

CONSENT TO PARTICIPATE IN THE

**SEVERE CHRONIC NEUTROPENIA
INTERNATIONAL REGISTRY (SCNIR)**

- ADULT PATIENT OR PARENT, FOR MINOR PATIENT -

ADDRESS:

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Patient Identification: _____

Introduction

We invite you to participate in the Severe Chronic Neutropenia International Registry (SCNIR).

First, you need to know that:

1. Participating in the SCNIR is entirely voluntary.
2. You may choose not to take part, or you may withdraw from the SCNIR at any time. In either case, you will not lose any benefits to which you are otherwise entitled.
3. Participating in the SCN International Registry does not necessarily result in personal benefits. However, the data and research to which you contribute will give us knowledge that may help other patients in the future.

Before you decide to join the SCNIR, please take as much time as you need to ask all the questions you may have and discuss this study with members of the SCNIR, or with family, friends, your personal physician or any other health professional.

Severe chronic neutropenia

The diagnosis "neutropenia" is made, if the absolute count of neutrophilic granulocytes, representing the number of the so-called neutrophils in the blood, is too low. Neutrophils are required to defend the body against bacterial infections. Therefore, a patient with too few neutrophils is more susceptible for bacterial infections.

Different diseases can cause the diminution or absence of neutrophilic granulocytes:

- a) Antibodies against neutrophils cause Autoimmunneutropenia.
- b) Severe congenital neutropenia (congenital neutropenia; Morbus Kostmann) and

- c) Cyclic neutropenia are caused by a defective maturation of precursor cells in the bone marrow.
- d) Chronic neutropenia can occur as a symptom of certain metabolic diseases, such as glycogen storage disease type 1b, or
- e) In combination with a functional defect of the pancreas in Shwachman-Diamond Syndrome.
- f) The term „idiopathic neutropenia“ summarizes a list of acquired neutropenias.

Causes of congenital neutropenia

The underlying genetic defect for the different types of neutropenia has not yet been identified. However, there are indications that changes in a specific gene, i.e. mutations of the gene coding for neutrophil elastase, may play a role in the development of neutropenia. Whether and how these elastase mutations are involved in the development of Kostmann syndrome is under current investigation.

Cooperative research of many different research groups is necessary to search for the genetic causes of the different types of congenital neutropenia and acquired changes that indicate late disease-related events and secondary diseases, such as secondary malignancies or osteoporosis. For these investigations, research laboratories need biological material from the patients themselves and, in case of genetic studies, also from family members. In addition, the SCNIR collects samples (blood and bone marrow), which are stored deeply frozen in liquid nitrogen in a so-called cell bank for future research projects. Participation in the cell bank and research projects requires a separate written consent (see cell bank and research consent form).

Description of the Severe Chronic Neutropenia International Registry (SCNIR)

The Severe Chronic Neutropenia International Registry (SCNIR) was founded in 1994 to monitor the clinical course, therapy, and disease outcome of patients with severe chronic neutropenia (SCN). The SCNIR has the largest collection of long-term data on patients suffering from this condition worldwide. Until December 2001, more than 1000 patients with different types of neutropenia all over the world were enrolled in the SCNIR. Long-term follow-up data of up to 13 years has been collected on the majority of patients. Since severe chronic neutropenia is a rare condition, it is of great benefit to identify as many patients as possible and collect their clinical data in a registry to allow for regular scientific analyses.

The main objectives of the SCNIR are:

- To monitor the long-term clinical course of severe chronic neutropenia in order to identify relevant clinical changes as early as possible.
- Examinations on frequency, development and prognosis of disease-specific accompanying symptoms and late secondary events: Osteoporosis, splenomegaly, vasculitis, thrombocytopenia, chromosomal changes, myelodysplastic syndrome and leukemia.

SEVERE CHRONIC NEUTROPENIA INTERNATIONAL REGISTRY (SCNIR)

- ADULT PATIENT OR PARENT, FOR MINOR PATIENT -

- Development of an international network of hematologists, pediatricians and other treating physicians, to increase the knowledge on diagnosis and therapy of severe chronic neutropenia.
- Expansion of the existing demographic database for future analyses to improve diagnosis and therapy.
- Documentation of pregnancies of neutropenia patients, to improve risk calculations for the patient's mother and the newborn and to establish recommendations for family planning.

The SCNIR is lead by an international Advisory Board of internationally acknowledged experts on SCN and hematology and non-medical professionals:

- Dr. Blanche Alter, National Cancer Institute, Rockville, MD, USA
- Dr. Mary Ann Bonilla, St. Joseph's Children's Hospital, Paterson, NJ, USA
- Dr. Laurence Boxer, University of Michigan, Ann Arbor, MI, USA
- Dr. Bonnie Cham, Manitoba Cancer Treatment & Research Foundation, Winnipeg, MB, Canada
- Dr. David C. Dale, SCNIR Co-Director, University of Washington, Seattle, WA, USA
- Dr. Jean Donadieu, Hôpital Trousseau, Paris, France
- Dr. Melvin Freedman, Hospital for Sick Children, Toronto, ON, Canada
- Dr. George Kannourakis, Marian House, Ballarat, Victoria, Australia
- Prof. Sally Kinsey, St James's University Hospital, Leeds, England
- Lee Reeves, Pinckney, MI, USA
- Prof. Karl Welte, SCNIR Co-Director, Medizinische Hochschule, Hannover, Germany
- Dr. Jerry Winkelstein, Johns Hopkins University, Baltimore, MD, USA

In Europe, a network of local liaison physicians (LLP), all experts in the field of severe chronic neutropenia within the individual countries, has been established.

- **Austria**
 - Dr. Katharina Clodi, St. Anna Kinderspital, Wien
- **Belgium**
 - Prof. Andries Louwagie, A.Z. Sint Jan
 - Prof. Christiane Vermeylen, U.C.L. St. Luc, Brüssel
- **France**
 - Dr. Jean Donadieu, Hôpital Trousseau, Paris
- **Germany**
 - Dr. Gundula Notheis, Dr. von Haunersche Spital, München
 - Prof. Dr. Karl Welte, Dr. Cornelia Zeidler, Medizinische Hochschule Hannover, Hannover
- **Greece**
 - Dr. Antonis Kattamis, „Aghia Sophia“ Children's Hospital, Athens
 - Prof. Helen Papadaki, University Hospital, Heraklion, Krete
- **Hungary**
 - Prof. Laszlo Marodi, University of Debrecen, Debrecen
- **Ireland**

- Dr. Owen Smith, Tallaght Hospital, Dublin
- **Israel**
 - Dr. Yigal Barak, Kaplan Hospital, Rehovot
- **Italy**
 - Prof. Pier Giorgio Mori, Istituto Giannini Gaslini, Genova
- **Netherlands**
 - Dr. Marie Bruin, Het Wilhelmina Kinderziekenhuis, Utrecht
 - Prof. Gert J. Ossenkoppele, Hospital Vrije Universiteit, Amsterdam
 - Dr. A.Y.N. Schouten-van Meeteren, Hospital Vrije Universiteit, Amsterdam
- **Norway**
 - Dr. Tore Abrahamsen, Dept. Of Paediatrics, Rikshospitalet, Oslo
 - Dr. Geir Tjonnfjord, Rikshospitalet, Oslo
- **Poland**
 - Dr. Krzysztof Kalwak, Uniwersitäts-Kinderklinik, Warschau
- **Russia**
 - Prof. Nadja Torubarova, Institute of Pediatrics RAMS, Moskau
- **Serbia**
 - Dr. Mirjana Gotic, Clinical Center of Serbia, Belgrad
- **Spain**
 - Dr. Evaristo F. Feliu, Hospital Germans Trias i Pujol, Badalona
 - Prof. Juan J. Ortega, Hospital Materno-Infantil Vall d'Hebron, Barcelona
- **Sweden**
 - Prof. Göran Elinder, Karolinska Institutet at Södersjukhuset, Stockholm
 - Prof. Jan Palmblad, Huddinge University Hospital, Huddinge
- **Tschechia**
 - MUDr. Jaroslava Voglova, Oddeleni klinicke hematologie, Hradec Kralove
- **Turkey**
 - Assoc. Prof. Aydan Ikinciogullari, Ankara University, Ankara
- **United Kingdom**
 - Prof. Sally Kinsey, St James's University Hospital, Leeds

Database and Data Analysis of the SCNIR

The SCNIR runs three data coordinating centers, where clinical information on registered patients is collected and entered into the database. Each data-coordinating center maintains close contacts to a research laboratory, where the cell bank for the storage of patient biological material is located and SCN related research is performed (see consent form for participation in the cell bank).

The personal data on the consent form will be stored separately from other registry forms. Using an identification number for data entry only will anonymize the personal data on the clinical record forms. If necessary, the data-coordinating center only can re-identify a patient by using the identification number. The staff members of the data-coordinating center are bound to observe medical confidentiality.

The SCNIR asks exclusively for those laboratory evaluations, which are indicated and required for the diagnosis and management of therapy. To establish a cell bank, the SCNIR also asks for additional blood and bone marrow samples, which can be drawn in addition to a routine blood or bone marrow examination. The purpose of the use and management of this material is described on the cell bank consent form in more detail and requires your written consent also. In addition to the routine checks for blood and bone marrow no further

SEVERE CHRONIC NEUTROPENIA INTERNATIONAL REGISTRY (SCNIR)

- ADULT PATIENT OR PARENT, FOR MINOR PATIENT -

examinations are requested by the SCNIR. In individual cases a cooperating research center may ask a patient through the SCNIR for material required for a specific research project. These research projects will be described to the patient in detail and the patient will be asked separately for his/her consent.

Enrollment in the SCN Registry

You/your child can be enrolled in the SCNIR, because you/your child were/was diagnosed with severe chronic neutropenia.

To register a patient, the SCNIR requires the following information:

1. **Complete blood counts**, indicating an absolute neutrophil count (ANC) of less than $500/\text{mm}^3$ for at least three times during the last six to twelve months (for patients with frequent infections less than $1000/\text{mm}^3$).
2. A **bone marrow evaluation** confirming the diagnosis „severe chronic neutropenia“.
3. A **cytogenetic evaluation**, if the patient is treated with G-CSF (Neupogen^R, Lenograstim^R or other brands) or if a start of therapy is planned already.
4. A positive **antibody result** for autoimmune neutropenia.
5. A **written consent** signed by the patient and/or the parents/legal guardian for patients of ages less than 18 years.

EXCEPTION:

Patients diagnosed with **Shwachman-Diamond-Syndrome (SDS)**, **Glycogenosis Type Ib (GSD Ib)** or **Barth-Syndrome**. These patients can be registered in the SCNIR regardless of their neutrophil counts or other blood counts.

Before enrollment, the SCNIR requires a written consent from you and/or your parents or legal guardian to collect medical information from treating physicians, and to read and document medical reports. A written consent to collect and store biological material will be obtained separately.

For enrollment in the Registry (registration) and for the yearly follow-up evaluations the following information are requested and will be obtained by yourself or your treating physician:

- Frequency of infections and type of infections prior to and at the time of registration, as well as during the yearly follow-up intervals
- Weight, height, state of development, clinical evaluations (like liver and spleen size)
- Information on treatment (name of the drug(s), dose, duration of treatment with start and stop dates, reason for change in therapy)
- Family history (additionally affected family members stating the relationship to patient)

The following reports are documented in addition:

- Bone marrow result
- Chromosomal analysis of bone marrow cells
- Blood counts (if possible prior to and during therapy)

Before registration, we will review the diagnostic reports on blood counts and bone marrow results to classify patients according to the above-mentioned diagnostic groups.

For enrollment in the International SCN Registry it is not required to physically come to one of the centers for neutropenia treatment.

No information that makes a personal identification possible will be forwarded to personnel outside the SCNIR. **All information will be coded (anonymized) prior to data entry in the SCNIR database.** A re-identification of patients is performed by the data-coordinating center exclusively, if the patient would benefit from the respective information (e. g. by receiving new research results that might help to better treat the patient or which have prognostic evidence)

Risks or Discomforts of Participation in the SCNIR

In individual cases it may be time consuming and may require patience to answer a part of the questions which your physician can answer in cooperation with your only. Participation in the SCNIR may lead you/your child to become aware of information about yourself or family members that you/your child previously did not know. Some examples of the information you/your child may learn include your/your child's personal genetic predisposition to cancers and related conditions, or details about the medical history of relatives.

We know very little about other potential risks of participating in a genetic research study. A potential risk may be increased tension, anxiety, or guilt as genetic predispositions are determined and fear of future in patients who learn about their individual predisposition to leukemia. There may be other unknown personal and social consequences. Because the study involves the testing of genetic material from family members, parents and their children, we may learn that a child was adopted or that the stated father is not the natural father of the child. Usually this information does not have to be revealed in order to proceed with the research study. Of course, you/your child have the right to decline to receive research information.

All results are bound to medical confidentiality and will be treated in confidence.

Potential Benefits of Participation in the SCNIR

We cannot guarantee for direct benefits of participation in the SCNIR for you/your child. However, it may be advantageous, that data on family history, clinical state, as well as all other clinical results will be looked at and reviewed by experts in hematology. It may also be advantageous for you or your treating physician to be able to contact the SCNIR with any question concerning your/your child's disease.

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Access to Research Information

The SCNIR does not plan to routinely provide you/your child with the results of research tests. You can apply for sending the information to you/your treating physician, if information is obtained from this study and becomes available that may be important for your/your child's health.

Research results may be misleading, because further research may be necessary before we understand what these test results really mean. Interpretation of research results should therefore always be discussed with experts.

Data Protection

To protect your/your child's privacy the SCNIR follows the guidelines for data protection of the European Community including differing rules for individual countries. The guidelines help us to protect you against the involuntary release of sensitive research information about you/your child collected during the course of this registry by anonymizing data in a way that authorized personnel can re-identify individual subjects only. You/your child or the researcher may choose to *voluntarily* disclose the protected information under certain circumstances. For example, if you/your child or your guardian requests the release of information about you/your child in writing (through, for example, a written request to release medical records to an insurance company), the Certificate does not protect against that voluntary disclosure.

Summary of Questions, You/Your Child Will be Asked for Registration in the SCNIR:

Obligatory:

- An adult family member should fill out the questionnaire on the family history.
- If applicable, the cell bank consent form is to be completed and signed by you/your child.
- The physician completing the registration forms will ask You/your child about your/your child's medical history, treatment and current state of health.

Optional:

- In case of a bone marrow puncture, please have a sample of the material being sent to the SCNIR.

Summary of Questions, You/Your Child Will be Asked for the Yearly Follow-up:

Obligatory:

- Update of family history form
- Information on current clinical status, documentation of significant changes

Optional:

- In case of a bone marrow puncture, please have a sample of the material being sent to the SCNIR.

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OTHER PERTINENT INFORMATION

1. Confidentiality. When research results of the SCNIR are reported in medical journals or at scientific meetings, the people who take part in the registry are not named and identified. In most cases, the SCNIR will not release any information about your research involvement without your written permission.

The data protection laws of the European countries protect the confidentiality of your SCNIR medical records. However, you should know that the data protection law allows release of some information from your medical record without your permission, for example, if the Ministry of health, law enforcement officials, or other authorized people requires it.

2. Problems or Questions. If you have any problems or questions about the SCNIR, or about your rights as a SCNIR participant, contact the Principal Investigator, Professor Dr. Karl Welte; Pediatric Hematology and Oncology, Medical School Hannover, phone: +49-0511-532-6710. Or you may contact Dr. Cornelia Zeidler or Dr. Beate Schwinzer at the office of the SCNIR (phone: +49-0511-557105).

3. Consent Document. Please keep a copy of this document in case you want to read it again.

COMPLETE APPROPRIATE ITEM(S) BELOW:		
<p>A. Adult Patient's Consent I have read the explanation about this project and have been given the opportunity to discuss it and to ask questions. I hereby consent to take part in the SCNIR.</p> <p>_____</p> <p>Signature of Adult Patient/Legal Representative Date</p>	<p>B. Parent's Permission for Minor Patient. I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby give permission for my child to take part in the SCNIR.</p> <p>_____</p> <p>Signature of Parent(s)/Guardian Date</p>	
<p>C. Child's Verbal Assent (If Applicable) The information in the above consent was described to my child and my child agrees to participate in the study.</p> <p>_____</p> <p>Signature of Parent(s)/Guardian Date</p>		
<p>THIS CONSENT DOCUMENT WAS APPROVED BY THE ETHICS COMMITTEE OF THE MEDICAL SCHOOL HANNOVER ON 02 OCTOBER 2002.</p>		
<p>_____</p> <p>Signature of Investigator</p>	<p>_____</p> <p>Date</p>	<p>_____</p> <p>Signature of Witness</p>