Imperial College Healthcare NHS
NHS Trust

Department of Investigative Medicine
Imperial College London
6th Floor, Commonwealth Building
Hammersmith Hospital
150 Du Cane Road
London W12 0NN

PATIENT INFORMATION SHEET FOR PARENT(S)/ LEGAL GUARDIAN(S)

STUDY TITLE: Investigating the physiological hormonal response to kisspeptin in delayed puberty

Thank you for reading this information sheet. We would like to invite your child to take part in our research study. Before you decide, it is important that you understand why the research is being done and what it involves. Please take time to read the following information carefully and discuss it with friends, relatives and your GP if you wish. You will have at least 24 hours to consider this information prior to consenting for this study. The study team will also be available to answer any further questions you may have prior to consenting to this research. Even if you provide consent for your child to participate in this study, you and your child are free to withdraw at any time without explanation.

WHAT IS A RESEARCH STUDY?

A research study is about finding new information about topics that are important to our health. Taking part in research is optional. This research may be too early to help you or your child directly, but the information generated during the research will be valuable in helping other people in future. This document explains the research so that you can decide whether you would like to let your child take part in the research or not. Please ask us for clarification if there are any aspects of the research that remains unclear.

WHY ARE WE DOING THIS RESEARCH?

Puberty is a time when a child's body changes to become more like that of an adult. It is a normal process that usually starts around the ages of 8 to 13 years in girls and 9 to 14 years in boys. During puberty, the body produces hormones such as testosterone and oestrogen that induce changes to the body such as deepening of the voice or hair growth in boys and breast growth or period onset in girls. The onset of puberty may differ amongst children and the process can take several years from start to finish. Some children do not enter puberty by the same age as most children (13 years old for girls and 14 years old for boys) and this is termed 'delayed puberty'. Most commonly, these children will enter puberty spontaneously with time (Constitutional delay of Growth and Puberty; CDGP). However, a small subset of these children have a genetic disorder causing the part of the brain that controls these hormones (hypothalamus) to not function normally. These children are less likely to enter puberty without treatment (Congenital Hypogonadotropic Hypogonadism; CHH). Currently, doctors do not have a good method for differentiating these two groups of children who require different management.

Over the last 15 years, a naturally occurring hormone called "kisspeptin" has been shown to play an important role in the regulation of puberty. Kisspeptin stimulates the part of the brain (hypothalamus) that regulates production of puberty hormones. Some children who have a genetic problem which prevents them from producing kisspeptin do not go through puberty. By contrast, if a child makes too much kisspeptin, they can go through puberty early. Therefore, kisspeptin has been proposed as a key regulator of puberty onset. While many studies have shown that kisspeptin can stimulate the secretion of these hormones in adulthood, few studies have assessed the hormonal response to kisspeptin in children with delayed puberty.

This study aims to evaluate the hormonal response to kisspeptin in children with delayed puberty. The knowledge gained through this research would be of great value in the development of tests to identify the cause of delayed puberty for children in future.

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WHY HAS MY CHILD BEEN ASKED TO TAKE PART?

Your child may have been invited to take part because he or she is aged 13 to 15 years with delayed puberty.

DO I HAVE TO LET MY CHILD TAKE PART?

Participation in the study is entirely voluntary and it is up to you and your child to decide if you would like your child to take part in the research. We will provide you with as much information as possible so that you can make an informed decision as to whether you consent for your child to take part.

Before your child take part in the study:

- You will be given this document to explain about the research. You can take as long as you need to consider the information, discuss with other people / or healthcare practitioners such as your GP and then decide whether you want to take part in the research.
- Your child will be given a patient information sheet written in language appropriate to their age group to explain the research.

Both you and or your child are free to stop taking part in the research at any time without giving a reason. If you decide to withdraw from the research, this will not affect the health care that your child receives.

WHAT WILL HAPPEN IF MY CHILD WANTS TO TAKE PART?

If after considering this information sheet and discussing the research study with the doctors in a screening visit, you are interested in taking part in the research, we will invite you to our study visits at the Paediatric Clinical Research Unit at St. Mary's Hospital. The two study visits will be on different days within 2 months of each other.

Screening visit

The screening study visit will begin with an explanation of the research study and addressing any remaining queries that you might have about the research. If, after the explanation of the research, you and your child are willing to proceed, we will ask you to sign a 'parental consent form' stating that you agree for your child to take part. Your child will be asked to sign an 'assent form' to state that they are also willing to take part. We will then ask you and your child some questions about your child's general health and details pertaining to delayed puberty. If you have self-referred, we will conduct a physical examination to ensure your child is fit and healthy and able to take part in the research. Examinations may include measuring your child's height, weight, listening to your child's chest with a stethoscope, feeling your child's abdomen and testing your child's senses such as vision or smell.

If your child is already under the care of the paediatrician for delayed puberty, we will ask for your consent to review the previous medical records / investigations pertaining to assessment of puberty (e.g. wrist radiograph to assess how developed the bones are or a scan of the brain called a magnetic resonance imaging scan (MRI) to ensure that there is no structural problem with the part of the brain (hypothalamus) which secretes puberty hormones). If you have self-referred, we will order routine investigations for delayed puberty. We will not request any additional imaging investigations beyond those that are required for routine medical care for participation in this study. We will also carry out a urine pregnancy test on girls who participate in the study to ensure that it is safe to proceed with the research.

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If any undiagnosed clinically significant illness is identified at screening, your child's direct healthcare provider e.g. the GP will be informed, and your child may not be eligible for the study.

Study Visit 1

After initial assessment, your child will be invited to have a GnRH test, which is a routine test used by paediatricians in the assessment of children with pubertal disorders. To carry out the GnRH test, we will insert a small plastic tube called a cannula in your child's vein. The cannula will allow us take blood tests and give the hormones without any more injections. Inserting the cannula can be uncomfortable, therefore before we insert the cannula, we will offer the use of a special cream / spray on the area to reduce the discomfort associated with this procedure. Following the insertion of the cannula, we will use it to take a blood sample (≤20mls) to assess the child's puberty hormones and general medical health. We will also test a blood sample for genes that are involved in producing puberty hormones.

After the baseline blood sampling, an injection of GnRH will be given through the cannula and a series of blood tests will be taken via the cannula. Blood sampling will occur not more frequently than every fifteen minutes up to a maximal duration of 3 hours. The maximum amount of blood taken in this study visit will be less than 50ml, which is less than the volume deemed safe for a 34kg child over 24 hours (less than 128 ml over 24 hours and less than 255 mls over an 8-week period).

The entire duration of the study visit should not therefore take more than 5 hours. Two experienced investigators will be present throughout the study period. The investigators will regularly monitor heart rate and blood pressure to ensure that your child remains well. You are invited to stay with your child throughout the study. We will encourage you to bring your child's preferred choice of food, snacks or drinks. Provision for CD, DVD, games and age appropriate books will be made available, but we encourage you / your child to bring any specific entertainment (e.g. lap top/tablet or video game) they would wish. We will reimburse you for the cost of food/drink and travel expenses incurred for each study visit

At the end of the study, your child will receive an Amazon voucher to thank them for participation in the study.

Study visit 2

We will invite you and your child to a second study visit within 2 months of the first study visit.

On the day of the second study visit, you and your child will be asked to arrive in the morning to our Clinical Research Unit at St Mary's Hospital. Your child is encouraged to rest well and to eat and drink as per normal prior to the study visit.

On arrival, a cannula (small plastic tube) will be inserted in your child's vein as previously. This cannula will allow us to take blood tests and give hormones without any further injections. We will offer the use of special cream/spray on the area of insertion to reduce any discomfort associated with the procedure.

Following the insertion of the cannula, we will take some blood samples via the cannula every 10 minutes for 1hr to measure baseline reproductive hormone levels. After an hour of baseline blood sampling, your child will receive an injection of the naturally occurring hormone "kisspeptin" through the cannula. Following this, we will take blood samples via the cannula every 10 minutes for a maximal duration of 7 hours. The total duration of blood sampling in this visit will be 8 hours. The maximum amount of blood taken during the study visit will be less than the volume deemed safe for a 34kg child over 24 hours (less than 128 ml over 24 hours and less than 255 mls over an 8-week period).

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Two experienced research doctors will be present throughout the study visit. The research doctors will regularly monitor heart rate and blood pressure to ensure that your child remains well. You are invited to stay with your child throughout the study. We will encourage you to bring your child's preferred choice of food, snacks or drinks and we will reimburse you for the cost of these and the travel expenses incurred for each study visit. Provision for CD, DVD, games and age appropriate books will be made available, but we encourage you / your child to bring any entertainment (e.g. lap top/tablet or video game) they would wish.

At the end of the study, your child will receive an amazon voucher to thank them for participation in the study.

WILL YOU BE FOLLOWING UP ON MY CHILD AFTER THE STUDY VISITS?

With your consent, we will contact you (either by phone or email) periodically following the original study participation to ask you some questions regarding your child's stages of pubertal development. We will not do this once your child is beyond the age of 18 years. If your child is under the care of a paediatrician, we may ask for your consent to contact them and enquire about the stages of your child's pubertal development. These follow up contact will not substitute any advice or treatment started by the paediatrician.

CAN MY CHILD BE RE-RECRUITED AGAIN?

If after 6 months, the stage of puberty in your child has changed, we may offer you and your child the option to be re-recruited into the study and repeat the two study visits (kisspeptin and GnRH). The purpose of these optional repeat study visits is to monitor for any changes in response to kisspeptin especially in children who experience a change in their clinical stage of puberty (e.g. showing signs of initial stages of puberty, or were started on treatment with testosterone or oestradiol by their paediatrician following reassessment). These optional additional visits are entirely voluntary and you or your child can withdraw from the research at any time without the need to give any reasons.

WHAT ARE THE SIDE EFFECTS OF THE HORMONES TESTED?

Kisspeptin and GnRH are both naturally occurring hormones that are present in the circulation. Kisspeptin stimulates the part of the brain (hypothalamus) that regulates production of puberty hormones. Children who have a genetic problem which prevents them from making kisspeptin normally do not go through puberty. By contrast if a child makes too much kisspeptin they can go through puberty early. Therefore, kisspeptin has been proposed as a key regulator of puberty onset. We have given kisspeptin to more than 300 adults without encountering any side effects. Kisspeptin has recently been given to ~15 children with no reported side effects. Kisspeptin is normally present in the blood at low levels and levels of kisspeptin increase to 7000-fold during normal pregnancy without any known side effects. We therefore do not anticipate any side effects during this study. Although kisspeptin has been implicated in regulating the onset of puberty, it will be given as a single injection during this study and will no longer be detectable after a few hours. Therefore, it is very unlikely that kisspeptin will have any impact on the onset of puberty for participants in this study as it will be present for too short a duration. Kisspeptin is manufactured by the company Bachem AG, a company which produces proteins for the pharmaceutical industry. The kisspeptin is tested to ensure that is free from bacteria and safe for use in humans.

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Gonadotrophin releasing hormone (GnRH) is another naturally occurring hormone which has been used for many years in routine clinical practice to diagnose hormonal problems in children with disorders of puberty. It is not known to be associated with any side effects.

If your child develops any side effects during the study, please let us know immediately. Contact details are supplied at the bottom of this information sheet.

WHAT ARE THE POSSIBLE DISADVANTAGES OR RISK OF TAKING PART?

On study visit days, insertion of the cannula can be uncomfortable and might leave a small bruise following removal. However, we will offer the use of a cream or spray to reduce the discomfort associated with insertion of the cannula. We will press on the cannula site following removal to minimize the chance of a bruise developing.

WILL THE STUDY HELP MY CHILD?

At present, there is not enough information on how kisspeptin stimulates puberty hormones at different stages of puberty for the results of the study to directly help your child directly. However, the information produced from the study will help doctors to develop tests and treatments for disorders of puberty in the future.

WHAT HAPPENS WHEN THE RESEARCH STUDY STOPS?

Once the study has finished, the results of the study can be made available to your and or your GP should you wish. If you have any problems immediately following the study, then you should contact one of the research doctors on the numbers provided below. Once the study is completed, you will be offered a summary of the research findings written in language that is easy to understand.

WHAT IF NEW INFORMATION COMES ALONG?

Sometimes, during research, new information becomes available. If this happens, one of our research doctors will discuss the new information with you whether you and your child would like to continue in the study. If you and your child decide to continue in the study, we will ask you to sign an updated consent form.

WHAT IF SOMETHING GOES WRONG?

Imperial College London holds insurance policies which apply to this study. If your child experiences serious and enduring harm or injury as a result of taking part in this study, you may be eligible to claim compensation without having to prove that Imperial College is at fault. This does not affect your legal rights to seek compensation.

If your child is harmed due to someone's negligence, then you may have grounds for a legal action. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been treated during this study then you should immediately inform the investigator (Prof Waljit Dhillo by email: kisspeptin@imperial.ac.uk). The normal National Health Service complaints mechanisms are also available to you. The Patient Advice and Liaison Service or complaints team can be contacted at pals@imperial.nhs.uk or at 020 3313 0088 (Charing Cross, Hammersmith Hospital) or at 020 3312 7777 (St Mary's Hospital). If you are still not satisfied with the response, you may contact the Imperial AHSC Joint Research Compliance Office.

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WILL MY CHILD'S INFORMATION BE KEPT CONFIDENTIAL?

All information about your child will be kept strictly confidential. Any information about your child which leaves the hospital will have their name and address removed so that they cannot be recognized from it. With your consent, we will inform your GP about your child's participation in this study. If there is any clinically significant illness that is identified at screening visit, we will inform your GP to ensure appropriate treatment is given.

HOW WILL THE STUDY DATA BE STORED?

Once the study is complete, all information will be kept for 10 years in secure storage in the Department of Investigative Medicine at Hammersmith Hospital under the authority of Professor Dhillo.

WILL YOU BE STORING MY CHILD'S SAMPLES FOR FUTURE USE?

If you and your child agree, blood samples will be kept after the study has finished for use in future research projects. We will be asking you and your child's permission to store your blood samples for use in future research up to a maximum period of 3 years. These blood samples will only be released to recognized researchers whose project has undergone ethical and scientific review. All the stored samples will be anonymized, and the researchers may be given some information about your child's health but will not be given any personal information that can be used to identify your child.

WILL ANY GENETIC TESTS OR OTHER TESTS BE DONE?

We will perform a blood test to look for any alterations in genes that may be associated with regulation of puberty. The blood samples collected for genetic analysis to be carried out in an expert laboratory.

WHAT WILL HAPPEN TO THE RESULTS OF THE STUDY?

When the study has finished, we will publish our findings in scientific journals and communicate our findings at scientific conferences attended by physicians in the field. We will ensure that participants cannot be identified from any published material. The findings of the study will also be communicated with members of the public. You will be offered a summary of the study in plain language so that you are aware of the findings from the research.

WHO IS ORGANISING AND FUNDING THE STUDY?

This study is organized by Imperial College London and is funded by NIHR who will pay Imperial College for the costs of this study.

WHO HAS REVIEWED THE STUDY?

This study has been reviewed by the West London & GTAC Research Ethics Committee and the AHSC Joint Research Office.

HOW CAN I FIND OUT MORE ABOUT THE RESEARCH?

If you experience any problems during the study, you may withdraw at any stage. The physician leading the study, Professor Dhillo, will be available by telephone and can be contacted through a secretary on 020 8383 3242 or the hospital switchboard (020 8383 1000). Emergency contact details for doctors working on the trial will also be provided.

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Thank you for taking time to read this- please do ask us any questions if any parts are still not clear.