A clinical research trial of a new intervention for brittle bone disease

Participant information Historical Control Group

Participant information for the BOOSTB4 clinical trial

We are conducting a clinical trial with the aim to improve the health of children with brittle bone disease (Osteogenesis Imperfecta, OI). In the trial, stem cells will be given to young children diagnosed with OI. With your agreement, we would like to collect information about you (the mother) and your child as part of a historical control group within the trial. This is why you have been given this information. You can read more about the trial below.

Important things you need to know

- Please take time to read the following information carefully. Discuss it with your partner, relatives and friends if you wish.
- You are free to decide whether or not the BOOSTB4 trial team are allowed to collect information about you and your child. If you choose not to, this will not affect the care your child receives from your doctors in any way.
- If you decide to participate as a historical control you will be asked to sign a consent form. You will get a copy of this information and the consent form to keep.
- Ask us if there is anything that is unclear or if you would like more information.

Summary of the research trial

- The trial is called BOOSTB4 (Boost Brittle Bones Before Birth).
- We want to find out if stem cell infusions are safe and can improve the health of children with OI.
- So that we can compare the effect of the stem cells, we would like to collect information about the health of children with OI who have **not** had stem cell infusions.
- Taking part as a control means we will collect information but your child will **not** receive stem cell infusions.

Content

How to contact us

If you want further information about the BOOSTB4 trial, contact a trial doctor:

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You are also welcome to contact the coordinator for the trial:

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More information is also available on our website: www.boostb4.eu

1 Why are we doing this clinical trial?

What is OI?

Osteogenesis Imperfecta (OI), or brittle bone disease, is a condition where collagen, the protein that is responsible for bone structure, is low or of poor quality. The minerals in the bone are therefore not supported, making the bone weak and in turn making it fracture easily.

There are four main types of OI:

Type 1 is often mild and usually not diagnosed until later in childhood.

Type 2 is very severe and means that babies unfortunately do not survive. It is detectable in the womb on ultrasound.

Type 3 and the severe forms of Type 4 are possible to detect whilst the baby is in the womb, or shortly after birth. These types of OI result in numerous fractures, stunted growth and pain.

In order to know for certain that a person has OI, a DNA test must be performed. This can be carried out on a blood sample.

If you want to know more about OI, please talk to the doctor who is treating your child.

How is OI usually treated today?

There is no cure for OI, but there are some treatments that can help reduce the symptoms of pain, fractures and bone deformation.

The main treatment is a drug called bisphosphonate, which prevents loss of bone mass by improving the imbalance between bone loss and formation which occurs in OI, thus it strengthens the bone by increasing bone density. The bone will however still fracture more easily than normal bone. Children with moderate to severe OI are normally given bisphosphonate infusions regularly.

Fractures are treated according to the advice from the orthopaedic doctors. Sometimes metal rods are inserted inside the larger bones.

What are we trying to find out?

Stem cell infusion with cells that have the potential to make bone is a possible new treatment for OI.

The main thing we want to confirm in this trial is whether stem cell infusion is safe to use in children with OI.

We also want to evaluate if the stem cell infusion improves the health of children with OI. Specifically we want to investigate if the number of fractures and chronic pain can be reduced and growth can be improved.

If this study is successful we aim to develop the stem cell infusion as a future clinical treatment for OI.

2 Why am I being asked for me and my child to take part?

You are being asked if we can collect information about you (the mother) and your child as a part of the BOOSTB4 trial because your child has OI type 3 or severe type 4.

3 The stem cell infusions in this trial

What are stem cells?

The human body is made up of many different cell types such as muscle cells, nerve cells and bone cells. Stem cells are primitive cells that can develop into these different specialized cell types.

There are several different types of stem cells. ‘Mesenchymal stem cells’ are the specific type of stem cells used in the BOOSTB4 trial as they can become cells that make bone, cartilage and muscle. Mesenchymal stem cells are special because data so far show they do not

cause immune reactions and they are very unlikely to lead to the development of cancer. The stem cells for the BOOSTB4 trial are prepared from fetal tissues obtained during legal terminations of pregnancy performed before 12 weeks' of pregnancy in Sweden. Women undergoing the terminations have given their approval that the stem cells can be used in this trial. Research has shown that fetal stem cells are able to form bone better than stem cells from adults. We also believe that giving fetal stem cells to a young child can give a better clinical result, compared to if adult cells are given.

We believe that if we give these stem cells to a child with faulty bone making cells, the stem cells may travel to their bone and become new bone producing cells. These may make healthy collagen which can support the damaged bone and help to develop more normal new bone.

What has previously been done?

More than 15 years ago, a trial was performed in the USA where six children were treated after birth with two infusions of adult mesenchymal stem cells. One treatable allergic reaction (hives) was observed after one of the 12 infusions. No other side effects were noted. The children did well with improved growth and reduced number of fractures.

Researchers within the BOOSTB4 consortium have previously given fetal mesenchymal stem cells to four children with OI. The children received an infusion of the stem cells after they were born or as an unborn baby while they were in the womb. The children have received further booster doses of the same stem cells after birth. Clinically, they did well after the stem cell infusions, growing better and having fewer fractures and less pain than would have been expected. Looking through a microscope at bone samples, we could see that the stem cells had engrafted (settled) into the bone and become bone producing cells. By 2018 the treated children were between 3 and 16 years old. No side effects have been detected so far. However, the number of children treated so far in the world is only ten.

Studies in animals suggest that stem cells given early in life reduce the number of fractures and the bones become stronger. We therefore believe that an early intervention could lead to better results.

Trial groups

There will be two different trial groups who receive stem cell infusions in this trial. The postnatal group will receive four infusions after birth up to 18 months of age. The children in the prenatal group will receive one stem cell infusion before birth followed by three infusions after birth.

To be able to better evaluate the results of the stem cells infusions, we will also compare the children who receive this infusion with children with OI type III or severe type IV, who have not received stem cell infusions.

The prospective comparison group will consist of children diagnosed with OI whose parents have declined the stem cell infusion but agreed to have information about their child collected. This group will receive the routine treatments.

The historical control group consists of children of ages up to 10 years that are diagnosed with OI type III or severe type IV and have been treated with routine treatments including bisphosphonates.

Which group will my child be in?

If you are happy for us to collect information about your child, we would like to include you (the mother) and your child in the historical control group.

4 What kind of information will be collected during the trial?

We will collect personal information related to your child's OI, from the timepoint when your child received the OI diagnosis up to 10 years

of age. If your child is under ten we would like to be able to access this information on an ongoing basis until they reach ten years of age. Data from you, the mother, includes available data from your pregnancy and delivery of your child diagnosed with OI. The information includes medical notes and data collected at the OI clinic and obstetrics and delivery clinic as well as medical notes and data collected within community outreach (i.e. their General Practitioner (GP) and other community services) and central records. No personal information from the father of the child will be collected.

We will collect this information directly from hospital records. You will not be required to attend any additional appointments or fill in any paperwork, other than signing the consent form, if you wish to take part.

5 What are the possible risks of taking part?

You or your child will not be exposed to any direct risks since their participation is limited to collection and analysis of data from patient records.

6 What are the possible benefits of taking part?

There are no direct benefits for you or your child to participate. The information we get from this trial may help us to improve treatment for individuals with OI in the future.

7 More information about taking part

Do me and my child have to take part in the BOOSTB4 trial?

No, it is up to you to decide whether you agree to let the BOOSTB4 study group collect information about you (the mother) and your child or not. Your decision will not affect the standard of care you or your child receive.

Can I and/or my child stop taking part after having joined the trial?

You and your child can stop taking part in the trial at any time and without you giving a reason. Your decision will not affect the care you or your child receive from your doctors in any way.

Information already collected from you and your child by the BOOSTB4 trial group will however not be destroyed.

If you want to take back your consent, contact the trial doctor (see page 1 for contact information).

What will happen to the information about me and my child collected during the trial?

If you decide to participate in the trial, we will collect information about you and your child and your childs development in a locked database. Only information related to the trial will be collected. The information will be kept so only authorised persons have access to it.

The Karolinska Institutet is responsible for the processing of your personal data. Your contact person for this is the trial coordinator (see page 1 for contact information). The Karolinska Institutet is a government agency and has an obligation to, among other things, comply with the rules for public documents, government archives and public statistics. The Karolinska Institutet will therefore also process the personal data in the ways necessary to be able to comply with applicable legislation.

The information will be coded and then made available (with a code instead of name) to the researchers who are part of the BOOSTB4 study in the United Kingdom, Germany, the Netherlands and Sweden, as well as national and international authorities and the trial monitors that control the trial's safety. This

information may be used in future studies approved by the Ethics Review Board.

The information we collect will be processed in accordance with the EU Data Protection Regulation (2016/679, GDPR), which is available to protect people with regard to the processing of personal data. In accordance with the regulation you have the right to once a year and free of charge request what information that has been recorded about your child and, if necessary, correct any errors. If you want to access the information, contact the trial coordinator (see page 1 for contact information). If you have comments on the Karolinska Institutet's processing of your personal data, you can contact dataskyddsombud@ki.se or +46 8-524 840 00. If you are not satisfied with the response from the Karolinska Institutet, you can contact the Data Inspectorate in Sweden with complaints about the processing of your personal data by the Karolinska Institutet; +46 8-657 61 00, datainspektionen@datainspektionen.se.

The samples taken in the trial are stored coded in a so-called biobank in accordance with the Swedish Biobank Act (2002: 297), which regulates how samples can be stored and used. The biobank's name is the Stockholm Medical Biobank (reg. No. 914). The Karolinska University Hospital is responsible for the biobank.

Samples will be sent to other countries within the EU / EEC for analysis. The code key is stored securely and is only available to authorized persons. The samples may only be used in the manner for which you have given consent. Should there be additional research that is not yet planned, the Ethics Review Board in Sweden will decide whether you should be asked to consent again.

What will happen to the results of the BOOSTB4 trial?

When the trial is completed, we will publish the results in a medical journal, so that other doctors can see them. You can ask your doctor for a copy of any publication. Your and your child's identity and any personal details will be kept confidential. No named information about either of you will be published in any report of this trial.

Who is organising and funding the trial?

This clinical trial is being run by the BOOSTB4 Consortium, a group of doctors and scientists from across Europe with a special interest in stem cell therapy and OI.

Your doctor is not receiving any money or other payment for asking you to be part of the trial.

The trial has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 681045 and from the Swedish Research Council.

Who has reviewed the BOOSTB4 trial?

This trial has been approved by competent authorities such as the Ethics Committee and the Medical Products Agency in Sweden. The trial will be conducted in accordance with EU directive 2001/20/EC and the Declaration of Helsinki. Ask your trial doctor if you want to have more information about this.

Compensation

No compensation is available for you or your child's participation in the clinical trial.

OI Support Group

If you want to find out more about OI you can contact: Osteogenesis Imperfecta Federation Europe (OIFE): www.oife.org

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Thank you for taking the time to consider taking part in the BOOSTB4 trial.
