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14 Appendix I – Clinical Study Documents

The areas in grey do not apply to the part of the study that you are participating in and can be disregarded



Department of Endocrinology
William Harvey Research Institute
Barts & The London Medical School
Charterhouse Square
London EC1M 6BQ

14.1 Patient information Sheet

Version 3, September 2008

Cardiac and skeletal muscle energy metabolism in abnormal growth hormone states

Ref: 06/Q0401/53

You are kindly invited to take part in this clinical research study carried out in the Endocrine Department in St. Bartholomew's Hospital. This information sheet is designed to help you make up your mind whether you want to participate in this study or not. Before you make up your mind, you should read carefully the information below and discuss it with your family, friends or your GP. Please take time to ask questions. You should clearly understand the potential benefits and the risks involved so that you make the decision that is right for you.

As participation is entirely voluntary you can change your mind at any time (before the start of the study or after the study has begun). This is entirely your decision and no reason needs to be given. Before this study can start, it must be approved by an independent body called the Research Ethics Committee. Declining to participate in this study or withdrawing from participation will not, in any way, affect negatively the care you receive from the medical staff.

What is the purpose of the study?

Abnormal growth hormone (GH) levels can have a profound effect on the function of your heart. In GH excess (acromegaly) this could result in an enlarged heart, in abnormal function of your heart and hypertension (high blood pressure). In GH deficiency it can result in narrowing of the arteries of the heart (the coronary arteries) and can result in heart disease. The study is designed to carry out a detailed investigation of your heart and of your muscles to detect the energy level of the heart muscle and skeletal muscle, and to see if you have any narrowing of in the coronary arteries.

Why Have I been chosen?

You have been chosen because you have abnormal growth hormone levels, either a high level (acromegaly) or growth hormone deficiency, and you are about to start therapy for one of these conditions.

Do I have to take part?

It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part 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 take part, will not affect the care you receive. If you

chose to withdraw from the study any information that has been formerly collected will be processed as part of the study.

What will happen to me if I take part?

The studies will be performed on three time points in next 24 months;

The first time point will be before you start treatment for your pituitary disease recommended by your doctor with either:

- Surgery, drug injections or radiotherapy if you have a high GH condition or
- GH replacement if you have a deficiency in growth hormone

On this occasion you will have investigations in Oxford and in London and we will provide instructions and a map where do you need to go.

The second group of investigations will be 3-6 months after your growth hormone and IGF-I levels (a hormone reflecting GH levels) reached the normal range. On this occasion you will have investigations in Oxford or in London.

The third investigation will be 1-2 years after starting therapy. On this occasion you will have investigations again both in Oxford and in London.

On each occasion you will need to attend the Magnetic Resonance Imaging (MRI) unit

We will ask you to travel to Oxford the day before the test (if you do not live in Oxford) and we will book accommodation for you next to the hospital. The next morning, on the day of the tests first you will have a blood sample taken for glucose, insulin, fatty acids and other metabolic samples. You will need to attend the investigations fasting (no food or drinks apart from water after 10 pm the evening before). Overall, 30 ml (approximately 3 tablespoons) of blood will be taken on each occasion.

A magnetic resonance study (MRS) will be performed on heart and skeletal muscle. This scan will allow us to measure the efficiency with which your heart muscle produces the energy it requires to maintain its function. This is done using a magnetic resonance scanner very similar to the one you experienced during investigations for your pituitary disease. The scanner can be noisy, therefore we will provide you with earplugs and headphones and you can listen to music of your choice during the scan. You may find magnetic resonance scans slightly uncomfortable as your head and upper body are in the scanner, particularly if you suffer from claustrophobia. We will be in contact with you throughout the scan and if you feel uncomfortable at all then we will stop the scan straight away.

First we will test your heart and leg muscles at rest. This scan will take approximately 40 minutes and you will then have a break and be given some refreshments before going on to the rest of the assessments.

Then we will test your heart and leg muscles during exercise. During exercise the heart and leg muscles require more energy and we would like to assess the efficiency with which they produce energy. This time we will ask you to exercise your legs for eight minutes (bending your feet up and down) whilst in the scanner. We will scan your heart both during and after exercise and after a short break we will perform a similar scan on the leg muscle and this time we will ask you to continue the leg exercises until you feel tired. These studies will take an hour to complete.

- We also would like to assess the heart size and function using another type of magnetic resonance machine to obtain magnetic resonance imaging (MRI) pictures. This will be similar to the MRS scan and this time we will ask you to hold your breath for up to 15 seconds during some scans. This test will take approximately 40 minutes.
- Physical examination by the study doctor and ECG (heart tracing).

- You will have a questionnaire to be filled regarding possible problems with disturbed sleep (“sleep apnoea”).
- Echocardiography (ultrasound of your heart) to assess your heart function, which will take about 15 minutes in total.
- Measurement of oxygen supply to your calf muscle. This is done using Near infra-red spectroscopy (NIRS) which is a simple test and does not involve any exposure to radiation. You will be asked to lie on a bed and have a small light probe placed over the calf muscle and then will be asked to exercise by moving your ankles for 8 minutes in the same way as earlier whilst in the magnetic resonance scanner, and for the same length of time as earlier. The whole test will take approximately 45 minutes

We may suggest that you undergo your heart MRI in Oxford or at our new cardiac MRI Unit at the London Chest Hospital, East London, part of Barts & the London NHS Trust. We will decide this based on the availability of slots. If you go the London Chest Hospital for cardiac MRI you will not need to fast for this part of the study. We may also perform you echocardiogram, ECG, examination and blood tests in London rather than in Oxford.

On the first and last time point (before start of therapy and 1-2 years after therapy) you will have an electron beam computer tomography (a CT scan) taken of you heart in the European Scanning Centre in London. This investigation studies your coronary arteries and gives information if you have an increased chance to develop a heart attack. It will also include a picture of your stomach to see the amount of fat tissue inside. The investigation will involve lying in the CT scanner and will last 10 minutes.

Your participation in the study will last for two years in total. We anticipate that all the participants will be tested in a period of three years between October 2008 and July 2011. Your travel costs to the investigation sites and the overnight stays will be reimbursed.

What do I have to do

- You will need to attend the cardiac investigations in Oxford three times when you will need to be fasting overnight and
- You may need to attend the London Chest Hospital three times and
- You will need to attend the electron beam CT investigation in London on two occasions at the very beginning and at the end of the study.

Your treatment for the abnormal growth hormone levels or other conditions will continue as usual.

If you are a woman of child bearing age and you became pregnant before or during the study, you should notify Dr Thomas or Dr Korbonits.

What are the potential risks associated with the study?

Apart from the usual mild discomfort while giving the blood sample, no side effects are associated with sample collection.

The CT scan will involve a very small amount of radiation; the risk is similar to taking two x-ray pictures.

In order to assess your heart as much as possible during the MRI we will give you two injections. Adenosine injection will cause your heart to beat fast to allow us to look for any previously undiscovered angina. This injection can give a sensation of palpitations, fast breathing and tightness in the chest. These feelings are short-lived. In very rare cases the heart can start to beat with a persistent fast or irregular rhythm after this injection. If this were to occur we would give treatment to make it go back to a normal rhythm. We will not give you this

injection if you have significant asthma. The second injection, gadolinium, allows us to look for any scarring or heart damage. We do not give this injection to anyone with significant kidney disease (which we will can tell from your blood tests). In very rare situations people may have an allergic reaction to these injections. In the unlikely event that this were to occur you would receive all appropriate medical care. The unit are very experienced with these injections and given them daily.

If you are a woman of child-bearing age and you became pregnant during the study, we will delay investigations for after the pregnancy.

What are the possible benefits of this study?

This research will help our understanding of the underlying abnormalities associated with growth hormone excess and growth hormone deficiency, particularly those relating to heart and muscle function and for coronary artery disease. It may help to explain the adverse effects of too much and of too little growth hormone in people with pituitary disease.

The result of your investigations may help us to recognise possible problems of your heart function and to detect coronary disease. Should any of the tests carried out lead to any new diagnoses, we would like to inform your GP about that. These could be potentially important results that might lead to initiation of further therapy for your disease. The study generally will help us to understand abnormal heart function patients with growth hormone abnormality. It is however important to recognise that this research may not benefit you directly. The information we get from this study may help us to improve treatment of future patients.

What if new information becomes available?

Sometimes during the course of a research project, new information becomes available which may influence your continual participation. 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.

What happens when the research study stops?

Your treatment will carry on as necessary. Your blood samples will be disposed of on completion of the study.

What are our responsibilities to you as investigators?

If you experience any ill effects as a result of your participation, then we will take care of your medical needs. If there are any new findings during the course of the study that may affect the validity of the study, or your participation in it, this will be made available to you. You will have access to the study team at all times by contacting Dr Julia Thomas, Dr Marta Korbonits or Professor Ashley Grossman (see below). You will continue follow-up in the Endocrinology Outpatient Clinic as usual.

What happens if there is a problem?

Queen Mary University of London has agreed that if you are harmed as a result of your participation in the study, you will be compensated, provided that, on the balance of probabilities, an injury was caused as a direct result of the intervention or procedures you received during the course of the study. These special compensation arrangements apply where an injury is caused to you that would not have occurred if you were not in the trial. These arrangements do not affect your right to pursue a claim through legal action. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms should be available to you.

If you need further advice please contact Patient Advice and Liaison Service (PALS) Telephone: 020 7943 1335, Minicom: 020 7943 1350
E-mail: pals@bartsandthelondon.nhs.uk

Will my taking part in this study be kept confidential?

All information which is collected about you during the course of the research will be kept strictly confidential. If you consent to take part in the research the people conducting the study will abide by the Data Protection Act 1998, and the rights you have under this Act. The result of the blood test and imaging investigations will be stored marked only with your initials and an ID number so that you cannot be recognised from it.

Your own GP and other medical practitioners involved in your care will be notified of your participation in the trial unless you indicate otherwise.

What will happen to the results of the research study?

The results will be published in a scientific medical journal and may be presented at national and international meetings. If you wish to obtain a copy of the publication, please contact the principal investigator. You will not be identified in any publication/presentation.

Who is organising and funding the study?

This study is based within the Department of Endocrinology at St. Bartholomew's Hospital. The principal investigator is Dr Marta Korbonits. This study is an independent research project within the Department and has been designed by the study investigators. We plan to obtain funding from Medical Research Organisations such as the British Heart Foundation as soon as we have pilot (preliminary) data from some patients.

Who has reviewed the study?

The Riverside Research Ethics Committee has reviewed the study.

Are there any payments involved?

Patients are not paid for their direct participation in this study. Additional costs (e.g. travel and accommodation costs and cost of breakfast on the Oxford study days) will be reimbursed.

IF YOU REQUIRE FURTHER INFORMATION

If you have any queries or questions about this study, or if you wish to withdraw from the study, you may do so without justifying your decision and your future treatment will not be affected. For additional information or if you need to contact the study team now or in the future, please contact us on the details below.

Thank you

Dr Márta Korbonits
Principal Investigator
Department of Endocrinology,
King George V building, St. Bartholomew's Hospital
West Smithfield, London EC1A, 7 BE, UK, Telephone 020 7882 6238

Dr Julia Thomas
Telephone 020 7882 6117 E-mail j.d.thomas@qmul.ac.uk

Prof Ashley Grossman
Telephone 020 7601 8343

CONSENT FORM FOR PATIENTS (Version 1 Dated 6.7.2006)

Title of project: Cardiac and skeletal muscle energy metabolism in abnormal growth hormone states

Principle Investigator Prof M Korbonits

14.2 Consent form

Centre Number: 1 Study Ref Number: 06/Q0401/53
Patient Identification Number for this trial:

Please initial box to indicate agreement

1.	I confirm that I have read and understand the information sheet dated September 2008 (version 3) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	
2.	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.	
3.	I understand that relevant sections of any of my medical notes and data collected during the study, may be looked at by responsible individuals from regulatory authorities or from the Barts and the London/ Queen Mary University of London , where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.	
4.	I agree to my GP being informed of my participation in the study.	
5.	I agree to take part in the above study.	

Name of Patient

Date

Signature

Name of Person taking consent
(if different from Investigator)

Date

Signature

Investigator

Date

Signature

14.3 ACROQoL

ACROMEGALY- QUALITY OF LIFE QUESTIONNAIRE

(ACROQoL)

Today's date

<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
----------------------	----------------------	----------------------	----------------------	----------------------	----------------------	----------------------	----------------------

Day

Month

Year

INSTRUCTIONS FOR ANSWERING THE QUESTIONNAIRE

In the following pages there are sentences that describe some of the problems that acromegaly causes to people who, like you, suffer from this illness.

Each sentence is followed by some response options. Some of these refer to the **frequency**, while others refer to **how much you agree or disagree** with them.

Please, read each sentence carefully. Then tick the response option which best describes what you think is happening to you.

Remember that there are NO correct or incorrect answers. We are only interested in what is currently happening to you because of your acromegaly.

It is very important to answer all the questions.

Thank you very much for your collaboration

Because of my Acromegaly....

1. My legs feel weak

- Always
- Most of the time
- Sometimes
- Rarely
- Never

2. I feel ugly

- Completely agree
- Moderately agree
- Neither agree nor disagree
- Moderately disagree
- Completely disagree

3. I get depressed

- Always
- Most of the time
- Sometimes
- Rarely
- Never

4. I look awful in photographs

- Completely agree
- Moderately agree
- Neither agree nor disagree
- Moderately disagree
- Completely disagree

5. I avoid going out very much with friends because of my appearance

- Always
- Most of the time
- Sometimes
- Rarely
- Never

6. I try to avoid socialising

- Always
- Most of the time
- Sometimes
- Rarely
- Never

Because of my Acromegaly...

7. I look different in the mirror

- Completely agree
- Moderately agree
- Neither agree nor disagree
- Moderately disagree
- Completely disagree

10. People stare at me because of my appearance

- Completely agree
- Moderately agree
- Neither agree nor disagree
- Moderately disagree
- Completely disagree

8. I feel rejected by people because of my illness

- Completely agree
- Moderately agree
- Neither agree nor disagree
- Moderately disagree
- Completely disagree

11. Some parts of my body (nose, feet, hands,...) are too big

- Completely agree
- Moderately agree
- Neither agree nor disagree
- Moderately disagree
- Completely disagree

9. I have problems carrying out my usual activities (e.g. working, studying, doing household tasks, family or leisure activities)

- Always
- Most of the time
- Sometimes
- Rarely
- Never

12. I have problems doing things with my hands, for example, sewing or handling tools

- Always
- Most of the time
- Sometimes
- Rarely
- Never

Because of my Acromegaly....

13. The illness affects my performance at work or in my usual tasks

- | | | | |
|--------------------|--------------------------|--------------------|--------------------------|
| • Always | <input type="checkbox"/> | • Always | <input type="checkbox"/> |
| • Most of the time | <input type="checkbox"/> | • Most of the time | <input type="checkbox"/> |
| • Sometimes | <input type="checkbox"/> | • Sometimes | <input type="checkbox"/> |
| • Rarely | <input type="checkbox"/> | • Rarely | <input type="checkbox"/> |
| • Never | <input type="checkbox"/> | • Never | <input type="checkbox"/> |

14. My joints ache

- | | | | |
|--------------------|--------------------------|--------------------|--------------------------|
| • Always | <input type="checkbox"/> | • Always | <input type="checkbox"/> |
| • Most of the time | <input type="checkbox"/> | • Most of the time | <input type="checkbox"/> |
| • Sometimes | <input type="checkbox"/> | • Sometimes | <input type="checkbox"/> |
| • Rarely | <input type="checkbox"/> | • Rarely | <input type="checkbox"/> |
| • Never | <input type="checkbox"/> | • Never | <input type="checkbox"/> |

17. It is hard for me to articulate words due to the size of my tongue

- | | | | |
|--------------------|--------------------------|--------------------|--------------------------|
| • Always | <input type="checkbox"/> | • Always | <input type="checkbox"/> |
| • Most of the time | <input type="checkbox"/> | • Most of the time | <input type="checkbox"/> |
| • Sometimes | <input type="checkbox"/> | • Sometimes | <input type="checkbox"/> |
| • Rarely | <input type="checkbox"/> | • Rarely | <input type="checkbox"/> |
| • Never | <input type="checkbox"/> | • Never | <input type="checkbox"/> |

15. I feel tired

- | | | | |
|--------------------|--------------------------|--------------------|--------------------------|
| • Always | <input type="checkbox"/> | • Always | <input type="checkbox"/> |
| • Most of the time | <input type="checkbox"/> | • Most of the time | <input type="checkbox"/> |
| • Sometimes | <input type="checkbox"/> | • Sometimes | <input type="checkbox"/> |
| • Rarely | <input type="checkbox"/> | • Rarely | <input type="checkbox"/> |
| • Never | <input type="checkbox"/> | • Never | <input type="checkbox"/> |

18. I have problems with sexual relationships

- | | | | |
|--------------------|--------------------------|--------------------|--------------------------|
| • Always | <input type="checkbox"/> | • Always | <input type="checkbox"/> |
| • Most of the time | <input type="checkbox"/> | • Most of the time | <input type="checkbox"/> |
| • Sometimes | <input type="checkbox"/> | • Sometimes | <input type="checkbox"/> |
| • Rarely | <input type="checkbox"/> | • Rarely | <input type="checkbox"/> |
| • Never | <input type="checkbox"/> | • Never | <input type="checkbox"/> |

Because of my Acromegaly....

19. I feel like a sick person

- Completely agree
- Moderately agree
- Neither agree nor disagree
- Moderately disagree
- Completely disagree

21. I have little sexual appetite

- Always
- Most of the time
- Sometimes
- Rarely
- Never

20. The physical changes produced by my illness govern my life

- Completely agree
- Moderately agree
- Neither agree nor disagree
- Moderately disagree
- Completely disagree

22. I feel weak

- Always
- Most of the time
- Sometimes
- Rarely
- Never

Finally, please check that you have answered all the questions.

Once again thank you very much for your collaboration.



QoL-AGHDA

Quality of Life

Assessment of GH Deficiency in Adults

Country:

Center:

Patient number:

Patient initial:

Visit date:

--	--	--	--	--	--	--	--

LISTED BELOW ARE SOME STATEMENTS that people may make about themselves.

Read the list carefully and put a tick in the box marked YES if the statement applies to you.

Tick the box marked NO if it does not apply to you.

Please answer every item. If you are not sure whether to answer YES or NO, tick whichever answer you think is most true in general.

	YES	NO
I have to struggle to finish jobs	<input type="checkbox"/>	<input type="checkbox"/>
I feel a strong need to sleep during the day	<input type="checkbox"/>	<input type="checkbox"/>
I often feel lonely even when I am with other people	<input type="checkbox"/>	<input type="checkbox"/>
I have to read things several times before they sink in	<input type="checkbox"/>	<input type="checkbox"/>

	YES	NO
It is difficult for me to make friends	<input type="checkbox"/>	<input type="checkbox"/>
It takes a lot of effort for me to do simple tasks	<input type="checkbox"/>	<input type="checkbox"/>
I have difficulty controlling my emotions	<input type="checkbox"/>	<input type="checkbox"/>
I often lose track of what I want to say	<input type="checkbox"/>	<input type="checkbox"/>

	YES	NO
I lack confidence	<input type="checkbox"/>	<input type="checkbox"/>
I have to push myself to do things	<input type="checkbox"/>	<input type="checkbox"/>
I often feel very tense	<input type="checkbox"/>	<input type="checkbox"/>

	YES	NO
I feel as if I let people down	<input type="checkbox"/>	<input type="checkbox"/>
I find it hard to mix with people	<input type="checkbox"/>	<input type="checkbox"/>
I feel worn out even when I've not done anything	<input type="checkbox"/>	<input type="checkbox"/>

	YES	NO
There are times when I feel very low	<input type="checkbox"/>	<input type="checkbox"/>
I avoid responsibilities if possible	<input type="checkbox"/>	<input type="checkbox"/>
I avoid mixing with people I don't know well	<input type="checkbox"/>	<input type="checkbox"/>

	YES	NO
I feel as if I m a burden to people	<input type="checkbox"/>	<input type="checkbox"/>
I often forget what people have said to me	<input type="checkbox"/>	<input type="checkbox"/>
I find it difficult to plan ahead	<input type="checkbox"/>	<input type="checkbox"/>
I am easily irritated by other people	<input type="checkbox"/>	<input type="checkbox"/>

	YES	NO
I often feel too tired to do the things I ought to do	<input type="checkbox"/>	<input type="checkbox"/>
I have to force myself to do all the things that need doing	<input type="checkbox"/>	<input type="checkbox"/>
I often have to force myself to stay awake	<input type="checkbox"/>	<input type="checkbox"/>
My memory lets me down	<input type="checkbox"/>	<input type="checkbox"/>

Now please go back to the first question and make sure that you have answered "YES" or "NO" to every question, on all two pages of the questionnaire. Thank you for your help.

An instrument developed and validated by Galen Research, Manchester, UK (1-9) on commission by Pharmacia AB, Stockholm, Sweden.

References:

- 1 Hunt S.M., McKenna S.P. and Doward L.C. Preliminary report on the development of a disease-specific instrument for assessing quality of life in adults with growth hormone deficiency. *Acta Endocrinologica*, vol 128 (Suppl 2), pp 37-40, 1993.
- 2 McKenna S.P. and Doward L.C. Quality-of-Life Assessment of Adults with Growth Hormone Deficiency; Implications for Drug Therapy. (Review Article) *Pharmacoeconomics*, vol 6, pp 434-441, 1994.
- 3 Holmes S.J., McKenna S.P., Doward L.C., Hunt S.M. and Shalet S.M. Development of a Questionnaire to Assess the Quality of Life of Adults with Growth Hormone Deficiency. *Endocrinology and Metabolism*, vol 2, pp 63-69, 1995.
- 4 Doward L.C. The Development of the AGHDA: A measure to assess quality of life of adults with growth hormone deficiency. *Quality of Life Research* 1995, vol 4, No 5, 420-421.
- 5 McKenna S.P. and Doward L.C. The AGHDA: An instrument for the assessment of quality of life in adults with growth hormone deficiency. Submitted.
- 6 McKenna S., Koppeschaar H., Zelissen P., Snel Y. The impact of replacement GH on quality of life of patients: results of a clinical trial in The Netherlands. *Endocrinol Metab* 1997; 4 (Suppl B): 167.
- 7 Badia X, Lucas A, Sanmartí A, *et al.* One-year follow-up of quality of life in adults with untreated growth hormone deficiency. *Clin Endocrinol* 1998; 49: 765-71.
- 8 McKenna SP, Doward LC, Alonso J, *et al.* The QoL-AGHDA: An instrument for the assessment of quality of life in adults with hormone deficiency. *Qual Life Res* 1999. In press.
- 9 Wirén L, Whalley D, McKenna S, *et al.* Application of a disease-specific, quality-of-life measure (QoL-AGHDA) in growth hormone-deficient adults and a random population sample in Sweden: validation of measure by Rasch analysis. *Clin Endocrinol* 1999. In press.

Pharmacia AB 2000

PHARMACIA

GBM Endocrine Care
KIGS/KIMS Outcomes Research
Lindhagensgatan 126
112 87 Stockholm
SWEDEN

PfCor Grafisk Service AB

14.5 MRI safety questionnaire

MRI scanning uses strong magnetic fields. For your own safety and the safety of others it is **VERY IMPORTANT** that you do not go near the Magnet with any metal in or on your body or clothing. You will be asked to remove any loose metallic objects and will be asked to change into a hospital gown. All personal belongings will be placed in a secure locker. For your own safety you will be offered ear protection and maybe monitored on CCTV while in the department.

Please answer the following questions carefully, circling YES or NO as appropriate, and ask if anything is not clear or if you want further information. All information is held in the strictest confidence.

Name:	DoB:
Reference:	Weight:

1. Do you have a heart pacemaker? YES NO
These may stop working near the MRI scanner
2. Do you have any implants, wires or other foreign bodies in your body? YES NO
For example replacement joints, drug pumps, shunts, shrapnel, contraceptive coil
3. Have you had surgery on your head, brain, eyes or heart? YES NO
4. Have you had any surgery in the past 2 months? YES NO
5. Have you ever had any metal particles in your eyes? YES NO
For example from welding or metalwork
6. Could you be pregnant? YES NO
7. Do you wear dentures, a dental plate or a brace? YES NO
8. Have you had blackouts, epilepsy or fits in the last 2 months? YES NO
9. Do you have any tattoos or trans-dermal patches (skin patches)? YES NO
10. Are you wearing coloured contact lenses? YES NO
11. Any problems with previous experience of medical scanning? YES NO
12. Do you consent to an injection of contrast agent (dye) if required? YES NO
13. Are you breast feeding? YES NO
14. Do you have any kidney problems? YES NO
15. Do you consent to your images being used for teaching/research? YES NO
Images will be anonymous, your name and all other details will be removed

I have read, understood and answered all the questions

Signature: _____ Date: _____
 Print name: _____
 From completed by: Patient Relative Doctor Radiographer

Checked by (MRI authorised person): _____ Date: _____

14.6 Healthy volunteer poster



Barts and The London
School of Medicine and Dentistry



*NIHR Cardiovascular
Biomedical Research Unit*

Volunteers Needed

We are studying the effect of growth hormone problems on heart size and function
(Regional Ethics Reference 06/Q0401/53)

We need healthy volunteers (male or female, any age) with no history of heart problems who are willing to have a cardiac MRI to provide normal data

- ♥ MRI takes 30 minutes
- ♥ Painless and safe test
- ♥ Travel expenses paid

If interested please contact:
Dr Julia Thomas
Centre for Endocrinology, WHRI, Charterhouse Square
j.d.thomas@qmul.ac.uk 07931 358369

14.7 Healthy volunteer information sheet

Version 4, June 2010

Protocol title:

Cardiac and skeletal muscle energy metabolism in abnormal growth hormone states

Ref: 06/Q0401/53

You are kindly invited to take part in this clinical research study carried out in the endocrine department in St. Bartholomew's Hospital. This information sheet is designed to help you make up your mind whether you want to participate in this study or not. Before you make up your mind, you should read carefully the information below, and discuss it with your family, friends or your GP. Please take time to ask questions. You should clearly understand the potential benefits and the risks involved so that you make the decision that is right for you.

As participation is entirely voluntary, you can change your mind at any time (before the start of the study or after the study has begun). This is entirely your decision and no reason needs to be given. Declining to participate in this study or withdrawing from participation will not, in any way, affect negatively the care you receive from the medical staff. Before this study can start, it must be approved by an independent body called the Research Ethics Committee (REC) at the hospital.

What is the purpose of the study?

Growth hormone is made in the pituitary gland in your head. Some patients can have a disease when too much or too little growth hormone is present. Abnormal growth hormone (GH) levels can have a profound effect on the function of the heart. In GH excess (acromegaly) this could result in an enlarged heart, in abnormal function of your heart and hypertension (high blood pressure). In GH deficiency it can result in increased sclerosis of the arteries of the heart (the coronaries) and can result in ischaemic heart disease. The study is designed to have detailed investigation on the heart and skeletal muscle of these patients before, during and after their treatment, to detect the energy level of the heart and skeletal muscle and to see if they have increased sclerosis in the coronary arteries. We are asking you to serve as a control for these patients, so we can compare your heart function to the heart function of the patients.

Why Have I been chosen?

You have been chosen because you have no major abnormality with your growth hormone levels and do not have any major disease.

Do I have to take part?

It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part 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 take part, will not affect the care

you receive. If you chose to withdraw from the study any information that has been formerly collected will be processed as part of the study.

What will happen to me if I take part?

You will have magnetic resonance imaging (MRI) investigation of your heart on one occasion. This will take place at the Cardiac MRI Unit of the London Chest Hospital, Bethnal Green, London. When you arrive you will be asked to change into a hospital gown and self-adhesive ECG leads will be attached to your chest. The MRI scan takes about 20 minutes. For some of the time you will be asked to hold your breath for short periods of time (up to 20 seconds). The scanner can be noisy, therefore we will provide you with earplugs and headphones and you can listen to music of your choice during the scan. You may find magnetic resonance scans slightly uncomfortable as your head and upper body are in the scanner, particularly if you suffer from claustrophobia. We will be in contact with you throughout the scan and if you feel uncomfortable at all then we will stop the scan straight away. When you have your scan will check your bloods pressure, weight and height.

On the day of the tests you may have a blood sample taken for metabolic measurements (this is optional)

Your travel costs to the investigation sites will be reimbursed.

What do I have to do?

You will need to attend the cardiac investigations at the London Chest Hospital and will have the option of giving a blood test at St Bartholomew's Hospital.

What are the potential risks associated with the study?

Apart from the usual mild discomfort while giving the blood sample, no side effects are associated with sample collection and no side effects from the heart scanning.

What are the possible benefits of this study?

This research will help our understanding of the underlying abnormalities associated with growth hormone excess and growth hormone deficiency, particularly those relating to heart and muscle function and for coronary heart disease. It may help to explain the adverse effects of too much and of too little growth hormone in people with pituitary disease.

The result of your investigations may help us to recognise possible problems of your heart function. These could be potentially important results which could lead to initiation of further therapy. If any abnormalities are detected during the blood test we will let you know and further investigations could be done for this. The study generally will help us to understand abnormal heart function patients with growth hormone abnormality. It is however important to recognise that this research may not benefit you directly. The information we get from this study may help us to improve treatment of future patients.

What if new information becomes available?

Sometimes during the course of a research project, new information becomes available which may influence the analysis of your results. If this happens, your research doctor will tell you about it and discuss with you.

What happens when the research study stops?

Your blood samples will be disposed of on completion of the study.

What are our responsibilities to you as investigators?

If you experience any ill effects as a result of your participation, then we will take care of your medical needs. If there are any new findings during the course of the study which may affect the validity of the study, or your participation in it, this will be made available to you. You will have access to the study team at all times by contacting Dr Marta Korbonits, Dr Julia Thomas or Prof Ashley Grossman (see below).

What happens if there is a problem?

Queen Mary University of London has agreed that if you are harmed as a result of your participation in the study, you will be compensated, provided that, on the balance of probabilities, an injury was caused as a direct result of the intervention or procedures you received during the course of the study. These special compensation arrangements apply where an injury is caused to you that would not have occurred if you were not in the trial. These arrangements do not affect your right to pursue a claim through legal action. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms should be available to you.

If you need further advice please contact the Chief Operating Officer for the Barts and The London, Queen Mary School of Medicine and Dentistry, Wardens Office, 32 Newark Street, Whitechapel, London E1 2AA.

Will my taking part in this study be kept confidential?

All information that is collected about you during the course of the research will be kept strictly confidential. If you consent to take part in the research the people conducting the study will abide by the Data Protection Act 1998, and the rights you have under this Act. The result of the blood test and imaging investigations will be stored marked only with your initials and an ID number so that you cannot be recognised from it.

Your GP will be notified of your participation in the trial unless you indicate otherwise.

What will happen to the results of the research study?

The results will be published in a scientific medical journal and may be presented at national and international meetings. If you wish to obtain a copy of the publication, please contact the principal investigator. You will not be identified in any publication/presentation.

Who is organising and funding the study?

This study is based within the Department of Endocrinology at St. Bartholomew's Hospital. The principal investigator is Dr Marta Korbonits. This study is an independent research project within the Department and has been designed by the study investigators. We plan to obtain funding from Medical Research Organisations such as the British Heart Foundation as soon as we have pilot (preliminary) data from some patients.

Who has reviewed the study?

The Riverside Research Ethics Committee has reviewed the study.

Are there any payments involved?

Participants are not paid for their direct participation in this study. Additional costs (e.g. travel costs) will be reimbursed.

IF YOU REQUIRE FURTHER INFORMATION

If you have any queries or questions about this study, or if you wish to withdraw from the study, you may do so without justifying your decision and your future treatment will not be affected. For additional information or if you need to contact the study team now or in the future, please contact:

Prof Márta Korbonits
Department of Endocrinology,
King George V building, St. Bartholomew's Hospital
West Smithfield,
London EC1A 7BE
Telephone + 44 (0) 20 7882 6238

Or

Dr Julia Thomas
Centre for Endocrinology
William Harvey Research Institute
Barts & the London Medical School
Charterhouse Square
London EC1M 6BQ
Telephone +44 (0) 20 7882 6117

Or

Prof Ashley Grossman
Department of Endocrinology,
King George V building, St. Bartholomew's Hospital
West Smithfield,
London EC1A 7BE
Telephone + 44 (0) 20 7601 8343

Thank you

Prof Márta Korbonits
Principal Investigator
Telephone + 44 (0) 20 7882 6238

15 Appendix II – Laboratory Protocols

Tissue Lysis Buffer

- 1) 50mM Tris-HCl, pH at 7.4 at 4°C
- 2) 50 mM NaF 2.095 g
- 3) 5 mM Na pyrophosphate (Na (PO₄)₄) 2.23 g
- 4) 1 mM EDTA 0.372 g
- 5) 10% (v/v) glycerol 100 ml
- 6) 1% (v/v) Triton X-100 10 ml
- 7) 1 mM DTT 0.015 g
- 8) 1 mM benzamidine 0.156 g
- 9) 1 mM phenylmethane sulfonyl fluoride (PMSF) 0.174 g (use a little heat to dissolve)*
- 10) 5 ug/ml soybean trypsin inhibitor (SBTI) 0.005 g
- 11) Make up to 1L with ddH₂O
- 12) Store in 45ml aliquots at minus 20°C
- 13) At defrosting add a protease inhibitor cocktail tablet (Roche, #11836145001) to each 45ml of buffer. This is most easily done by dissolving it in 8ml of buffer and then adding this to the rest of the ice-cold tube

* or make 10 mM PMSF stock solution (0.085g in 50ml of 100% ethanol) and use 100ml of this solution in place of the figure given above.

Cell lysis Buffer

- 1) 50 mM Tris-HCl at pH 7.4 at 4°C 7.88 g
- 2) 50 mM NaF 2.10 g
- 3) 5 mM Na pyrophosphate 2.23 g
- 4) 1 mM EDTA 0.37 g
- 5) 250 mM mannitol 45.55 g
- 6) 1% (v/v) Triton X-100 10 ml
- 7) 1 mM DTT 0.015 g
- 8) 1 mM benzamidine 0.156 g
- 9) 0.1 mM phenylmethane sulfonyl fluoride (PMSF) 0.0174 g (use heat to dissolve)
- 10) 0.1 mM soybean trypsin inhibitor (SBTI) 0.005 g
- 11) Make up to 1 L with ddH₂O
- 12) Store at -20°C in 50 ml aliquots

Immunoprecipitation (IP) Buffer

- | | |
|--|--|
| 1) 50 mM Tris-HCl, pH at 7.4 at 4°C | 7.88 g |
| 2) 150 mM NaCl | 8.76 g |
| 3) 50 mM NaF | 2.095 g |
| 4) 5 mM Na pyrophosphate (Na (PO ₄) ₄) | 2.23 g |
| 5) 1 mM EDTA | 0.372 g |
| 6) 1 mM EGTA | 0.38 g |
| 7) 1 mM DTT | 0.015 g |
| 8) 0.1 mM benzamidine | 0.0156 g |
| 9) 0.1 mM phenylmethane sulfonyl fluoride (PMSF) | 0.174 g (use a little heat to dissolve)* |
| 10) 5 µg/ml soybean trypsin inhibitor (SBTI) | 0.005 g |
| 11) Make up to 1L with ddH ₂ O | |
| 12) Store in 45ml aliquots at minus 20°C | |

High Sodium Immunoprecipitation (NaIP) Buffer

- | | |
|--|--|
| 1) 50 mM Tris-HCl, pH at 7.4 at 4°C | 7.88 g |
| 2) 1 M NaCl | 58.44 g |
| 3) 50 mM NaF | 2.095 g |
| 4) 5 mM Na pyrophosphate (Na (PO ₄) ₄) | 2.23 g |
| 5) 1 mM EDTA | 0.372 g |
| 6) 1 mM EGTA | 0.38 g |
| 7) 1 mM DTT | 0.015 g |
| 8) 0.1 mM benzamidine | 0.0156 |
| 9) 0.1 mM phenylmethane sulfonyl fluoride (PMSF) | 0.174 g (use a little heat to dissolve)* |
| 10) 5 µg/ml soybean trypsin inhibitor (SBTI) | 5 mg |
| 11) Make up to 1L with ddH ₂ O | |
| 12) Store in 45ml aliquots at minus 20°C | |

Hepes-Brij (HB) Buffer

- 1) Na Hepes (pH 7.4) 13 g
- 2) DTT 0.0154 g
- 3) Brij 35 0.02% w/v 0.2 g (use a little heat to dissolve)
- 4) Make up to 1L with ddH₂O
- 5) Can be kept at 4°C for a few days, otherwise store in 45ml aliquots at minus 20°C

100mM Unlabelled ATP

- 1) Slowly dissolve 0.5111g ATP in 10ml HB buffer, whilst stirring, keeping the pH just above 7.0 with NaOH
- 2) ATP solutions must be neutralised *before* addition of MgCl₂, otherwise an insoluble MgATP complex will precipitate during neutralisation.
- 3) Store at minus 20°C in 1.5ml eppendorfs

1mM AMP

- 1) Dissolve 0.0347g AMP in 100 ml HB = 100mM AMP
- 2) Store at minus 20°C in 1.5ml eppendorfs