Universität zu Köln

Registry for neonates, infants, children, adolescents, and adults with newly diagnosed and/or relapsed neuroblastic tumors (NB Registry 2016)

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Protocol code: NB Registry 2016

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1. Signatures

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Principal Coordinating Investigator (PCI) signature date

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National Coordinator for High Risk Neuroblastoma Trials

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Clinical coordinator of the NB registry 2016 signature date

National Coordinator for Low- and Intermediate Risk
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2. Synopsis

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Title:	Prospective multicenter registry for neonates, infants, children, adolescents, and adults with neuroblastic tumors
Indication:	Neuroblastic tumors diagnosed according to the inclusion criteria of the registry
Phase:	Clinical registry
Type of study, design, methodology:	The registry collects clinical and molecular data of patients with neuroblastic tumors prospectively. Therapeutic interventions are not planned and require separate clinical trial protocols and/or guidelines
Number of subjects:	Approximately 150 patients per year
Primary Objectives	Prospective collection of key characteristics of all patients with primary and relapsed neuroblastic tumors diagnosed in Germany regardless of, if applicable, additional inclusion into clinical trials with the aims: • To establish a prospective demographic registry of all patients with primary and relapsed neuroblastic tumors, • To facilitate standardized central review of key diagnostic procedures of all patients with neuroblastic tumors, particularly of patients currently not included in clinical trials, • To facilitate counselling of physicians and patients, • To facilitate combined analysis of patient cohorts treated within subsequent neuroblastoma trials during the last decades, • To facilitate long term follow-up of patients with neuroblastic tumors diagnosed in Germany, • To identify late effects of disease and treatment, • To establish the data base for the correlation of clinical and molecular data derived from ongoing and future molecular research, • To provide clinical data for retrospective subgroup analyses, • To make key characteristics of German patients with neuroblastic tumors available for ongoing and future national and international cooperation, e.g. with the German Children's Cancer Registry, the LESS consortium for evaluation of late effects, the INRG consortium, the European SIOPEN group, the Dutch DCOG, the American COG, the Russian neuroblastoma trial group, and other partners • To provide a data base for allocation of patients into phase I-II trials on targeted therapies,
Medical Condition and Principal inclusion criteria:	• Diagnosis or suspicion of a neuroblastic tumor - either histologically or cytologically proven neuroblastic tumors such as neuroblastoma, ganglioneuroblastoma, and ganglioneuroma (at diagnosis or at relapse) - OR suspected neuroblastoma in newborns and infants (e.g. suprarenal lesions), detected at least during two independent ultrasound investigations • any age, • any stage, • any MYCN status, • written Guardians' informed consent of parents or legal guardians and / or of the patient's informed consent if appropriate according to age and status of psycho-intellectual development.
Time plan:	Opening for registration of patients on January 01, 2017
Financing:	Funding by the Deutsche Kinderkrebsstiftung, Grant-No. DKS 2016.07

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4. Introduction

Neuroblastoma is the most frequent extracranial solid malignancy in pediatric oncology. In Germany, about 130 neuroblastoma patients are diagnosed per year [1]. Despite common clinical and histological characteristics the clinical course of the disease varies from spontaneous regression to aggressive progression [2]. Although many clinical and molecular risk predictors have been described, the molecular basis of heterogeneity is not fully understood, yet. However, important molecular differences between individual neuroblastoma patients such as MYCN, ALK, ATRX, and TERT-status have been detected [3-6].

During the last decades, large national clinical trials included all German patients with neuroblastoma [7, 8]. Due to the heterogeneity of the clinical course and the molecular characteristics, future clinical trials on neuroblastoma will increasingly focus on selected patient subgroups defined by clinical and molecular characteristics and risk profiles. Accordingly, the German neuroblastoma study group decided to establish separate clinical neuroblastoma trials on low- and intermediate risk neuroblastoma [9] and high-risk neuroblastoma. Further, several prospective trials on relapsed neuroblastoma are currently open or expected to open in the future.

As a consequence not all patients with neuroblastic tumors will be included in clinical trials. Other patients are very likely to enter multiple clinical trials during the complex treatment particular in high-risk neuroblastoma. This will lead to (1) fragmentation of patient treatment histories by inclusions into different sequential clinical trials and (2) to inclusion of carefully selected patients into several parallel clinical trials.

This demographic NB Registry 2016 will serve as an overarching data base in order to facilitate standardized diagnostics, central review of staging procedures, and standard base line molecular analysis, correlation of molecular and clinical data, long-term follow up, patient allocation to early clinical trials, and international cooperation.

5. Objectives

Major objective of the NB Registry is the collection of key characteristics of patients with neuroblastic tumors diagnosed in Germany regardless of, if applicable, additional inclusion into clinical trials. Detailed aims of data collection are:

- To establish a prospective demographic registry of all patients with primary and relapsed neuroblastic tumors,
- To facilitate standardized central review of key diagnostic procedures of all patients with neuroblastic tumors, particularly of patients currently not included in clinical trials,
- To facilitate counselling of physicians and patients,
- To facilitate combined analysis of patient cohorts treated within subsequent neuroblastoma trials during the last decades,
- To facilitate long term follow-up of patients with neuroblastic tumors diagnosed in Germany,
- To identify late effects of disease and treatment,
- To establish the data base for the correlation of clinical and molecular data derived from ongoing and future molecular research,
- To provide clinical data for retrospective subgroup analyses,
- To make key characteristics of German patients with neuroblastic tumors available for ongoing national and international cooperation such as the German Children's Cancer Registry, the national Late Effects Surveillance and Study Group (LESS) for the evaluation of late effects, the International Neuroblastoma Risk Group Consortium (INRG; http://web.ci.uchicago.edu), the Dutch Children`s Oncology Group (DCOG), and the European Neuroblastoma Study Group of the International Society of Pediatric Oncology (SIOPEN).

- To make key characteristics of German patients with neuroblastic tumors available for future national and international cooperation, e.g., the international INRG consortium, the European SIOPEN group, the American COG, the Russian neuroblastoma trial group, and other partners,
- To provide a data base for allocation of patients into phase I-II trials on targeted therapies.
- To collect biomaterial for central assessment,
- To provide pseudonymized biomaterial for research projects by application of researches according of the regulations of the tumor tissue repository.

6. Registration process and structure of the registry

The prospective data collection is based on the MARVIN web-based eCRF system.

At first diagnosis of neuroblastic tumors, key data are entered as soon as informed consent of the patient and/or the guardians of the patient is available. The key data set includes demographic data on the patient, time of diagnosis, extent of disease at diagnosis, and general type of treatment.

At any relapse, key data on time, relapse pattern, and type of treatment is registered by the NB Registry. If key data on first diagnosis have not been registered before, data on first diagnosis will be registered retrospectively as outlined.

If patients then enter clinical trials on first-line or relapse treatment, no further data are registered by the registry as long as the treatment in the respective clinical trial continues. At regular intervals, a limited set of key data are transferred from the clinical trial database to the database of the NB Registry. This data set will not allow to answer any trial question of the respective clinical trial.

Long term follow up data are requested by the registry in regular intervals as this has been done by the national neuroblastoma trials during the past decades.

6.1. Time plan

The registry opens on January 01, 2017 and will be maintained continuously.

7. Selection of patients

7.1. Target population

Since key characteristics of the patients are important for most clinical and molecular research projects, the NB Registry 2016 serves as an overarching data base collecting a key data set of each patient with any neuroblastic tumor making these data available to different researchers considering all regulations for data protection.

The registry will include four different groups of patients:

- Newly diagnosed patients with neuroblastic tumors currently included in clinical trials
- Patients with neuroblastic tumors currently not included in clinical trials such as infants with suspected neuroblastoma, adults with neuroblastoma, and patients with ganglioneuroma. These subgroups are currently not covered by clinical trials because the number is too small or the group is too heterogeneous. However, high quality clinical and molecular epidemiologic data are of high value particularly in these small groups and may serve as the foundation for new clinical trials in the future.
- Relapsed patients with neuroblastic tumors currently included in clinical trials
- Relapsed patients with neuroblastic tumors currently not included in clinical trials

7.2. Inclusion criteria

Each patient must meet the following criteria:

1. Diagnosis or suspicion of neuroblastic tumor in patients
   - either histologically or cytologically proven neuroblastic tumors such as neuroblastoma, ganglioneuroblastoma, and ganglioneuroma (at diagnosis or at relapse)
   - OR suspected neuroblastoma in newborns and infants (e.g. suprarenal lesions), detected at least during two independent ultrasound investigations
2. any age,
3. any stage,
4. any MYCN status,
5. written Guardians' informed consent of parents or legal guardians and / or of the patient's informed consent if appropriate according to age and status of psycho-intellectual development.

7.3. Exclusion criteria

For this registry, no exclusion criteria are defined. Each patient meeting the inclusion criteria given above may be registered.

7.4. Withdrawal of subjects

At any time, the patient or legal guardians can withdraw the consent for documentation of the patient's data. In this case, either all data collected until this time will be stored, but anonymized and not updated anymore, or all data will be deleted, depending on the wish of the patient or legal guardians.

8. Organizational and administrative aspects of the registry

8.1. Principal Coordinating Investigator

Thorsten Simon, Prof. Dr., Department of Pediatric Oncology and Hematology, Cologne University Hospital, Kerpener Strasse 62, 50937 Cologne, Germany.

8.2. Steering Committee

A list of the members of the Steering Committee is given in Appendix 2: Registry steering committee on page 20.

8.3. Central organization units

The Cologne office, the GPOH tumor repository for embryonal tumors, and the molecular laboratory are located at the children's hospital of the University of Cologne. The project and data management is provided by the Neuroblastoma trial office, University hospital, University of Cologne, Kerpener Straße 62, 50924 Cologne

8.4. Network of reference institutions of the registry

The registry is coordinated by the neuroblastoma trial office located in Cologne. The tumor tissue collection and distribution to the reference laboratories is coordinated by the GPOH tumor repository for embryonal tumors also located in Cologne.

Unless not otherwise required by the respective trial protocol, the baseline molecular analysis of tumor tissue at first diagnosis of neuroblastic tumors is done centrally by the molecular genetics laboratory in Cologne. Further, reference pathology by the Kiel Pediatric Tumor Registry is strongly recommended. Central cytology and immunocytology of bone marrow is done by in the bone marrow laboratory in Cologne. Bone marrow PCR and sequencing projects are subject to separate guidelines within separate clinical trials.

Central radiology and nuclear medicine are currently offered by the Cologne trial center.

Counselling of treating institutions is available in Cologne for low/intermediate risk neuroblastoma patients and in Berlin (high-risk neuroblastoma patients).

If surgery or radiotherapy is planned, the Cologne site offers the possibility to discuss the individual patients with the cooperating surgeons and/or radiotherapists in order to give clear recommendation on local therapy of the patients.

The addresses of all central laboratories and reference institutions are found in Appendix 1 on page 19.

8.5. Investigators and participating sites

This registry is open for all national centers treating patients with neuroblastic tumors. Most of the patients are expected to be diagnosed and treated in pediatric oncologic centers meeting all criteria defined by the "Richtlinie zur Kinderonkologie des Gemeinsamen Bundesausschusses über Maßnahmen zur Qualitätssicherung für die stationäre Versorgung von Kindern und Jugendlichen mit hämato-onkologischen Krankheiten gemäß § 137 Abs. 1 Satz 1 Nr. 2 SGB V für nach § 108 SGB V zugelassene Krankenhäuser". However, patients of subgroups such as adults and patients with ganglioneuroma are expected to be treated in hospitals not meeting these criteria. These centers can join the NB Registry 2016 network. The Neuroblastoma Trial office at the University of Cologne will provide administrative support for ethical approval, where applicable and needed.

8.6. Financing

Funding of the Neuroblastoma 2016 registry is provided by the Deutsche Kinderkrebsstiftung (Grant DKS 2016.07)

9. Recommended standardized patient assessment

9.1. Assessment prior to treatment

Initial assessment of the patient must establish the diagnosis of neuroblastoma, reveal the extent of the disease, and determine the clinico-molecular risk profile the disease. The complete staging should be performed prior to any chemotherapy or surgery. Staging should allow classifying the patient according to INSS (section 17.1) and INRG (section 17.2). Also, image defined risk factors must be recorded (section 17.3).

9.1.1. Clinical and laboratory assessment

Clinical status,

Full blood count,

Electrolytes, liver function tests, kidney function tests, coagulation group tests,

Lactate dehydrogenase (LDH),

Ferritin,

Neuron-specific enolase (NSE),

Urinary excretion of catecholamine metabolites vanillymandelic acid (VMA) and homovanillic acid (HVA), (spontaneous urine sample is sufficient if values are normalized to creatinine levels)

Virology screening for at least HIV, CMV and viral Hepatitis.

9.1.2. Imaging

Ultrasound of the involved region,

Ultrasound screening of head (if possible) and neck,

Chest x-ray,

Magnetic resonance imaging (MRI) of involved region,

MRI of the cranium in stage 4/stage M patients,

I-123-meta-iodobenzylguanidine (MIBG) Scintigraphy including SPECT Reconstruction according to the published guidelines [10-12],

18F-FDG PET in MIBG negative patients.

9.1.3. Bone marrow assessment

Bone marrow is not homogenously infiltrated in most of the neuroblastoma patients. Therefore, bone marrow aspirates from multiple puncture sites are mandatory. In general, aspirates from four different sites are recommended. The request form is available online (https://kinderklinik.uk-koeln.de/zuweiser-professionals/downloads-kinderonkologie/). At least 5 unstained smears from each puncture site are requested by the bone marrow laboratory in Cologne. If the bone marrow involvement exceeds 30%, molecular analysis using FISH can also be done using bone marrow smears but requires additional 5 smears from each puncture site. If the aspirates do not appear to be representative, two aspirates and two trephine biopsies may be used instead.

Bone marrow of all neuroblastoma patients prior to staging information will be assessed centrally in Cologne by conventional microscopy and anti-GD2 immunocytology. Additional studies such as PCR and next-generation sequencing approaches are subject to separate clinical trials.

9.1.4. Liquid Biopsies

For high-risk neuroblastoma patients a new liquid biopsy platform will be established in Berlin. Separate guidelines for collection and shipment of the required blood and urine samples will be provided to all 58 GPOH clinical centers.

9.1.5. Tumor tissue collection

Tumor histology and molecular genetics are crucial for risk stratification for all neuroblastoma patients. Therefore, tumor biopsy is required at time of initial diagnosis. The only exception are otherwise healthy infants with suspected neuroblastoma. Tumor biopsy can be delayed to the 6th months of life or longer if substantial regression is observed at this time.

During first operation, tumor tissue must be collected for routine diagnostic histology and for molecular analysis.

Details of tumor tissue collection are available online (https://kinderklinik.uk-koeln.de/zuweiser-professionals/downloads-kinderonkologie/). In brief, tissue from morphologically different areas of the tumor should be collected. The samples must be processed by the pathologist under sterile conditions within 30 minutes in order to avoid degradation of RNA. Depending on the amount of tissue at least one sample should be used for touch preparations for FISH analysis and then put in 4% buffered formalin for diagnostic histology. The other samples should be snap frozen. In very small biopsies the local pathologist has to decide whether a small part of the biopsy can be snap frozen for molecular analysis.

About 5 ml of citrate blood should be collected from each patient as reference material for molecular investigations. The blood should also be snap frozen. Normal tissue not infiltrated by the tumor can be used as reference material as well. Of note is that extended resection only for collection of normal tissue is unacceptable.

The frozen biomaterial can be stored at –70 to –80 C. It must be sent to the Cologne tumor repository on dry ice using the *Tumorbox.*

9.1.6. Histology

Paraffin embedded tumor tissue is first assessed by the local pathologist. As soon as the diagnosis of a neuroblastic tumor has been established, at least one representative block and representative slices of all other blocks are sent for central review. The request form is available online (https://kinderklinik.uk-koeln.de/zuweiser-professionals/downloads-kinderonkologie/). When applicable, the histology result must consider the INPC (International Neuroblastoma Pathology Committee) classification including the mitosis-karyorrhexis index [13].

9.1.7. Standard molecular analysis

Molecular markers such as MYCN have been introduced for risk classification of neuroblastoma patients many years ago. Therefore, analysis of selected molecular analyses is considered as standard in every patient with neuroblastic tumors prior to inclusion in a trial or registry. Within the NB registry the status of well-established molecular markers such as status of MYCN [14, 15], status of chromosome 1p [16, 17], status of chromosome 11q [17, 18], status of ALK gene [3] will be analyzed in the molecular reference centers in Cologne or Berlin. The request form is provided online (https://kinderklinik.uk-koeln.de/zuweiser-professionals/downloads-kinderonkologie/).

Additional molecular analyses will be performed in Cologne within the NB2015-LR trial and in Berlin for high-risk neuroblastomas (separate guidelines). They do require additional funding and extra informed consent. Meeting these crucial prerequisites these additional molecular data can be linked to clinical data available in the registry.

9.2. Assessment during treatment

Unless the patient is treated according to a clinical trial with different requirements, the following guidelines on patient's assessment are considered clinical standard and should be followed.

9.2.1. Assessment prior to each chemotherapy cycle or tumor operation

Clinical examination,

Routine blood tests such as full blood count, electrolytes, liver function tests, kidney function tests, LDH, according to the local standards,

Liquid Biopsy bone marrow and blood samples according to separate guidelines for high-risk neuroblastoma patients

Tumor markers: NSE in serum, VMA and HVA in urine,

Ultrasound of the tumor region,

ECG and heart ultrasound prior to anthracycline containing chemotherapy,

Hearing test prior to platinum containing chemotherapy.

9.2.2. Toxicity monitoring during and after any treatment element

Clinical examination and blood tests according to the standards of the local hospital.

9.2.3. Assessment of tumor status during treatment

The standard assessment of the tumor status includes tumor markers, MRI of the involved region, MIBG scan, and bone marrow puncture. For high-risk neuroblastoma patients additional liquid biopsy analyses will be done in Berlin (separate guidelines).

9.3. Follow-up assessment after chemotherapy

This paragraph gives recommendations on the follow-up of neuroblastoma patients after treatment. However, modalities and time points may be modified according to the disease pattern and the remission status of the patients. According to legal regulations the exposure to ionizing radiation for imaging such as x-ray, computed tomography and nuclear medicine is only justified by a defined clinical indication ("rechtfertigende Indikation"). Moreover, the exposure to ionizing radiation as well as general anesthesia always requires balancing the patient´s individual risks and benefits.

Tumor markers alone are able to detect only about 25-50% of relapses or progressions, more events are diagnosed by clinical examination and imaging [19]. In general, the recommended assessment intervals are short in the first five years after treatment, and longer thereafter since life table analysis shows a lower event rate 5 years or more after diagnosis.

Of course, follow-up assessments must be repeated in shorter intervals if unclear symptom or abnormal test results are observed. Staging includes MRI, MIBG scan, and bone marrow assessment multiple sites in order to rule out or to identify disease recurrence.

Further, long term follow-up is also important for detection of late effects such as hearing impairment, renal function impairment, hypothyroidism, scoliosis, and secondary malignant disease [20].

9.3.1. Follow-up of observation patients <u>without</u> residual tumor

	1st year	2nd – 5th year	After the 5th year
Clinical assessment Urinary catecholamines Ultrasound of primary tumor site	Every 6 weeks	Every 3 months	Every 6-12 months

Chest X-Ray for thoracic neuroblastoma	Every 3 months	Every 3-6 months	Every 12 month
LDH and NSE	With every venous blood sample required for MRI or scintigraphy		
MRI	Only once 3 month after surgery, Thereafter only if ultrasound or chest x-ray gives equivocal results.		
Scintigraphy	Only if ultrasound or chest x-ray gives equivocal results		

Table 1 **Follow-up of observation patients without residual tumor**

9.3.2. Follow-up in observation patients with residual tumor

	1st year	2nd – 5th year	After the 5th year
Clinical assessment Urinary catecholamines Ultrasound of primary tumor site	Every 6 weeks	Every 3 months	Every 6-12 months
LDH and NSE	With every venous blood sample required for MRI or scintigraphy		
MRI	3 months after surgery for documentation of surgical result, thereafter every 6 months if primary clearly seen in ultrasound, otherwise consider 3 months	every 12 months, consider shorter intervals for intraspinal/intraforaminal residual tumor	not routinely if previously normal
Scintigraphy	Only if ultrasound, x-ray, and/or MRI give equivocal results		

Table 2 **Follow-up of observation patients with residual tumor**

9.3.3. Follow up of patients of the intermediate and high-risk group

	1st year	2nd – 5th year	After the 5th year
Clinical assessment Urinary catecholamines Ultrasound of primary tumor site	Every 6 weeks	Every 3 months	Every 6 months
LDH and NSE	With every venous blood sample required for MRI or scintigraphy		
MRI	Every 3 months	Every 3 - 6 months	Every 6 months
Scintigraphy	every 6 months until normalization, thereafter not routinely		
bone marrow 4 sites	every 6 months until normalization, thereafter not routinely		
ECG/Echocardiography Audiometry Kidney function test TSH, fT3, fT4 growth chart puberty assessment	at the end of every year		every 2nd year

Table 3 **Follow-up of patients of the intermediate and high-risk group.**

9.4. Central review and counseling

The registry offers central review of bone marrow, tumor histology, molecular markers, and imaging.

9.4.1. Counseling for physicians

Counseling of the treating physicians is offered by the Cologne neuroblastoma trial office (low/intermediate neuroblastoma) and the Berlin trial office (high-risk neuroblastoma) for patients currently not included clinical trials. Please provide sufficient clinical information of the patient. For contact information see page 19.

9.4.2. Central review of MRI, CT, MIBG and PET scans

Reference assessment is provided for radiological investigations (MRI, CT) and nuclear medicine investigations (MIBG-scintigraphy, 18F-FDG-PET). Until an online upload of images is established, images as DICOM files on CD/DVD have to be sent to the trial office by regular mail. Please provide also at least the imaging at first diagnosis and the most recent images for review. For contact information see page 19. The imaging data need to be sent as DICOM files on CD/DVD until an online upload system for images has been established. The request form is provided online (https://kinderklinik.uk-koeln.de/zuweiser-professionals/downloads-kinderonkologie/).

9.4.3. Surgery and radiotherapy

In cooperation with the reference surgeon panel and reference radiotherapy board, counseling for timing, extent and risk estimation of local treatment is provided. In general, reference assessment of high quality imaging is the crucial prerequisite for decisions on the appropriate local treatment. Please send at least the CT/MRI images from diagnosis and the most recent images as DICOM files to the neuroblastoma trial offices in Cologne and Berlin. After the discussion with the members of the reference board a recommendation will be sent to the hospital. For contact information see page 19.

10. Treatment

This registry gives no treatment recommendation. Moreover, the registry was not designed to collect detailed data on single drugs. Only data on time and type of standard chemotherapy cycles are collected. These data do not allow conclusions on safety and harmlessness of single drugs. However, all drugs have been evaluated in previous clinical trials and are considered as standard medications in the treatment of neuroblastoma. Treatment is left at the discretion of the treating institution following national or international treatment guidelines published elsewhere.

11. Documentation

11.1. General aspects of quality assurance

The registry was designed in close collaboration with the neuroblastoma trial steering committee of the GPOH network, representing experienced pediatric oncologists from different German hospitals and representatives of related sub disciplines.

The central assessment of bone marrow involvement, radio diagnostic and scintigraphy imaging contributes to the quality of the data. These quality measures are already implemented in the clinical care of German neuroblastoma patients, are considered standard and are covered by the health insurance companies.

High quality of tumor collection is facilitated by standardized tumor tissue collection established by the Competence Net for Pediatric Oncology and Hematology (BMBF 01GI0416) and the experience of the participating sites.

11.2. Documentation and Data management

Medical data relevant for the NB Registry 2016 will be documented via the validated web based database MARVIN by qualified staff at the participating sites. Data locally assessed will be documented soon after assessment into the eCRF. Entering data may be delegated to qualified members of the team; however the eCRF will be finally signed by an investigator.

The neuroblastoma trial office in Cologne is responsible for the data management of the registry. During data entry at the sites, automated plausibility checks are run. In addition, qualified staff at the neuroblastoma trial office will regularly check data entries for plausibility and completeness. Discrepancies and implausibility will be solved with the participating sites by electronic queries via the MARVIN database.

11.3. International Cooperation

At regular intervals, selected pseudonymized data of the registry will be forwarded to the International Neuroblastoma Risk Group Database (INRGdb; http://web.ci.uchicago.edu), as far as informed consent is given, and thus will be made available to International scientists. The registry also offers possibilities of combined data analysis with other neuroblastoma trial groups such as the Dutch Children`s Oncology Group (DCOG), and the European Neuroblastoma Study Group of the International Society of Pediatric Oncology (SIOPEN). Of course, all aspects and regulations on protection of personal data have to be followed.

11.4. Archiving

All relevant study documents including informed consent forms will be archived for at least 10 years. Biomaterial will be stored in the biomaterial repository without time limit.

12. Ethical and regulatory aspects

12.1. Independent ethics committee

The clinical registry will not be started before approval of the ethics committee of the University of Cologne. In many centers, the local ethics committee must be informed about the registry but no formal application is required. In other centers, full application for ethics approval is necessary. If this is the case, the Neuroblastoma Trial office at the University of Cologne offers administrative support for ethical approval.

12.2. Ethical basis for the clinical registry and regulatory aspects

The high standard of neuroblastoma treatment in Germany is depended on the unique national structure of pediatric oncology with nationwide clinical trials offering central review and central counseling as important elements of quality control. All patients benefit from precise risk assessment based on prognostic clinical and molecular markers. Most of these markers are considered standard-of-care and not subject of current research. Moreover, not all patients will enter a nationwide neuroblastoma trial covering all subgroups of neuroblastoma patients.

Therefore, it seems an ethical requirement to make these resources available to all future patients regardless of participation in a clinical trial.

The NB Registry 2016 has been established in accordance with the Declaration of Helsinki in the version of 19th October 2013 (64th General Assembly of the World Medical Association, Edinburgh, Scotland) and is based on ICH guidelines of good clinical practice. The study will be registered at the German Clinical Trials Register (DKRS: www.drks.de).

12.3. Obtaining informed consent

Prior to entering any data in the registry, parents or legal guardians (and / or patients, depending on age and psycho intellectual development) will be informed on the data and biomaterial collection within the registry as well as on the right to withdraw the consent at any time. They will provide written informed consent. Confidentiality will be protected at any time.

The originally signed consent form will be archived in the investigator's site file. Parents resp. patients will receive copies of the patient information, and the signed informed consent form.

At any time point, the most recent versions of the patient information and informed consent forms will be provided to the participating sites by the registry office.

12.4. Data protection

All requirements of data protection legislation will be observed. It is assured that all materials and data for scientific investigations will be pseudonymised in accordance with data protection legislation before scientific processing and at the time when clear data are not required for any reason. The parents or legal guardian and patient will be informed that non-pseudonymised medical information will be forwarded for central review and counseling, but that only pseudonymised data will be passed on to further recipients.

13. Reports and publication

It is planned to publish registry results in scientific journals and at national or international congresses. Publication of the results of the registry as a whole is not intended.

Any analysis and publication planned requires discussion by the Steering Committee. National scientists interested in neuroblastoma may apply for analysis and publication of subgroups. Any publication requires approval by the principal coordinating investigator, by the Chair of the German Neuroblastoma Study group and by the national coordinators for High-Risk, low and Intermediate Risk, or Relapsed Neuroblastoma.

Any publication will take account of the 'Uniform requirements for manuscripts submitted to biomedical journals (International Committee of Medical Journal Editors' (ICMJE) [JAMA 1997; 277:927-34]).

Any published data will consider data protection legislation covering the registry subjects and investigators. Individual findings at individual participating sites are known only to the principal coordinating investigator and the registry office in Cologne. Publications or lectures on the findings of the registry as a whole or at individual investigation sites must be approved by the principal coordinating investigator in advance. The principal coordinating investigator reserves the right to review and comment on such documentation before publication.

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17. Appendix 3: Neuroblastoma staging systems

17.1. INSS Neuroblastoma stages

[21]

Stage	Definition
Stage 1	Localized tumor with complete gross excision, with or without microscopic residual disease; representative ipsilateral lymph node negative for tumor microscopically (nodes attached to and removed with the primary tumor may be positive for the tumor). A grossly resected midline tumor without ipsilateral (with = stage 2A) or contralateral (with = stage 2B) lymph node involvement is considered stage 1.
Stage 2A	Localized tumor with incomplete gross excision; representative ipsilateral nonadherent lymph nodes negative for tumor microscopically.
Stage 2B	Localized tumor with or without complete gross excision, with ipsilateral nonadherent lymph node positive for tumor. Enlarged contralateral lymph nodes must be negative microscopically.
Stage 3	Unresectable unilateral tumor infiltrating across the midline with or without regional lymph node involvement; or localized unilateral tumor with contralateral regional lymph node involvement; or midline tumor with bilateral extension by infiltration (unresectable) or by lymph node involvement. The midline is defined as the vertebral column. Tumors originating on one side and crossing the midline must infiltrate to or beyond the opposite side of the vertebral column.
Stage 4	Any primary tumor with dissemination to distant lymph nodes, bone, bone marrow, liver, skin and/or or other organs except as defined for stage 4S.
Stage 4S	Localized primary tumor (as defined for stage 1, 2A, or 2B) with dissemination limited to liver, skin and bone marrow (limited to infants <1 year of age). Marrow involvement in stage 4S should be minimal, i.e., <10% of total nucleated cells identified as malignant on bone marrow biopsy or on marrow aspirate. More extensive marrow involvement would be considered to be stage 4. The MIBG scan should be negative in the marrow.

Table 4 **INSS Staging System**

Multifocal primary tumors (e.g., bilateral adrenal primary tumors) should be staged according to the greatest extend of disease as defined and followed by a subscript letter M (e.g., 3M)

17.2. INRG Staging system

[2, 22]

Stage	Definition
L1	Localized tumor not involving vital structures as defined by the list of image-defined risk factors and confined to one body compartment
L2	Locoregional tumor with presence of one or more image-defined risk factors
M	Distant metastatic disease (except stage MS)
MS	Metastatic disease in children younger than 18 months with metastasis confined to skin, liver and/or bone marrow. Bone marrow involvement should be limited to less than10%of total nucleated cells on smears or biopsy. MIBG scintigraphy must be negative in bone and bone marrow. The primary tumor can be L1 or L2 and there is no restriction regarding crossing or infiltration of the midline.
Patients with multifocal primary tumors should be staged according to the greatest extent of disease as defined in the table.	

Table 5 **INRG staging system**

17.3. Image defined risk factors

[22, 23]

Ipsilateral tumor extension within two body compartments: Neck-chest, chest-abdomen, abdomen-pelvis	
Neck	Tumor encasing carotid and/or vertebral artery and/or internal jugular vein
	Tumor extending to base of skull
	Tumor compressing the trachea
Cervico-thoracic junction	Tumor encasing brachial plexus roots
	Tumor encasing subclavian vessels and/or vertebral and/or carotid artery
	Tumor compressing the trachea
Thorax	Tumor encasing the aorta and/or major branches
	Tumor compressing the trachea and/or principal bronchi
	Lower mediastinal tumor, infiltrating the costo-vertebral junction between T9 and T12
Thoraco-abdominal	Tumor encasing the aorta and/or vena cava
Abdomen/pelvis	Tumor infiltrating the porta hepatis and/or the hepatoduodenal ligament
	Tumor encasing branches of the superior mesenteric artery at the mesenteric root
	Tumor encasing the origin of the coeliac axis, and/or of the superior mesenteric artery
	Tumor invading one or both renal pedicles
	Tumor encasing the aorta and/or vena cava
	Tumor encasing the iliac vessels
	Pelvic tumor crossing the sciatic notch
Intraspinal tumor extension whatever the location provided that: More than one third of the spinal canal in the axial plane is invaded and/or the perimedullary leptomeningeal spaces are not visible and/or the spinal cord signal is abnormal	
Infiltration of adjacent organs/structures	Pericardium, diaphragm, kidney, liver, duodeno-pancreatic block, and mesentery
Conditions to be recorded, but not considered IDRFs	Multifocal primary tumors
	Pleural effusion, with or without malignant cells
	Ascites, with or without malignant cells

Table 6 **Image defined risk factors (IDRFs) in neuroblastic tumors**

17.4. Response criteria of neuroblastoma patients

[21]

Response	Primary tumor	Metastatic site
CR	No tumor	No tumor; catecholamines normal
VGPR	Decreased by 90-99%	No tumor; catecholamines normal; residual 99Tc bone changes allowed
PR	Decreased by >50%	All measurable sites decreased by >50%. Bones and bone marrow: number of positive bone sites decreased by >50%; no more than 1 positive bone marrow site allowed (if this represents a decrease from the number of positive sites at diagnosis)
MR	No new lesions; >50% reduction of any measurable lesion (primary or metastasis) with <50% reduction in any other; <25% increase in any existing lesion	
NR	No new lesions; <50% reduction but <25% increase in any existing lesion	
PD	Any new lesion; increase of any measurable lesion by >25%; previous negative marrow positive for tumor	

Table 7 **Response criteria of neuroblastoma**

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