# Randomized controlled trial on the use of EPO to reduce top-up transfusions in neonates with red blood cell alloimmunization treated with intrauterine transfusions.

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| **Ethical review** | Approved WMO |
| **Status** | Recruitment stopped |
| **Health condition type** | Haemolyses and related conditions |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON50421

**Source**
ToetsingOnline

**Brief title**
EPO-4-Rhesus Study

### Condition

- Haemolyses and related conditions
- Neonatal and perinatal conditions

**Synonym**
anemia; hemolytic disease of the newborn due to red cell

**Research involving**
Human

## Sponsors and support

**Primary sponsor:** Leids Universitair Medisch Centrum
**Source(s) of monetary or material Support:** Sanquin Bloedbank,Sanquin Blood Supply

## Intervention

**Keyword:** Darbepoetin alfa, Hemolytic Disease of the Newborn, Red cell alloimmunization, Top-up transfusion

## Outcome measures

### Primary outcome

* Number of top-up transfusions required per infant.

### Secondary outcome

* The percentage of infants requiring a top-up transfusion up to 3 months of

life;

* Number of days of admission for top-up transfusions;

* The percentage of infants with hypertension (>/= 2SD);

* The percentage of infants with high ferritin levels (>/= 200).

Exploratory outcome:

* Long-term neurodevelopmental outcome at 2 years of age using the BSID-III

test.

# Study description

### Background summary

The mainstay of antenatal treatment of fetal anemia due to red cell alloimmunization is (serial) IUT. The mainstay of postnatal treatment in HDN is (1) intensive phototherapy and exchange transfusion to treat hyperbilirubinemia and prevent kernicterus, and (2) top-up transfusions to treat anemia. Up to 80%

of infants with HDN treated with IUT require at least one top-up transfusions for late anemia during the first 3 months of life.
Several risk factors for late anemia have been reported, including serial IUT (due to bone marrow suppression), severity of HDN, reduced use of exchange transfusions during the neonatal period and reduced survival of transfused red blood cells. Finally, erythropoietin deficiency is also considered as a possible contributing factor to late anemia.
EPO has been increasingly used in neonates to prevent or reduce neonatal anemia without short or long-term adverse effects. Several small studies and casuistic reports suggest that neonates with HDN may benefit from treatment with EPO to reduce the risk of delayed anemia and subsequent top-up transfusions. However, other authors found that EPO may be less effective than expected. Due to the lack of evidence, routine use of EPO is currently not recommended. To determine a role for EPO in this group of patients, a well-designed randomized controlled clinical trial of sufficient sample size is required. Potentially, EPO stabilizes the hemoglobin levels of these infants and thus prevents top-up transfusions and extra admissions, creating a more stable and natural postnatal course for patients with HDN.

**Study objective**

The primary objective of this study is to investigate whether darbepoetin alfa is effective in reducing the incidence of late anemia in infants with HDN treated with IUT and therefore in decreasing the number of top-up transfusion required per infant. As secondary objectives the percentage of infants that require top-up transfusions will be assessed, as well as the number of days of admission for top-up transfusions, occurrence of hypertension and high ferritin levels and, as exploratory otoc long-term neurodevelopmental outcome at 2 years of age using the BSID-III test.

**Study design**

Randomized controlled trial. Included neonates will be randomized at birth to treatment with EPO (intervention group) or *standard of care*, 1:1 allocation. In the treatment group, EPO (darbepoetin alfa) is administered subcutaneously at a dosage of 10 mcg/kg once a week, starting at day 7, for a period of 8 weeks. Treatment is administered during weekly home visits. Concomitant therapy with folate (0.25 mg/day) is given in both groups (standard practice). Concomitant iron therapy is given if ferritin level drops below 75 microg/l.19 Weekly routine measurements of complete blood counts (including hemoglobin level and reticulocyte count) will be performed in both groups (standard practice). EPO is discontinued if hemoglobin level is >= 13 g/dL after at least 4 weeks of treatment with EPO. Monthly measurements of liver enzymes (aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT), gamma-glutamyl transferase (γGT) and lactate dehydrogenase (LDH)) will also be performed in all groups (standard practice). In addition, EPO-level will be determined at

the start of the treatment with EPO. The number of top-up transfusions received during the first 3 months of life and hemoglobin levels prior to the top-up transfusion are recorded. After initial discharge from the LUMC, top-up transfusions are performed when hemoglobin levels fall below 7.2 g/dL or when hemoglobin is between 7.2 and 8.8 g/dL if clinical symptoms of anemia (lethargy, feeding difficulties or failure to thrive) are present.

At two years of age a physical and neurological examination and an assessment of cognitive and neurological development using the Dutch version of the Bayley Scales of Infant Development, third edition (BSID-III) will be performed (standard practice). BSID-III scores provide mental developmental indexes (MDI) and psychomotor development indexes (PDI).

### Intervention

Darbepoetin alfa subcutaenous injection once a week for a period of 8 weeks after birth, dosage 10mcg/kg.

### Study burden and risks

The burden to the intervention group seem small, though cannot be neglected as the intervention group receives weekly subcutaneous injections for a period of 8 weeks. However, these injections seem of minor burden compared to the weekly (routine) blood draw. Risks are considered mild as no severe adverse effects have been reported in term neonates.

## Contacts

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# Trial sites

## Listed location countries

Netherlands

# Eligibility criteria

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

## Inclusion criteria

All (near)-term neonates (gestational age = 35 weeks) with hemolytic disease of the newborn(HDN) (due to Rhesus-D, -C, -c, -E, Kell or other red blood cell alloimmunization) treated with intrauterine transfusion(s) (IUT) and admitted to the Leiden University Medical Center (LUMC)

## Exclusion criteria

Gestational age < 35 weeks

# Study design

## Design

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| Study phase: | 3 |
| Study type: | Interventional |
| Intervention model: | Parallel |
| Allocation: | Randomized controlled trial |
| Masking: | Open (masking not used) |

**Primary purpose:** Prevention

## Recruitment

NL

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|---|---|
| Recruitment status: | Recruitment stopped |
| Start date (anticipated): | 31-10-2017 |
| Enrollment: | 40 |
| Type: | Actual |

### Medical products/devices used

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| Product type: | Medicine |
| Brand name: | Aranesp |
| Generic name: | darbepoetin alfa |
| Registration: | Yes - NL outside intended use |

## Ethics review

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| Approved WMO Date: | 01-06-2017 |
| Application type: | First submission |
| Review commission: | METC Leiden-Den Haag-Delft (Leiden)<br><br>metc-ldd@lumc.nl |

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|---|---|
| Approved WMO Date: | 11-08-2017 |
| Application type: | First submission |
| Review commission: | METC Leiden-Den Haag-Delft (Leiden)<br><br>metc-ldd@lumc.nl |

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|---|---|
| Approved WMO Date: | 06-10-2017 |
| Application type: | Amendment |
| Review commission: | METC Leiden-Den Haag-Delft (Leiden)<br><br>metc-ldd@lumc.nl |

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| Approved WMO Date: | 16-05-2018 |
| Application type: | Amendment |
| Review commission: | METC Leiden-Den Haag-Delft (Leiden) |

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| | metc-ldd@lumc.nl |
| Approved WMO Date: | 13-01-2021 |
| Application type: | Amendment |
| Review commission: | METC Leiden-Den Haag-Delft (Leiden) |
| | metc-ldd@lumc.nl |

# 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 | EUCTR2017-000583-15-NL |
| ClinicalTrials.gov | NCT03104426 |
| CCMO | NL60858.058.17 |

# Study results

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| Date completed: | 31-07-2022 |
| Actual enrolment: | 44 |