# Transient myeloproliferative disease in children with Down syndrome
# Part A: Screening newborns with Down syndrome for TMD
# Part B: Treatment and follow-up of children with Down syndrome and TMD

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Primary aims:1. To perform a population-based screen to estimate the exact frequency ot transient leukemia in Dutch newborns with Down syndrome2. To investigate the realtionship between transient leukemia and the occurrence of DS ML and ALL at later...

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| **Ethical review** | Approved WMO |
| **Status** | Recruitment stopped |
| **Health condition type** | Leukaemias |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON31343

**Source**
ToetsingOnline

**Brief title**
TMD in children with Down syndrome

### Condition

- Leukaemias
- Chromosomal abnormalities, gene alterations and gene variants
- Neonatal and perinatal conditions

**Synonym**
Down syndrome acute myeloid leukemia, transient myeloproliferative syndrome

**Research involving**
Human

## Sponsors and support

**Primary sponsor:** Erasmus MC, Universitair Medisch Centrum Rotterdam
**Source(s) of monetary or material Support:** subsidieaanvraag preventie fonds,Sophia Stichting. Stichting Kinderoncologisch centrum Rotterdam;Stichting Kinderoncologie Nederland

## Intervention

**Keyword:** Down syndrome, Leukemia, Screening, Treatment

## Outcome measures

### Primary outcome

- to estimate the population-based frequency of transient leukemia in children

with Down syndrome

- to describe the percentage of children with TL who develop later on leukemia,

and whether treatment is able to reduce this progression to leukemia

- to compare minimal residual disease data obtained with flowcytometry and PCR

- to describe the number of children being GATA1-PCR negative at the end of

week 12

### Secondary outcome

- to study whether children with DS who later develop ALl had a a detectable

pre-leukemic clone in their neonatal blood sample

- to study genetic aberrations involved in the progression from TMD to DS ML

- to study whether DS ML can occur in children without TMD

- to describe the clinical and hematological variables of children with and

without TMD

# Study description

**Background summary**

Children with Down syndrome have an increased risk of developing both acute myeloid leukemia and acute lymphoblastic leukemia. The prognosis of myeloid leukemia in children with Down syndrome is better than in children without Down syndrome, which is due to a specific type of myeloid leukemia these children develop, referred to as *myeloid leukemia of Down syndrome* (ML DS). This leukemia is characterized by occurrence at a very young age, low diagnostic white blood cell count (WBC), enhanced chemosensitivity, GATA1 mutations, and the occurrence of a transient myeloproliferative syndrome (TMD) in newborns. Due to the enhanced sensitivity to chemotherapy, and to a greater susceptibility for treatment- related complications, children with ML DS are usually treated with reduced- intensity treatment protocols. TMD occurs in approximately 10% of Down syndrome newborns, although this was only studied in selected populations of hospitalized children. Approximately 15-20% of children with symptomatic TMD die from their disease, mainly due to liver fibrosis, effusions, and organomegaly with high WBCs. Furthermore, approximately 20% of children who survive from TMD subsequently develop ML DS. It is unknown why only a subgroup of children develops true leukemia at follow-up, and what drives this progression. It is also unknown if ML-DS can occur without preceding TMD.

So far, no protocol was available to screen for TMD, and provide uniform treatment and follow-up guidelines. In this study, we will perform a population-based screening of DS children in the Netherlands for the occurrence of TMD, by testing a blood sample that will be drawn within 4 weeks after birth (part A of the study). As there is a nation-wide registry for children with Down syndrome, we will be informed about the number of children who will participate in the screening program. When TMD is diagnosed, children will be included in the TMD protocol, which provides treatment guidelines for treatment of symptomatic TMD, and aims at reducing the morbidity and mortality associated with this disease (part B of the protocol, in collaboration with the AML-BFM Study Group). The overall aim of part B of the protocol, however, is not only to reduce the TMD-related morbidity and mortality, but also to reduce the number of children that subsequently develop ML DS. This is supported by data from a pilot-study from the AML-BFM SG that showed a reduction in subsequent ML-DS development when comparing children with symptomatic TMD that had been treated with children with non-symptomatic TMD that did not receive treatment. To further study this concept of chemo-prophylaxis, we will also treat TMD children with persisting residual disease levels, as determined by flowcytometry or by GATA-1 quantative PCR at week 8 after birth, with low-dose chemotherapy (cytarabine). The hypothesis is that slow spontaneous clearance of blasts is a risk-factor for later leukemia development. This study will

therefore also prospectively test whether chemo-prophylaxis of ML DS by treating the pre-leukemic clone is feasible, and reduces the number of subsequent leukemias.

**Study objective**

Primary aims:
1. To perform a population-based screen to estimate the exact frequency ot transient leukemia in Dutch newborns with Down syndrome
2. To investigate the realtionship between transient leukemia and the occurrence of DS ML and ALL at later age.
3. To include children with transient leukemia in the DCOG protocol for treatment and follow-up of TMD (part B). In this prootcol it is investigated whether selected children can be saved from the mortality associated with TMD and whether progression to DS ML can be prevented.

Secondary aims:
1. To indentify novel egnetic aberrations involved in the progression from transient leukemia to DS ML.
2. To investigate whether ALL in DS children is also preceded by a pre-leukemic clone detectable in the neonatal blood from DS children.
3. To describe the differences in hematological and clinical parameters between children with and without transient leukemia.

**Study design**

This is a prospective non-randomzied multicenter study.

All Ducth hospitals with a pediatric ward will be asked for participation in teh screening part of the protocol. We need to screen 811 evaluabel children with Down syndrome, which implicates that there is a blood sample available which allows screening for TMD, and that 3-year follow-up of a particular child is possible. This means that we have to screen more than 811 children, as some may be lost to follow-up due to other problems such as cardiac disease, etc.

In case TMD is diagnosed, patients will be referred to a pediatric oncology center for treament and follow-up of TMD (part B of the study). Children with TMD may be treated because of disease-related symtoms, or because they do not sufficiently clear their TMD at the age of 8 weeks. The latter is an new treatment approach, and is based on preliminary observations from the AML-BFM SG, who observed that children who were treated showed a lower rate of progression to DS ML.

To reach the number of children required in part A and B the study will last around 6 years.

**Intervention**

This study includes 2 different types of interventions:

1. chldren included in part A will have to undergo peripheral blood sampling, in most of the cases in combination with a diagnostic sample, to diagnose whether transent leukemia is present
- children included in the transient leukemia treatment protocol may be treated with cytarabine in case of symptomatic transient leukemia or high minimal residual disease levels. Approximately 30% of children will be treated for this indication.

**Study burden and risks**

The major burden for children without transient leukemia is that they need to undergo peripheal blood sampling, although this may often be combined with regular blood sampling needed for clinical care.

Children with TMD will beincluded in the TMD protocol and may be exposed to cytarabine treatment, in case of clinical symptoms or high minimal residual disease levels. The latter is a new treatment indication, based on the assumption that slow clearance of leukemia is associated with later progression to DS ML. The side-effects of this low-dose chemotherapy are minimal - as described in the protocol.

# Contacts

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# Trial sites

### Listed location countries

Netherlands

## Eligibility criteria

**Age**
Children (2-11 years)

### Inclusion criteria

Inclusion criteria part A:
- Newborns with Down syndrome born in the Netherlands
- Diagnosis between 01-07-2007 and 01-07-2012
- Age at peripheral blood sampling below 4 weeks
- Patients with demonstrable transient myeloid leukemia elsewhere are also eligible, even if no blasts can be detected in the peripheral blood
- signed informed consent;Inclusion criteria part B:
- proven TMD
- Down syndrome
- detectable GATA1-mutation in leukemic cells
- age below 3 months
- infromed consent

### Exclusion criteria

Key exclusion criteria, part A:
- no consent,
- no confirmation of diagnosis of Down syndrome,
- complications which prohibit the analysis of a peripheral blood sample.;Key exclusion criteria, part B:
- complications or underlying disease that interferes with the possibility to treat
- presence of another hematological disease

## Study design

### Design

Study type: Interventional

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| Intervention model: | Other |
| Allocation: | Non-randomized controlled trial |
| Masking: | Open (masking not used) |
| Control: | Active |
| Primary purpose: | Diagnostic |

### Recruitment

NL

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|---|---|
| Recruitment status: | Recruitment stopped |
| Start date (anticipated): | 21-01-2008 |
| Enrollment: | 811 |
| Type: | Actual |

### Medical products/devices used

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| Product type: | Medicine |
| Brand name: | Cytarabine |
| Generic name: | Cytarabine |
| Registration: | Yes - NL intended use |

## Ethics review

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| Approved WMO Date: | 03-09-2007 |
| Application type: | First submission |
| Review commission: | METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam) |

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| Approved WMO Date: | 04-09-2007 |
| Application type: | First submission |
| Review commission: | METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam) |

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| Approved WMO Date: | 04-06-2009 |
| 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 |
|---|---|
| EudraCT | EUCTR2006-002962-20-NL |
| CCMO | NL17304.078.07 |