

Subject information for participation in medical-scientific research

Study into the determinants of weak bones (SINTER)

Introduction

Dear Sir/Madam,

You are invited to take part in a medical research study. Taking part is entirely voluntary. You are receiving this letter because you are being treated for a condition that may affect your bone strength. This letter explains what the study is about, what participation would involve you, and what the possible benefits and risks are. Please take the time to read this information carefully. You can decide at your own pace whether you would like to participate. If you choose to take part, please complete the consent form in Appendix E.

Asking questions and making your decision

You can base your decision on the information in this letter. We also encourage you to:

- Ask any questions you may have to the researcher who provided this information
- Discuss the study with your partner, family members, or friends
- Contact the independent expert if you would like additional advice (see Appendix A for contact details)
- Read general information about medical research at:
www.rijksoverheid.nl/onderzoek

1. General information

This medical research study was initiated by Erasmus MC, referred to in this letter as the “sponsor.” The study is carried out by researchers at Erasmus MC, including doctors, research assistants, and research nurses.

The study has been reviewed and approved by the Medical Ethics Review Committee of Erasmus MC.

2. What is the purpose of the study?

At present, it is not clear why some people maintain strong bones despite having a chronic illness, while others develop weak bones even though they are otherwise healthy. With the SINTER study, we aim to understand which factors explain these differences.

Approximately 6,000 patients who visit various outpatient clinics at Erasmus MC will be invited to take part. By comparing people who are more or less susceptible to developing weak or strong bones, we hope to gain better insight into bone health. In the future, this knowledge may help to detect bone weakness or osteoporosis earlier, improve treatment, and prevent bone fractures.

3. What is the background to the research?

Bone strength is influenced by several factors, including genetic makeup, age, lifestyle (such as diet and physical activity), and certain medical conditions. Your genes do not directly determine how strong your bones are, but they can indicate how susceptible someone may be to developing weak or strong bones.

In the SINTER study, we are investigating how genetic predisposition and other factors contribute to differences in bone strength.

4. How does the study work?

The study lasts approximately 18 months. During a regular blood draw for your outpatient appointment, one extra tube of blood will be collected for this study.

The blood sample will be used to analyze genetic profiles that help classify bone strength as “weak,” “average,” or “strong.”

- If your profile indicates “weak” or “strong” bones, you will be invited to visit the ERGO (Erasmus Rotterdam Health Study) research center at Erasmus MC (Briandplaats 15, Ommoord, Rotterdam) for additional measurements.
- If your profile indicates “average” bone strength, you will not be invited for further examinations. In that case, your participation ends after the blood sample, and no further action is required. You will not receive a separate notification.

Examination and Measurements

During your visit to our research center, the following measurements will be taken:

- We will measure your height and weight.
- We will take images of your entire skeleton using an X-ray machine, and detailed images of your bones using a small CT scanner.
- We will measure your bones, muscles, and body fat using special X-rays of your whole body, hips, and back.
- We will assess your bone quality with a device that gently pricks your lower leg bone with a very small needle.
- We will test your muscle function by measuring your hand grip strength and the strength of your legs while jumping.

This visit will take approximately 1.5 hours.

Additional Measurements

- **Physical activity and diet:** You will be asked to fill out questionnaires at home about your exercise habits and diet. This takes about 30 minutes.
- **Stool sample (microbiome):** We may ask you to collect a stool sample at home and send it to us for analysis.
- **Opinion on genetic testing:** You may also be asked to complete a short questionnaire about your views on genetic testing, which takes about 15 minutes.

How is this different from regular care?

Participating in this study will **not affect your regular medical care**. You will continue to receive your usual treatment in the same way as always.

5. What agreements do we make with you?

To help the study run smoothly, we ask you to agree to the following:

- You are willing to come to the research center for the scheduled measurements.

- You will contact the researcher in the following situations:
 - You no longer wish to participate in the study.
 - Your phone number, address, or email address changes.
 - You are pregnant during the study.

Are you pregnant during the study?

Pregnant women **cannot** visit the research center for measurements. X-ray examinations can affect an unborn child. Please inform the researchers if you are pregnant when you are invited to the study center.

6. What side effects, adverse effects, or discomfort might you experience?

Some measurements may cause mild side effects or discomfort:

- **X-rays:** The study involves X-rays. You will receive approximately 0.104 mSv of radiation, which is very low and considered safe. For comparison, the average annual background radiation in the Netherlands is about 2.9 mSv. This small additional exposure is not harmful, even if you undergo other medical X-ray procedures. Please inform the researcher if you are having other X-ray exams.
- **Bone measurement with a small needle:** We will press on the lower leg bone with a small needle under local anesthesia. This may cause mild discomfort, pain, minor bleeding, or bruising at the site.

7. What are the benefits and risks of participating in the study?

Participating in this study may have both benefits and risks. Please read carefully and discuss with family, friends, or your doctor if needed.

- **Benefits:**
 - Participation will **not affect your medical treatment** or the symptoms of your condition.
 - By taking part, you help researchers learn more about bone strength and weakness. This knowledge may help prevent fractures and improve treatment in the future, including for people with conditions like yours.
- **Possible disadvantages:**
 - Some measurements may cause mild discomfort.

- Participation takes **about two hours** in total.
- You must follow the study procedures and attend scheduled appointments.
- Occasionally, the study may reveal information that is not directly related to the research but may be important for your health or that of your family. (See Section 10 for more about incidental findings.)

Choosing not to participate

- Participation is **voluntary**. You do not have to do anything if you do not want to participate.
- You do not need to sign anything or explain your decision.
- If you choose to participate, you can **withdraw at any time**, even during the study.
- Choosing to participate or not will **not affect your current medical care**.

8. When does the study end?

The study will stop for you in the following situations:

- You decide to stop participating at any time. Please inform the researcher immediately; you do not need to give a reason.
- The study as a whole ends.
- One of the following authorities decides to stop the study:
 - Erasmus MC
 - The government
 - The medical ethics committee overseeing the study

What happens if you stop participating?

If you decide to withdraw from the study, the researchers **may still use the data and biological samples** (such as blood) collected up to the time you withdrew.

9. What happens after the study? Will you receive the results?

Several years after your participation, you will be informed of the **overall results of the study**, for example via newsletters.

9. What do we do with your data and biological material?

If you take part in the study, you also give permission for your data and biological material to be collected, used, and stored.

Which data do we store?

We store the following data:

- Your name, sex, address, and date of birth
- Information about your health
- (Medical) data collected during the study

Which biological material do we store?

We collect, use, and store your blood sample.

Why do we collect, use, and store your data and biological material?

We collect, use, and store your data and biological material in order to answer the research questions of this study and to publish the results.

In the biological material (blood and stool samples), we will investigate, among other things, hereditary (genetic and epigenetic) and biological factors related to nutrition and the microbiome, and in the future also hormonal, immunological, inflammatory, and metabolic status, as well as environmental influences (for example, endocrine-disrupting substances and metals). These analyses may provide important insights into the development of bone weakness in relation to various diseases.

Because these analyses have no direct consequences for you as a participant, you will not receive individual feedback on the results.

How do we protect your privacy?

To protect your privacy, we assign a code to your data and biological material. Only this code is used on all your data and biological material. The key linking the code to your identity is stored securely in the hospital. Whenever your data and biological material are processed, only the code is used. In reports and publications about the study, it will not be possible to trace the information back to you.

Who can access your data?

Some individuals may be able to view your name and other personal data without a code.

This may include data collected specifically for this study as well as information from your medical record.

These individuals are responsible for checking whether the study is being conducted properly and reliably. The following people may have access to your data:

- Members of the committee that monitors the safety of the study
- A monitor working on behalf of Erasmus MC
- National and international regulatory authorities
- Members of the research team

These individuals are required to keep your data confidential. We ask for your consent to allow these individuals to access your data. The Dutch Health and Youth Care Inspectorate (Inspectie Gezondheidszorg en Jeugd) may access your data without your consent.

How long do we store your data and biological material?

We store your data and biological material for **15 years** at Erasmus MC. Your biological material is stored at Erasmus MC so that additional analyses related to this study can be performed during the course of the research. Once this is no longer necessary, your biological material will be destroyed.

May we use your data and biological material for other research?

Your collected data and your (remaining) biological material may also be valuable for other medical research into your disease(s) and/or for the use of genetic information in the development of new studies. For this purpose, your data and biological material will be stored at Erasmus MC for **15 years**. In the consent form, you can indicate whether you agree to this. If you do not give consent, you can still participate in this study.

May we store and use your data for training and educational purposes?

The data we collect may be used for training and educational purposes, for example to train new staff members or students. This may take place at Erasmus MC as well as at other hospitals or educational institutions. Your **name, address, and date of birth will never be used** for this purpose. If you do not agree, you can indicate this on the consent form. These data will be stored for **up to 15 years after the study ends**.

What happens in the case of unexpected findings?

It is possible that, during the study, something is discovered incidentally that is not directly

relevant to the research but may be important for your health or that of your family members. Where possible, we will discuss relevant results of the measurements directly with your specialist. You can then discuss with your general practitioner or specialist what further steps are required. The costs of this follow-up fall under your health insurance. By signing the consent form, you give permission to inform your general practitioner or specialist.

Data from questionnaires or results of analyses of blood samples, such as results of (epi-)genetic research, cannot be communicated to you individually.

Can you withdraw your consent for the use of your data?

You may withdraw your consent for the use of your data at any time. This applies both to the use within this study and to use in other studies. Please note, however, that if you withdraw your consent after researchers have already collected data for a study, they may still use the data already collected. If you indicate this, your data will no longer be used for new research.

The same applies to your biological material: if analyses have already been performed on your biological material, the researcher may continue to use the results of those analyses.

We may send your data to countries outside the European Union

We collaborate with several (inter)national research partners, both within the Netherlands and outside the European Union (EU). Your coded data and biological material may be used and shared within these collaborations. In countries outside the EU, the same EU privacy regulations do not apply. When data is shared with countries outside the EU (so-called “third countries”), such as the United States, the same level of protection as within the EU cannot be guaranteed. We take measures to protect your data as much as possible outside the EU. In any case, **only your coded data** will be shared.

When your data and biological material are shared, it will always involve **only a small portion of your data**. Agreements are made to ensure that the parties receiving your data handle it carefully and reliably.

For genetic studies, coded data may be sent to servers of institutions outside the EU to perform more detailed genetic analyses using reference data; this process is called **genetic imputation**. This further data processing is performed using specialized software

on a high-performance computer with extensive security controls, which has been deemed secure.

Do you want to know more about your privacy?

- To learn more about your rights regarding the processing of personal data, visit www.autoriteitpersoonsgegevens.nl.
- If you have questions about your rights or complaints regarding the processing of your personal data, please contact **Erasmus MC** and/or the **SINTER research team**. See Appendix A for contact details and the website.
- If you have complaints about the processing of your personal data, we recommend first discussing them with the research team. You may also contact the **Data Protection Officer of Erasmus MC** (see contact details at the end of this letter) or file a complaint with the **Dutch Data Protection Authority (Autoriteit Persoonsgegevens)**.

Where can you find more information about the study?

More information about the study can be found on the following website: <https://www.sinteronderzoek.nl/>. After the study is completed, the website will provide a summary of the study results.

11. Will you receive compensation for participating in the study?

You will **not receive payment** for participating in this study. However, you **will be reimbursed for your (extra) travel expenses**.

When you visit our research center, a form can be completed for this purpose. However, the costs of research instruments, extra tests, and treatments that are part of the study are fully covered.

12. Are you insured during the study?

Insurance has been arranged for everyone participating in this study. The insurance covers damages caused by the study, but **not all damages**. More information about the insurance and its exceptions can be found in **Appendix B**, including who to contact to report damages.

13. We inform your treating specialist

The researcher will send an email to your treating specialist to inform them that you are

participating in the study. This is for your own safety. Your treating specialist will also be informed of any incidental findings discovered during the study that may be relevant to your health. If you do not agree with this, you can indicate your objection on the consent form in **Appendix E**.

14. Do you have questions?

Questions about the study can be directed to the research team. If you want advice from someone independent, you can contact the **independent expert**. Contact details are provided in **Appendix A**. This person is knowledgeable about the study but is not involved in conducting it.

Do you have a complaint?

Discuss it with the researcher or your treating physician. If you prefer, you can contact the **complaints committee** of your hospital. See **Appendix A** for contact details.

15. How do you give consent for the study?

You can first take your time to consider the study. Then, you inform the researcher whether you understand the information and whether you want to participate. You can do this via email at SINTERonderzoek@erasmusmc.nl.

If you choose to participate, the researcher will send the consent form so that it can be completed **digitally with an electronic signature via ValidSign** (see **Appendix D** for instructions on electronic signing). If you prefer to sign with a traditional pen, you can do so at the appointment for the blood sample. Both you and the researcher will receive a signed copy of this consent form.

Thank you for your time.

16. Appendices to this information

- **A. Contact information**
- **B. Information about insurance**
- **C. Schedule of study procedures and overview of measurements**
- **D. Information about electronic signatures via ValidSign**
- **E. Consent form for visits to the research center**

Appendix A: Contact Information for Erasmus MC

Researcher:

Dr. Fernando Rivadeneira, Principal Investigator, Professor of Translational Skeletal Genomics, Department of Internal Medicine, Erasmus MC, Rotterdam

Email: f.rivadeneira@erasmusmc.nl

Tel: 010-704 40 15

Independent Expert:

Dr. Alice Brooks, Clinical Geneticist, Department of Clinical Genetics, Erasmus MC, Rotterdam

Tel: 010-703 20 48

Complaints:

If you are not satisfied with the research or the treatment, you can contact the independent complaints officer at Erasmus MC. A digital complaints form is available on the Erasmus MC website at: <https://www.erasmusmc.nl/nl-nl/patientenzorg/klachtenopvang-en-klachtenbemiddeling>

After completing the form, it will automatically be sent to the complaints officer.

If you are unable to submit the digital form, you can also send your complaint by post: Erasmus MC, Secretariat Complaints Handling (GK-745), Antwoordnummer 55, 3000 WB Rotterdam.

Please include your name, patient number (if applicable), the name of the study, and your contact information. The complaints officer will contact you after receiving your letter.

Data Protection Officer of the Institution:

The Data Protection Officer at Erasmus MC can be reached via the Secretariat of the Legal Affairs Department.

Email: functionaris.gegevensbescherming@erasmusmc.nl

Tel: 010-703 4986

For more information about your rights:

For questions or more information about your rights, you can contact the Data Protection Officer or the Dutch Data Protection Authority (Autoriteit Persoonsgegevens).

Appendix B: Information about Insurance

Did you suffer damage as a result of the study? If so, report it to this insurer:

Erasmus MC has taken out insurance for everyone participating in the study. This insurance covers damage caused by your participation in the study. It applies to damage that occurs during the study or within four years after the end of your participation. Any damage must be reported to the insurer within four years.

De verzekeraar van het onderzoek is:

Naam verzekeraar:	Centramed B.A.
Adres verzekeraar:	Postbus 7374 2701 AJ Zoetermeer
Telefoon:	070 301 70 70
E-mail:	schade@centramed.nl

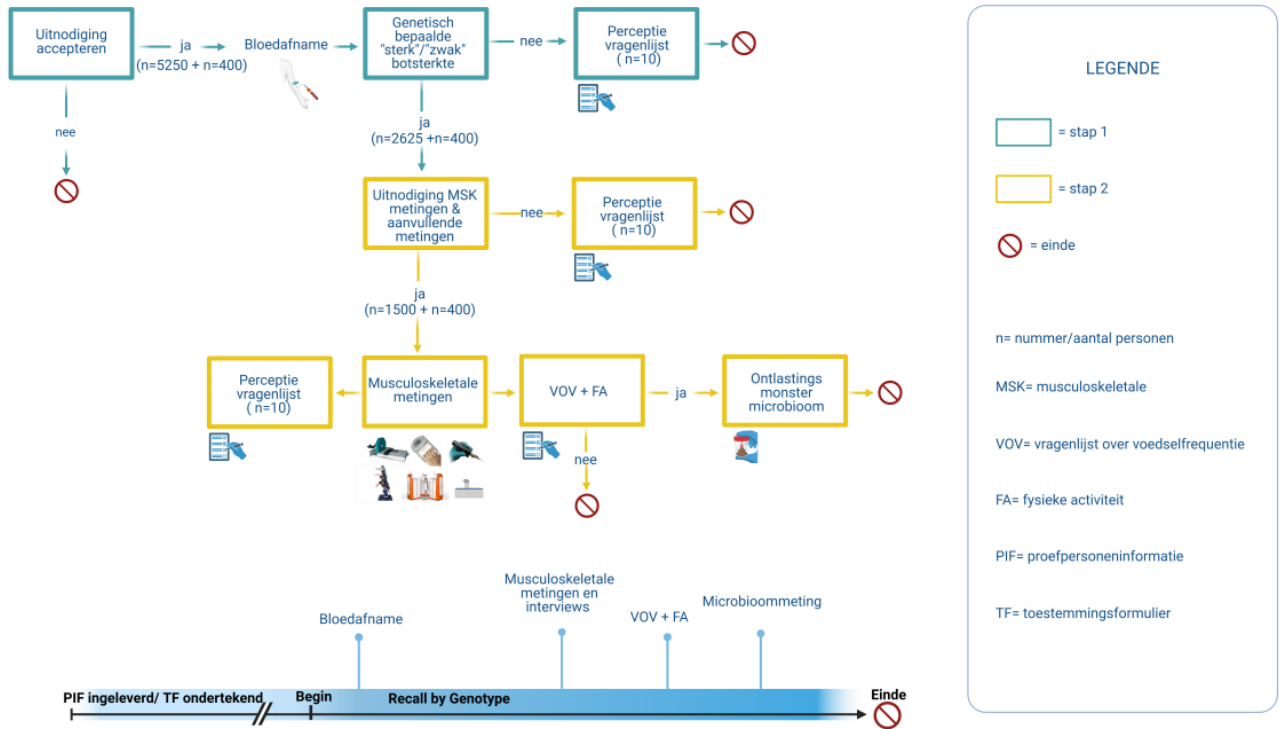
The insurance covers up to €650,000 per participant, with a total ceiling of €5,000,000 for the entire study, and a maximum of €7,500,000 per year for all studies by the same sponsor.

Please note: the insurance does **not** cover the following:

- Damage caused by a risk that was described to you in this letter. However, this does not apply if the risk turned out to be greater than expected or if the risk was very unlikely.
- Damage to your health that would have occurred even if you had not participated in the study.
- Damage caused because you did not follow instructions or guidance properly.
- Damage to the health of your children or grandchildren.
- Damage caused by an existing treatment method or research into an existing treatment method.

These provisions are included in the “*Besluit verplichte verzekering bij medisch-wetenschappelijk onderzoek met mensen 2015*”. This decision is available in the Dutch Government’s legal database: <https://wetten.overheid.nl>.

Appendix C: Schedule of Study Procedures and Overview of Measurements



Appendix D: Information about Electronic Signatures via ValidSign

This appendix explains how to digitally sign the consent form for your visit to Erasmus MC for blood collection. If you have any questions or encounter problems, please contact the SINTER research staff at sinter-onderzoek@erasmusmc.nl.

Step 1: Preparation

SINTER prepares the consent form for you in ValidSign. For this, SINTER uses your email address and mobile phone number. If we do not yet have these details, we will ask you to provide them.

Step 2: Sending

You will receive an email (sender: Erasmus MC – name of research staff member) asking you to electronically sign the consent form. Use the link **“Check the documents”** in the email to open ValidSign, the platform where you can sign the form. We recommend doing this on a computer, as text and fields may be too small on a smartphone.

Step 3: Log in with access code

ValidSign will ask you to log in using an access code sent to your email address. Erasmus MC uses this extra step (two-step verification) to ensure the consent form reaches the correct person. Enter the code you received online to proceed.

Step 4: Review documents

Once logged in, you will see the information folder and the consent form, which needs to be signed on the last pages. Please read everything carefully and fill in all marked fields; otherwise, the form is not legally valid. Clicking a field will show you what to do. If an item does not apply—for example, if you are not participating in the measurements at the research center—select **“No.”**

Step 5: Signing

After reviewing the documents, you can sign the consent form on the last pages. Make sure all marked fields are completed; incomplete forms are not legally valid. If a field does not apply, such as measurements you are not participating in, click **“No.”**

Step 6: Confirmation of signing

You will receive confirmation in the ValidSign platform that the document has been successfully signed. You can still view or download the documents via the button on the screen.

Step 7: Downloading

After both you and the SINTER team have signed the consent form, you will receive an email allowing you to download the signed document. Click the **“Download the documents”** button in the email to open ValidSign again, where you can download and save the document to your computer.

Appendix E: Participant Consent Form – Research Center Visit

Belonging to: **Erasmus Medical Center Skeletal Fragility (SINTER) Study**

- I have read the information letter and had the opportunity to ask questions. My questions have been answered satisfactorily, and I have had enough time to decide whether I want to participate.
- I understand that participation is voluntary. I also know that I can decide at any time not to participate or to withdraw from the study. I do not have to explain why I wish to stop.
- I give the researcher permission to inform my treating specialist(s) that I am participating in this study.

- I give the researcher permission to request medical information from my treating specialist(s).
- I give the researcher permission to inform my specialist of any unexpected findings from the study that may be important for my health.
- I give the researchers permission to collect and use my data and biological material. This will only be done to answer the research question of this study.
- I understand that some people may access my full data to monitor the study. Who these people are is described in the information letter. I give these people permission to view my data for this purpose.
- I understand that my coded data may be sent to countries outside the EU where EU privacy regulations do not apply. If my data are processed outside the European Economic Area (EEA), the researcher will take measures to protect my privacy as much as possible. I give my consent for this.

Please indicate “Yes” or “No” in the table below.

I give permission for my data to be stored and used for other research, as described in the information letter.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
I give permission for my (remaining) biological material to be stored and used for other research, as described in the information letter. The biological material will be kept for 15 years for this purpose.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
I give permission to be asked, after this study, if I would like to participate in a follow-up study.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
I give permission for my data to be used for training and educational purposes.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
I give the researchers permission to inform me, after the study, which group I was assigned to.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

- I declare that I wish to participate in this study.

My name is (participant):

Date of birth:

Patient number:

Signature:

Date: __ / __ / __

NL79302.078.24/ eraSmus medlsch ceNTrum skEletaal bReekbaarheid (SINTER) study

Page | 17 of 15

Version 1.2

I declare that I have fully informed this participant about the above-mentioned study.
If, during the course of the study, information becomes available that may influence the participant's consent, I will inform the participant in a timely manner.

Name of researcher (or representative): **Fernando Rivadeneira**

Signature:

Date: __ / __ / __

<if applicable>

Additional information was provided by:

Name:

Position:

Signature:

Date: __ / __ / __