UMBRELLA PROTOCOL SIOP-RTSG 2016 Integrated research and guidelines for standardized diagnostics and therapy for paediatric renal tumours

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Ethical review	Approved WMO
Status	Recruiting
Health condition type	Renal and urinary tract neoplasms malignant and unspecified
Study type	Observational invasive

Summary

ID

NL-OMON54547

Source
ToetsingOnline

Brief title
UMBRELLA PROTOCOL SIOP-RTSG 2016

Condition

- Renal and urinary tract neoplasms malignant and unspecified

Synonym
Nefroblastoma, Wilms tumour

Research involving
Human

Sponsors and support

Primary sponsor: Universität des Saarlandes

Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Adolescents, Children, Nefroblastoma, non-Wilms tumours, Renal tumors, Wilms tumours

Outcome measures

Primary outcome

Study parameters:

- 1q gain and other copy number variants

- Radiological parameters (including diffusion-weighted imaging, DWI) for

histological subtype

- Blastemal volume

Outcome:

- Overall survival

- Event-free survival

- Relapse-free survival

Secondary outcome

Study parameters:

- Mutations in individual known Wilms tumour genes (including WT1, CTNNB1,

AMER1, TP53, MYCN, FBXW7, GPC3, MLLT1, DIS3L2, DICER1, DROSHA, DGCR8, SIX1 and

SIX2)

- miRNA as biomarker in blood, urine and tumour samples

Outcomes:

- Overall survival

- Event-free survival

- Relapse-free survival

Study description

Background summary

See also page 10-11 of the UMBRELLA protocol:

The main mission of the International Society of Paediatric Oncology (SIOP) Renal Tumour Study Group
(RTSG) is to increase survival and to reduce acute treatment toxicity and late effects in all children, adolescents and young adults diagnosed with any renal tumour. In this context, SIOP-RTSG is aiming to offer all these patients the same standardized high quality diagnostics and treatment, independent of the tumour type, the socio-economic status or the geographic region where the patient is living. To achieve these goals, the UMBRELLA protocol was developed.

Given the relative rarity of paediatric renal tumours and in particular rare subgroups, our previous studies demonstrated that it is necessary to recruit as many patients as are available at a population level. Over the last decades more than 10,000 children have been prospectively enrolled in SIOP Wilms Tumour studies and trials. Since SIOP 93-01 SIOP-RTSG registered nearly 8,000 patients with a renal tumour from 261 centres across 28 countries. All of them have been treated according to consensus European trials and protocols. This has resulted in more standardised diagnostic procedures, improved risk stratification, and adjusted treatment recommendations for most renal tumours.

The UMBRELLA SIOP-RTSG 2016 protocol (part A) serves as an entry for including all children with a renal tumour in Europe and other participating centres in the SIOP-RTSG. Subsequently, treatment of each participant*s renal tumour is recommended according to the UMBRELLA treatment guidelines (part B), which provides treatment strategies for all Wilms tumour patients and all children with other renal tumours. These recommendations are based on previous studies and trials performed by the International Society of Paediatric Oncology (SIOP), Children's Cancer and Leukaemia Group (CCLG), Associazione Italiana Ematologia Oncologia Pediatrica (AIEOP) and National Wilms Tumor Study Group (NWTSG) / Children*s Oncology Group (COG).

Study objective

The overall aim of the SIOP 2016 UMBRELLA protocol is to harmonize the clinical relevant standard

diagnostic procedures for all paediatric renal tumours within SIOP and to provide imaging studies and
biomaterial from all of these patients, to find new and better risk factors for treatment stratification and
molecular targets for novel therapeutic approaches. This will help to improve short and long term
outcomes for all children with renal tumours through the introduction of a more *personalised*
approach.

Primary aim (see pages 18-19 in the UMBRELLA protocol)

1. To show the feasibility of storing serial blood, urine samples, tumour and germline material at diagnosis and at specific time points during treatment for international collaborative studies. These will be used to validate and quantify in multivariate analysis, the relative adverse prognostic significance of specified somatic molecular biomarkers (listed in aim 2) in relation to blastemal volume (aim 3). They will also be used for exploratory analyses of potential novel biomarkers, including circulating nucleic acids detectable in blood and urine, for diagnosis and prognosis.

2. To assess genomic 1q gain and other copy number variants as a prognostic biomarker in WT. Moreover, the feasibility of returning biomarker results to treatment centres within a clinically relevant time frame will be tested.

3. To optimize the definition of high risk WT, *blastemal type* through accurate measurement of the residual blastemal cells volume including centralized *real time* pathology and radiology review. The blastemal cell volume will be assessed in relation to other biomarkers and outcome measures including overall and event-free survival.

4. To optimize radiological diagnostics/review by (real time) central review to monitor and give appropriate feedback on diagnostic imaging quality, harmonies diagnostic procedures and standardize reporting of radiology findings. Additionally, diffusion-weighted imaging (DWI) results will be linked to pathological assessment of the tumour. (See also chapter 7.1 on page 27-28).

5. To optimize pathological diagnostics/review by (real time) central review to monitor and give appropriate feedback on local pathological diagnosis, stratify treatment based on central pathological review and store biological material according to standardized guidelines. (See also chapter 7.2 and 7.3 on page 28-34).

Secondary aims

1. To explore whether aberrations in any or a combination of the following genes have a significant impact on event-free or overall survival WT: WT1,

CTNNB1, AMER1, TP53, MYCN, FBXW7, GPC3, MLLT1, DIS3L2, DICER1, DROSHA, DGCR8, SIX1 and SIX2.

2. To explore the role of miRNAs in blood and tumour as biomarkers for kidney tumours.

3. To establish a surgical review process for guiding local centres in performing nephron sparing surgery (NSS) in uni - and bilateral WT or minimal invasive surgery in unilateral renal tumours.

4. To perform explorative epidemiological analyses of the collected data.

5. To validate new tools developed within the e-Health project such as p-medicine [4] and similar projects, to improve clinical treatment decision-making based on integrated risk assessment and response modelling in silico, in a selected well documented large subset of patients. The validation will be performed against the background of the ALEA registered complete dataset.

6. To characterise at a molecular level all subtypes of WT and non-WT and their associated nephrogenic rests, using whole genome, epigenomic and proteomic approaches.

7. To assess the feasibility of developing a targeted *next generation* sequencing panel for WT and other childhood renal tumours.

8. To contribute to the development of ex vivo models for functional validation of newly discovered molecular aberrations and biomarkers.

Study design

The study design of the UMBRELLA protocol includes data registration, biological sample collection and biological studies:

Data registration
Participating patients will be registered in the SIOP database using the eCRF system ALEA®. This system provides tools for patient registration, data collection, querying and (remote) monitoring. In addition, Electronic Case Record Forms (eCRFs) have been developed for baseline characteristics, treatment details, pathology and outcome measures. Methods for allowing reference centres to get access to imaging data (DICOM files) are being developed. The SIOP database is located at the statistical centre of the SIOP-RTSG in Amsterdam lead by Harm van Tinteren. All information in this database will be coded.

Biological sample collection
Blood, urine and tumour samples will be collected at specified time points to

answer biological questions. Blood samples (1-2 tubes, 5-7,5 mL) will be taken during routine blood exams needed for diagnosis and therapy monitoring, without requiring additional invasive procedures. In the Netherlands, blood and urine samples will be taken at diagnosis, before surgery, week 1 after surgery and at the end of treatment. Tumour samples (fresh and frozen) will be taken during surgery. Additionally, a small amount of blood will be taken from each parent (1-2 tubes, 10-20mL) and stored for biological research questions. All samples will be stored in the Princess Máxima Centrum Biobank (also DCOG/SIOP), according to the Princess Máxima Centrum Biobank rules and regulations (referentie: 2016-JD-0068).

Biological studies
Data and biological samples will be used for laboratory studies to answer the above mentioned research questions (aims) of UMBRELLA.

Study burden and risks

Burden and risks associated with participation are considered to be minimal. Possible burdens include the collection of extra blood and urine samples. Blood samples will be taken during routine blood exams needed for diagnosis and therapy monitoring, without requiring additional invasive procedures.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Children (2-11 years)
Babies and toddlers (28 days-23 months)
Newborns
Premature newborns (<37 weeks pregnancy)

Inclusion criteria

All children, adolescents or young adults with a primary or relapsed renal tumour diagnosed in a participating SIOP-RTSG centre are eligible for inclusion in the SIOP 2016 UMBRELLA study.

Exclusion criteria

The only exclusion criterion is missing informed consent.

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	07-06-2019
Enrollment:	1050
Type:	Actual

Ethics review

Approved WMO Date:	25-02-2019
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	15-05-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	08-02-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	16-02-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	02-05-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	11-11-2024
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL62763.078.17