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Patient Information Letter and Informed Consent

PATIENT INFORMATION SHEET

Interferential Stimulation for Maintaining Bone Mineral Density During GnRHa Treatment

Part 1

Introduction

You have been asked to be part of a research study. Before you can be entered into the study, you must be given information about the study to help you decide if you want to participate. The study doctor or study staff will go over the information in this form with you and will answer your questions about what this form is for, your rights as a participant, and about other issues related to the study. You should not sign this form unless you are satisfied with the answers to your questions and decide that you want to be part of this study.

What is the purpose of the study?

You are being asked to participate in a research study for a device called the RS-4i Sequential Stimulator.

The purpose of this study is to gather data on the use of the RS-4i Sequential Stimulator in the treatment of patients receiving Zoladex®.

It is not expected that the stimulator will be used as standard therapy for patients receiving Zoladex. Women using Zoladex therapy are being selected for this study because they may benefit from the stimulator.

The study doctor and study centre are being paid by RS Medical, the study sponsor, to conduct this study.

If you decide to enter the study, you will be one of 30 participants in the UK, ages 18 and older, in this study. This study will take place at The Women's Centre, John Radcliffe Hospital, Oxford, UK.

Your participation in the study should last approximately six months. You will come to the study doctor's clinic for at least eight visits.

Why have I been chosen?

You are being considered to participate in this clinical trial because you are a pre-menopausal woman between the ages of 18 and 46 who is scheduled to receive a GnRH agonist (Zoladex).

One of the drawbacks of Zoladex is that it may cause a small amount of bone density loss, which is the main reason its use is limited to six months. These changes in bone density mimic those that occur around the time of menopause. Electrical stimulation may be a safe way to reduce or eliminate loss of bone density.

Do I have to participate?

It is up to you to decide whether or not to participate in this study. If you do decide to participate, you will be given this information sheet to keep, and you will be asked to sign a consent form. If you decide to participate, you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time or a decision not to participate will not affect the standard of care you receive.

What will happen to me if I participate?

If you agree to participate, and you meet the entry requirements, your participation will last for about 6 months. The explanation below indicates what will happen at each stage of the study. However, you will continue to receive routine care and check-ups as would be the case if you did not enter the study.

This study will have three groups with ten patients in each group. Two groups will receive electrical stimulation and drug treatment, and the third (or *control*) group will receive the current standard-of-care: only the injected drug. If you qualify and agree to participate in this study, you will be assigned randomly to one of three groups:

Group 1: Drug treatment with electrical stimulation at a constant level for one hour per day

Group 2: Drug treatment with electrical stimulation at a continuously varying level for one hour per day

Group 3: Drug treatment only, with no electrical stimulation

Electrical current will be generated by a hand-held device. The device connects to four pads (electrodes), which are placed on the middle and lower spine. If you are fairly sensitive to electrical current, you may feel the sensations associated with receiving electrical stimulation from either type of electrical stimulation used in this study. In addition, you will have the RS-LB Low Back Conductive Garment available as an optional accessory to assist with proper and consistent electrode pad placement in the difficult-to-reach low back area.

If you are assigned to one of the first two groups, you have an equal chance of receiving either type of electrical stimulation in this study. You will not know and the study doctor will not know which type of electrical stimulation you are receiving. Most people experience little noticeable sensation from the electrical stimulation.

A member of the study staff will teach you how to use the study device and how to place the electrodes. Everyone in Groups 1 and 2 of the study will use the same kind of study device, but Group 1 participants will receive *constant* small electrical nerve stimulation from the study device, and Group 2 participants will receive *varying* small electrical nerve stimulation. You will receive the first one-hour stimulation session in the study centre. You should ask any questions you have about doing it yourself at home at this time. After you have learned how to use the device, you will take it home and use it one hour every day for six months.

The study device must be used only by the person taking part in this study. It must be kept out of reach of children and others who might not be able to understand that the device is only for the use of the person taking part in this study.

If you have questions about electrical stimulation or the study device, please speak only to the research nurse who taught you how to use the study device. This ensures that the study doctor will not find out which type of stimulation you are getting. The study doctor and other staff are deliberately not told

which type of stimulation you are getting to avoid influencing their opinions about the treatment. Please avoid speaking to them about the device and about any sensations you experience while using the device.

Medications and Other Treatments

You must not start any new treatments that interfere with bone metabolism while you are in the study (check with the study doctor to determine which new treatments are acceptable). You may continue with your current treatments.

The study doctor will explain your options for various medications. If you and/or your study doctor believe that your symptoms require other treatments not provided in the study due to other health concerns, you will be asked to drop out of the study.

Initial Visit

Once you decide you want to be in the study and you have signed this consent form, you will come to the study centre for an initial visit. During this and any other visits, you do not have to answer any questions that make you feel uncomfortable.

During this initial visit, the study doctor or study staff will do the following:

- Verify that you meet specific criteria to be in the study. As part of the criteria, you will be asked to have a bone scan of your spine and hip.

- Take a short medical history.

- Teach you how to use the electrical stimulation device, if applicable.

- Teach you how to use the optional RS-LB Low Back Conductive Garment to assist with proper and consistent electrode pad placement in the difficult-to-reach low back area, if applicable.

Once you have finished the questionnaires, if you qualify for the study, you will be assigned randomly to one of the three study groups described above, and you will receive your first dose of Zoladex®.

Follow-Up Visits

After the initial visit, you will return to the study centre every 28 days to receive Zoladex® injections for six months after you start the study. The 3-Month and 6-Month visits to the clinic will include additional assessments and should last about 60 to 90 minutes each.

3-Month Visit

After three months of using the study device, you will return to the study doctor's clinic. At this visit, the study doctor or study staff will have you fill in questionnaires and administer your fourth dose of Zoladex®. At this visit, the study doctor or study staff will take a bone scan of your spine.

6-month Visit

After six months of using the study device, you will return to the study doctor's clinic for your final visit. At this visit, the study doctor or study staff will take a bone scan of your spine.

Your participation in the study will end after this visit.

What do I have to do?

If you decide to participate in this research study, following instructions and completing study visits are important to make sure that the study results are accurate. If you wish to stop participating in the study or if you find you have not followed the instructions listed above, it is important that you notify the study doctor or study staff. Your study doctor will give you more information.

What is the device that is being tested?

The device being tested is the RS-4i Sequential Stimulator, an external electric stimulator that incorporates traditional muscle stimulation and interferential current stimulation into one unit (only one modality operates at a time). When operating in the interferential current modality for pain relief, the RS-4i has been regulatory-approved for the following indications: relief of acute pain; and relief of and management of chronic pain. This study will allow the Sponsor, RS Medical, to investigate a new indication and to determine which of the two forms of interferential stimulation to be administered is more effective in reducing patients' bone loss as a result of GnRH agonist therapy.

What are the alternative treatments?

Participating in this study should not be a substitute for obtaining usual or ongoing medical care.

Since a loss in bone mineral density (BMD) is associated with Zoladex, some patients receiving this treatment choose to use an "add-back" therapy to minimize the loss of bone mineral density. If you choose to use add-back therapy, you have the option of using it either during or after your six-month-long Zoladex treatment; however, patients choosing to use add-back therapy during the six-month treatment period will not be included in this study.

The study doctor will explain more about the risks and benefits of your participation in this study as compared to the risks and benefits of other treatments. You are not required to participate in this study to receive treatment for your condition.

What are the potential risks?

The risks associated with this study are those normally associated with transcutaneous (on-the-skin) electrical stimulation therapy. These risks or potential complications include the following:

- Skin irritation at the electrode site (allergic reaction to electrode material)
- Surface burns at the electrode site (electrical burn)
- Electrical shock

Please notify the person who taught you how to use the device if you experience any of these or any other side effects during the study. You will be monitored throughout the study to minimize risks. These risks will be minimized if you follow the instructions provided by the study staff on the use and care of the stimulation study device.

Additionally, the study device has built-in checks to make sure that malfunctions, such as the delivery of a higher level of stimulation than anticipated, do not occur. The study device will not allow electrical delivery if it detects device malfunctions, and it also has a limit on the amount of electrical energy it can deliver.

As with any medical device use, there may be unanticipated adverse (bad) side effects. If new information is discovered that might change your decision to stay in this study, your study doctor will tell you about it.

Risks for women who could become pregnant

The risks to an unborn baby from the device are not known. If you are pregnant or become pregnant, the study device or the Zoladex may cause problems to your unborn baby. You must confirm that you are not pregnant and don't plan to become pregnant during the study. Your study doctor may ask you to have one or more pregnancy tests during the study.

If you think there is a chance that you have become pregnant during the study, you must tell the study doctor immediately. If you become pregnant, you will return the study device and be removed from the

study. The study doctor will track your pregnancy and report the outcome to the sponsor and the Ethics Committee.

What are the potential benefits?

By participating in the study, you will help provide information that will determine which of the potential two types of electrical stimulation may be more appropriate for preventing bone loss. The benefit of electrical stimulation to you directly cannot be guaranteed. Your condition might not improve or might get worse while you are in this study. Information gained from this study may help RS Medical understand the role of electrical stimulation in the treatment of patients who might otherwise suffer bone loss.

What happens when the research study stops?

When this study comes to an end, should you require further treatment, your study doctor will discuss the treatment options available to you.

What if there is a problem?

Any complaint about the way you have been treated during the study or any possible harm you might suffer will be addressed. Detailed information is provided in Part 2 of this document.

Will my taking part in this study be kept confidential?

Yes. All the information about your participation in this study will be kept confidential. Details are included in Part 2.

Contact for Further Information

Please ask your study doctor if you require any more information about this treatment. You may ask any questions at any time about your rights as a participant in a research study or about the research study itself. You may also contact your GP or consultant if you would like some independent advice before entering the study. You may contact Dr. Kennedy at 01865/22.10.03 to discuss the study further. For emergencies, you may contact the study team doctor on call at 01865/74.11.66.

This completes Part 1 of the Information Sheet.

If the information in Part 1 interests you, and you are considering participation, please continue to read the additional information in Part 2 before making any decisions.

Part 2

What if new information becomes available?

Sometimes, during the course of a research project, new information may become available about the device that is being studied. If this happens, your research doctor will tell you about it and discuss with you whether you want to continue in the study. If you decide to withdraw, your research doctor will make arrangements for your care to continue. If you decide to continue in the study, you will be asked to sign an updated consent form. Also, on receiving new information, your research doctor might consider it to be in your best interests to withdraw from the study. He will explain the reasons and arrange for your care to continue. If the study is stopped for any other reason, you will be told why, and your continuing care will be arranged.

What will happen if I don't want to carry on with the study?

You are free to withdraw from the study at any time, and doing so will not affect your access to medical care; however, we will need to use the data collected up to the point of your withdrawal.

What if there is a problem?

Complaints:

If you have a concern about any aspect of this study, you should ask to speak with the researchers, who will do their best to answer your questions (Telephone number 01865/221003). If you remain unhappy and wish to complain formally, you can do this through the National Health Service (NHS) Complaints Procedure. Details can be obtained from the hospital.

Harm:

In the event that something does go wrong and you are harmed during the research study, there are no special compensation arrangements. If you are harmed due to someone's negligence then you may have grounds for a legal action for compensation against RS Medical or the NHS Trust, but you may have to pay your legal costs. The normal National Health Service complaints mechanism will still be available to you (if appropriate).

RS Medical (the study sponsor) does not believe that you will suffer injury by participating in this study. You should know, however, that in the event you do suffer injury as a result of participating in this study, medical treatment, including emergency treatment and follow-up care, will be provided or arranged by your physician. Your study doctor is qualified and knows how to treat you if such an event occurs.

Compensation for any injury caused by taking part in this study will be in accordance with the guidelines of the Association of the British Healthcare Industry (ABHI). The ABHI has some clear guidelines about compensation, and if you wish to read the ABHI Guidelines, your hospital study doctor will give you a copy. RS Medical has agreed to abide by the ABHI Guidelines.

To clarify, RS Medical will pay compensation if the injury probably resulted from either of the following:

- The device being tested as part of the trial protocol
- Any test or procedure you received as part of the trial

Any payment would be without legal commitment. Please ask if you would like more information about this.

RS Medical would not be bound by these guidelines to pay compensation where the following occur:

The injury resulted from a procedure outside the trial protocol
The protocol was not followed

The Directives of the European Union and the law concerning medical devices require that RS Medical take out an insurance policy for patients participating in a clinical study of this nature. This insurance policy has been purchased from Gerling General Insurance Company, UK Branch (1 Great Tower Street, London, EC3R 5AA), under the policy number 62/904917/D.

Compensation and additional costs

You will receive up to a maximum of £100 to reimburse travel expenses you incur during your participation. You will be sent compensation from the sponsor at the completion of all of your study visits. The study doctor or study staff can tell you more about when and how you will receive compensation.

If you have any questions, please ask the study doctor or the study staff.

Will my taking part in this study be kept confidential?

If you consent to take part in the research, any of your medical records identifying yourself and the data collected about yourself and your trial participation may be inspected by researchers or the company sponsoring and/or the company organizing the research for purposes of analyzing the results. Your records and data may also be reviewed by people from the sponsor company, the hospital Trust Research & Development department, and regulatory authorities for audit and monitoring purposes to ensure that the study is being carried out correctly. Your name will not be disclosed outside the hospital.

British law requires the study doctor to protect the privacy of your records. However, absolute privacy cannot be guaranteed because of the need to disclose information as described above. After the study doctor shares your records with the sponsor and others, the law may no longer protect the privacy of your records, and they might be further disclosed.

If you would like to know how the sponsor, RS Medical, will protect the privacy of your records, ask your study doctor how to obtain this information.

You have the right to see and copy your records in the study doctor's possession. However, by signing this consent you agree that you might not be able to review some of your records related to the study until after the study is done. At that time your right to access will be restored.

With your agreement, your involvement in the study will be made known to your General Practitioner and/or care clinician; however, you will be asked to consent to this within the consent form before they are contacted.

What will happen to the results of the research study?

At the end of the study the results will be analyzed and may be used to get approval for the device in the indication for which it is being clinically tested. The results may also be published in scientific journals. If you choose to join this trial and the results are published, your identity will not be disclosed. You may contact your hospital study doctor for any further information about the study results.

Who is organizing and funding the research?

RS Medical, the manufacturer of the devices to be used in this study, is the sponsor of the study.

Who has reviewed the study?

This study has been reviewed by the Medicines and Healthcare products Regulatory Agency, MHRA (a UK central government office responsible for overseeing the development of new products), the Oxford Research Ethics Committee B (REC Reference 06/Q1605/56), and the research ethics committee at your local hospital. All of these official bodies have approved the study and have agreed that it may proceed.

The Oxford Research Ethics Committee B is an ethics committee that is independent of the study doctor and the company paying for this research to be done (the sponsor). The purpose of the Ethics Committee is to protect the rights and safety of people who volunteer to take part in research studies. You may call if you have questions about your rights as a research participant or if you have any concerns about participating in this study.

Contact for Further Information

Before beginning the study and any time during the study, the study doctor and/or the study staff will answer any questions you have regarding the study or your participation in the study. You may call the following numbers if you have any questions about the study or your experience in the study. You should call right away if you feel you have had an injury, illness, or side effect.

Study Doctor: Dr. Stephen Kennedy **Telephone Number:** 01865/22.10.03

Study Coordinator: Fenella Roseman **Telephone Number:** 01865/22.10.03

After Office Hours: 01865/74.11.66

Please ask your study doctor if you require any more information about this study. You may ask any questions at any time about your rights as a participant in a research study or about the research study itself. You may also contact your GP or consultant if you would like some independent advice before entering the study.

Thank you for taking the time to read this information sheet.

You will be given a copy of the information sheet and a signed consent form to keep.

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Oxford, OX3 9DU, U.K.

Centre Number:
Study Number:
Patient Identification Number for this trial:

PATIENT CONSENT FORM

Title of Project: Interferential Stimulation for Maintaining Bone Mineral Density During GnRHa Treatment

- Please initial box
- I confirm that I have read and understand the information sheet (version 27062007 1407) for the above study, and I have had the opportunity to ask questions.
 - I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.
 - I understand that sections of my medical notes may be reviewed by responsible individuals from RS Medical, their designates, or regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records.
 - I understand that my data will be held confidentially on a computer at the hospital and by RS Medical or their designates. I give permission for these data to be held on computer by these parties
 - I consent to my data being sent outside the European Union for use by RS Medical and/or any party where responsibility has been delegated on behalf of RS Medical, providing that the same level of protection of my privacy is applied.
 - I give permission for staff treating me to contact my General Practitioner (GP) or my primary care clinician.
 - I agree to take part in the above study.

Patient (or legal representative if patient is unable to give consent):

Name Signature Date

Investigator:

Name Signature Date

Name of person taking consent Signature Date
(if different from researcher)

copy 1: patient; copy 2: researcher; copy 3: hospital notes