA. The extracted DNA will only be used to perform genetic tests relevant to the study of connective tissue disorders.

[ ]  **Aortic biopsy**

In case of aortic or arterial surgery, part of the aortic or arterial wall, which would normally be removed and destroyed, can be used to establish a cell culture or to perform additional analyses. As such, no extra material needs to be removed for establishing this cell culture.

[ ]  **Urine sample**

A urine sample can be used for the diagnosis and further study of connective tissue disorders.

[ ]  **Skeletal muscle biopsy**

This tissue is used for assessment of the respiratory chain of the mitochondria (energy production entities) and for immunohistological staining, and electron microscopy.

Your (child’s) samples and data will be stored in the laboratory of the Center for Medical Genetics Ghent (Medical Research Building 1). Once the Belgian law concerning biobanking and storage of human samples of 19/12/2008 (article 22) is implemented, your (child’s) samples will be stored in the biobank of the department of Medical Genetics (Medical research building 1).

It may be necessary to take a new blood sample and/or skin biopsy for study purposes when no/insufficient DNA is left in the laboratory or when no skin biopsy was performed in diagnostic setting, but that a skin biopsy is of importance for studying the underlying mechanisms of your (child’s) condition.

What are the risks involved when taking part in this study?

Blood sampling

Puncturing the skin causes short lasting pain. Occasionally, some prolonged bleeding of the puncture site can occur or a bruise can appear. This will disappear within two weeks. There is a small risk of fainting or of infection at the puncture site.

Prelevation of a skin biopsy

A biopsy with a maximal diameter of 5 mm will be taken from a non-visible place, mostly at the inner side of the upper arm. The biopsy will be taken after injection of a local anesthetic. After the procedure, the skin will be sutured or Steri-strips will be applied. The injection of a local anesthetic can cause short lasting pain. There is a small risk of prolonged bleeding or wound infection after the procedure. The wound should be healed within two weeks after the procedure, and can leave a small round scar.

Prelevation of an aortic biopsy

If aortic surgery is being performed on you or your child, part of the aortic wall, that would normally be removed and destroyed, will be preserved for research purposes. As such, no extra material needs to be removed and there are no additional risks associated with this procedure.

There are no risks involved in the prelevation of a **urine sample**.

Prelevation of a muscle biopsy

A skeletal muscle biopsy is taken on the anterior muscle of the upper leg (quadriceps muscle). This is done under full anesthesia. The operation site may hurt a little in the days following the surgery. The associated risks are those of regular low-risk surgery including adverse reactions on anesthesia, local pain, bleeding, infection.

Injury resulting from participation in the study?

The researcher provides compensation and/or medical treatment in case of damage and/or injury resulting from participation in the study. For this purpose, we have a no-fault insurance in accordance with the Act of May 7th 2004 concerning experiments on humans. At that moment your (child’s) data may be passed to the insurer.

What will happen with your (child’s) medical information obtained during the course of this study?

In accordance with the Belgian law of December 8th 1992 en August 22th 2002, your (child’s) privacy will be guaranteed and you will have access to the collected data. At your request, incorrect information can be adjusted.

Representatives of the principal investigator, auditors, the ethical committee and the certified governmental instances will have direct access to your (child’s) medical records to control the experimental procedures and/or data, without violating the confidentiality of these records. This access is confined within the boundaries set by the aforementioned legislation. By signing this informed consent form, you agree with this.

If information is derived from this study that is relevant for your (child’s) health and/or your (child’s) treatment and follow-up, the Center for Medical Genetics will invite you (and your child) to discuss these results. If information relevant to family members results from this study, we will ask you to contact your family or – if you do not wish to do this yourself – to give us permission to contact your family. If you do not wish that family members are informed, this decision will be respected.

If the study yields information that is relevant to healthcare in general, the results may be published in a scientific journal. This means that results obtained from specific clinical investigations such as echocardiography, ophthalmologic examination, medical imaging, etc. can be included after anonymization. Exceptionally, it may be relevant to publish clinical photographs. In this case, you will be asked to sign a separate informed consent form.

Who to contact in case you (your child) have additional questions about this study or you (your child) want to terminate your (child’s) participation in this study?

It is recommended to directly contact the physician who enrolled you (your child) in this study. You can find his or her contact information on the last page of the informed consent form. If you are unable to reach this physician, you can contact the Center for Medical Genetics Ghent at (0032)9/332.36.03. You will be put in contact with one of the responsible investigators, as soon as possible.

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| --- |
| Informed consentYou will receive a copy of this informed consent. The original will be kept in your (child’s) medical record at the Center for Medical Genetics Ghent. |
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I, \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

voluntarily give my consent for participation in this study for which analyses on my (child’s) genetic material will be performed to identify genetic disorders in the context of my (child’s) condition

\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_.

I have received and read the patient information leaflet and I had sufficient time to ask questions. I have been sufficiently informed about the objectives of this study. I have had the opportunity to ask questions about this study and all my questions have been answered in sufficient manner.

I am aware of the fact that this study has been approved by the independent ethics committee of the Ghent University Hospital and that the study will be performed according to the rules of good clinical practice (ICH/GCP) and the Declaration of Helsinki (i.e. ethical principles regarding human experimentation). The fact that this study has been approved by the ethics committee did not influence my decision to take part in this study.

I therefore agree with the use of information derived from questioning (personal history taking), physical and technical examinations for scientific purposes only. My identity will be kept confidential, will not be disclosed and the professional confidentiality will be respected. I have been informed and consent that my personal details and medical records will be processed and stored for at least 20 years. I am aware that I have access to and can correct this information. Since these data are being processed in the context of medical-scientific purposes, I understand that access to these records can be postponed until completion of this study. If I want to access my personal data, I will contact the supervising physician, responsible for data processing.

I understand that auditors, representatives of the principal investigator, the ethics committee or the certified governmental instances may want to inspect my records to control the collected information. By signing this document, I consent to this. Furthermore, I am aware and I consent that my (child’s) anonymized samples/data may be passed on to the principal investigator and may be shared with (non-)European collaborators. My privacy will be guaranteed at all time. My (child’s) data/samples will not be used for commercial purposes.

I have understood the content of this research and I am prepared to participate or have my child(ren), mentioned below and represented by me, participate in this study. At any time, I will have the possibility to withdraw from this study.

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| **(1) Consent for adults****place and date**\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ .**name and signature** \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ . |  | **(2) For patients incapable of giving consent, represented by the legal representative****name patient**\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ .**CONSENT****place and date**\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ .**name and signature** **of** **the legal representative**\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ . |
| **(3) For child(ren) in the presence of their parents****name child**\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ .**name child**\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ .**CONSENT****place and date**\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ .**name and signature** **of** **the father**\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ .**name and signature** **of** **the mother**\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ . |  | **(4) For child(ren) not under the responsibility of their parents****name child**\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ .**CONSENT****place and date**\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ .**name and signature** **of tutor, relative or legal representative**\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ .**relation to the child(ren)**\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ .**justification for replacing the parents**\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ . |
| **(5) For child(ren) over 12 years of age****CONSENT****place and date**\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ .**name and signature of the child over 12 years of age:**\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ .**CONSENT****place and date**\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ .**name and signature of the child over 12 years of age:**\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ . |  | **(6) Consent physician**I hereby declare to have sufficiently informed the aforementioned participant about the aims of this study. The participant agreed to participate voluntarily by signing and dating the informed consent form.**place and date**\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ .**name and signature**\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ . |