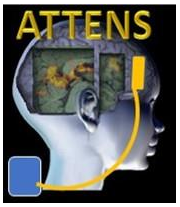
PARTICIPANT INFORMATION SHEET

A multi-centre, double-blind, randomized, parallel-group, phase IIb study to compare the efficacy of real versus sham external Trigeminal Nerve Stimulation (eTNS) on symptoms in youth with Attention-Deficit/Hyperactivity Disorder (ADHD)

*The **ATTENS project (ADHD trial of external trigeminal nerve stimulation)***



We would like to invite your child and yourself to take part in some research at the Department of Child & Adolescent Psychiatry/Social Genetic and Developmental Psychiatry Centre (SGDP) at the Institute of Psychiatry, Psychology & Neuroscience at King's College London or at the Centre for Innovation in Mental Health (CIMH), School of Psychology, University of Southampton. Joining the study is entirely up to you and your child. Before you decide, we would like you to understand why the research is being done and what it would involve. We would like to thank you for taking the time to read the information carefully and would like you to feel free to talk about it with your family, friends, or doctor. One of our team will go through this information sheet with you and answer any questions or give clarification if there is anything that you do not understand. Please take your time in deciding whether you want your child to take part.

What is the purpose of the study

The aim of this study is to test a new treatment for children with Attention-Deficit/Hyperactivity Disorder (ADHD). The best current treatment for children with ADHD is with stimulant medication. However, there are side effects and the effect of long-term use of stimulant medication is unclear.

This research is testing a new non-drug treatment, called external Trigeminal Nerve Stimulation (eTNS). eTNS has been shown to work well in children with ADHD in a study in the USA, and it has no serious side effects. eTNS is worn during sleep and has been shown to be safe and effective for ADHD; it is the first device based non-drug treatment that has been approved for children with ADHD by the US Food and Drug administration (FDA) in 2019 so it is a very new treatment.

The purpose of the study is to test the eTNS treatment in a larger group of ADHD children and adolescents across two centres (London and Southampton). The study will establish whether eTNS is effective in reducing symptoms of ADHD and other problems such as mood, concentration, memory, and sleep. It will also establish whether it improves performance in attention and self-control. This will be done using computer tests. The questionnaires and computer tests will be done before using the device, after four weeks of using the eTNS device while sleeping and then again after 6 months to see whether the effects remain. We will also test whether eTNS improves brain activation in a magnetic resonance imaging scanner (MRI). This part is optional, and scanning will only be done at King's College London.

To find out if eTNS is effective, two different devices will be tested, one with real stimulation and one with fake stimulation (sham). The children will be randomly allocated by a computerised system to one or the other treatment (like tossing a coin). The researcher that you will meet will also not know whether your child has been allocated the real or sham eTNS treatment. This means that both you, your child and the researchers are "blinded" or masked. We only expect the group who gets the real eTNS treatment to get improvements in their behaviour.

We expect that this research may lead to the establishment of a new non-drug treatment for ADHD which has minimal side effects. We expect that this treatment may improve the behavioural difficulties children with ADHD have and that it will also improve their attention and self-control skills. We also expect to see increases in brain activation in the brain regions like the frontal lobes, that are normally not working so well in children with ADHD. If this study is successful, it could establish eTNS as a non-drug treatment for ADHD.

What is external Trigeminal Nerve Stimulation (eTNS)?
The eTNS device is an approved treatment for ADHD in the USA. It is a non-invasive medical device that stimulates the trigeminal nerve using an external electric conductive patch, which resembles a large plaster directly on the forehead. The trigeminal nerve stimulates the brain and there is some indication that it increases the activity in the frontal lobes in people with ADHD. Below are images of the device.

Why has my child been invited?
Your child has been invited to participate because they have been diagnosed with ADHD. The clinicians involved in their care thought that this may be of interest to you. You may also have been invited to participate via parent support groups, GPs, social media or via advertisement. We will ask 150 children with ADHD between the ages of 8 and 18 to take part in the study.

Does my child have to take part?
No, it is up to you to decide whether you and your child should join the trial. We would like to ask you to take your time to decide whether you want to take part in the research. Please take at least 2 days and no longer than 6 months to decide whether you would like to take part. If you agree to take part, we will ask you to sign a consent form allowing your child to take part in the study. We will also ask your child to assent to the trial. You need to understand what the trial involves and what it will mean for your child before you can consent and we will go through this, with you. In order to limit the times that you would need to travel to the research centre, we will first ask you to consent digitally by email or similar and we would then ask for an ink signature during your first visit to the research centre. If you or your child would lose the capacity to consent to the study, they would be withdrawn from the study. Identifiable data already collected with consent would be retained and used in the study. No further data would be collected, or any other research procedures carried out.

What happens if I change my mind?
You can still change your mind at any time, and you do not have to say why. If you decide to change your mind, this will not affect your child's treatment in any way. We will retain only the information collected up to that point. We would, however, ask that you return any equipment and patches etc.

How will I know if my child can take part?
There are a few reasons why your child may not be included in this study, and we may not know this at the time when you consent to be part of the trial. However, we will be able to tell after completion of the first assessment. Your child may be excluded if:

- We find that they may have other mental health conditions such as for example Autism Spectrum Disorders (ASD). However, if your child has some conditions such as conduct disorder or oppositional defiant disorder or mild anxiety and depression, they can still be part of the project.
- They are taking non-stimulant medication such as Atomoxetine (Strattera) or Guanfacine (Intuniv, Tenex), as these drugs may have a similar effect to the brain as the device and we would not be able to disentangle the drug effects from the eTNS effects.
- They have any neurological conditions (like epilepsy).
- They suffer from alcohol or drug abuse.
- They have any implanted devices (like cardiac devices) or presence of body worn devices (like insulin pump) (contraindication to eTNS).
- As part of the project, we will assess the severity of your child's ADHD and also your child's IQ and it may be that your child may not be able to be part of the project because of the outcome of this. Please note that this is an assessment completed in a research setting and does not affect your child's diagnosis of ADHD in any way.
- They have drug holidays or breaks when using stimulant medication. If they are on stimulant medication, they need to take their medication every day during the four weeks of treatment of the trial participation to be eligible.

What would I be asked to do if we took part?
If you decide to take part as a parent, we would ask you to:

- Be interviewed and asked some questions about your child's symptoms and behaviour and also provide some background information and medical history. These will be similar questions to those that you had when your child was first assessed for ADHD. This can be done either virtually or face to face and be split into more than one session.
- Agree to take your child to the research centre at either London or Southampton for at least four visits.
- Once you have been given the eTNS device, we will ask you to fill in some questionnaires about your child every week as well as a daily sleep diary (to record for how long your child wore the device every day) for four weeks. This can be done virtually together with the researcher, or you could fill these in and send these to us.
- During the first visit you will receive training on how to use the eTNS device and how to look after it. Depending on the age of your child and their abilities, they may be able to manage this part by themselves after a while. However, you will have to be able to supervise this.
- You would need to ensure that the batteries for the device are charged every other day.
- At each visit, you will be asked some questions about your child's behaviour and symptoms.
- You will be asked for contact details of your child's teacher to ask them to fill in some questionnaires about your child if they are happy to do so. You can still take part even if your child's teacher does not want to fill in some questionnaires.
- Provide us with contact details of your GP and NHS prescriber so that they are aware that your child is participating in this project.

We would also like to record the interview but only if you are happy for us to do that. This is to ensure that the researchers are interpreting what you say in the same way. At the end of the project, this recording will be deleted.

What would my child be asked to do if we took part?
For your child to take part in this project, they would be asked to:

- Be interviewed and asked to answer questions about their behaviour.

- Have their IQ tested.
- Use the eTNS device while they are sleeping for 7-9 hours per night for four weeks; this is a disposable patch as shown above with a battery that can be attached to their pyjamas or placed under their pillow.
- For four weeks during the treatment, answer weekly questions virtually.
- Wear a device on their wrist for 3-4 hours on some visits to the research centre- this is not expected to be too uncomfortable as it is very similar to a "fitbit".
- Come to the research centre four times to complete some cognitive tasks on the computer and answer some questions about their behaviour.
- At the centre, they will have their height, weight, vital signs, and pupils measured.

We would also like to record the interview but only if your child is happy for us to do that.

Can my child still take their usual medication or what happens if they want to start taking medication treatment for the first time?
If your child is taking stimulant medication for ADHD, then they can still participate in the research, but we will ask not to make any change in their usual treatment (i.e., the same dose for the four weeks of the treatment period). We would prefer it if your child was not taking any medication and if you were ok with that, we would ask your child to stop medication for 1 week before the treatment starts and during the 4-week treatment (i.e., 6 weeks). However, this is optional. If you decide for your child to keep taking their medication then we would ask you for the child to take the same dose as usual during the entire 4 weeks and not stop the medication on weekends or on holidays.

How much time will this take?
After you and your child have consented to the study, we expect the time commitment to be:

- **Eligibility phase:** we expect it to take about **two to three hours for you** to answer questions about your child. This does not have to be at the same time, and it can be split between different days and will be all done virtually.
- **Eligibility phase at research centre:** your child will answer questions and do IQ test which will take about 1.5 hours.
- **First research centre assessment visit:** you and your child will answer questions, your child will complete computer tasks, physical measures, and you will both receive training in using the eTNS device, which in total will take about 2-**3 hours.**
- **Four weeks of weekly measures:** filling in sleep diary, answering similar questions as before and also regarding the effect of using the device. This will take about **20 min each** per week and this will be completed digitally.
- **Four weeks of charging the battery every other day for the device:** this is expected to take **1 min** each time.
- **Second and third research centre assessment visits:** this will be completing the computer tasks again and some of the physical measures and are expected to last for **2-3 hours.**

We have not counted the hours that your child will be sleeping with the patch on their forehead.

There is also the option that your child can do a fMRI scan and this would mean an additional visit at the research centre to allow your child to go into the mock scanner (fake scanner). This is to ensure that your child is happy to take part in this part of the project and to show him/her the tasks he has to do in the MRI scanner. The fMRI scan would then be done on the following visit to the research centre when you will also get the eTNS device and then four weeks later. But this is optional.

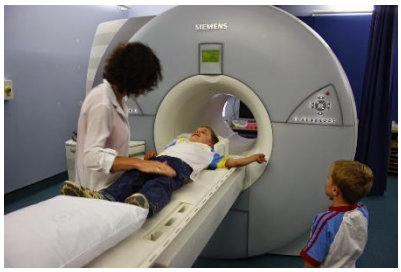
What does the optional fMRI brain scanning involve?
The brain scan is perfectly safe, does not hurt and no side effects have ever been reported. In each of the two scanning sessions your child will be in the MRI scanner for about 60 minutes, and during each scan they will have to do three computer tasks which test attention, self-control, and short-term memory, followed by a resting scan. They will have been trained in the tests before, so they are familiar to them. There is a microphone inside the scanner so that your child can talk to us if at any time they want the scan to stop.

Below is a picture of the scanner. Your child will be lying in the scanner the entire time and will be able to see the screen with the computer game through a mirror that is attached in the ceiling of the scanner.

We will show your child how the scanner works before in a dummy scanner. Your child will be able to talk to the researchers at any time and you can be in the same room if you have no counterindications to the MRI scanner.

Each fMRI scanning session is overseen by UK state registered radiographers with specialised neuro-experience and the whole team will try to ensure that you and your child have stress-free visits. There is no special preparation prior to the scan, and they may eat and drink as normal.

Because we would like the best possible images of your child's brain they will be asked to lie as still as possible in the scanning machine (as you would expect with an old-fashioned camera). The scanner is noisy, and your child will hear loud banging noises during the scan, but we will give them headphones to lower the noise.



How will I know if my child can take part in the imaging part of the project?
The imaging part of the project is optional, and we aim to recruit mostly children who have never used stimulant medication or are currently off stimulant medication or are willing to come off for one week before the study starts. If your child is of 10 years of age and older and has no metal in his/her body (braces, metallic tattoos, pacemaker) then they can also take part in the imaging part of the study. If they take part, then we will ask them to not have any new metal tattoos or metal piercings such as ear piercings made in the 4 weeks during which they are using the eTNS device. Also, if your child is afraid of enclosed spaces then the scanning experience will not be pleasant for them and it is better, they don't take part. If you wish to take part in this part of the project, you need to be prepared to travel to London.

What are the possible disadvantages and risks of my child taking part?
Possible discomfort: It could potentially be a bit uncomfortable to sleep with the eTNS device at night. However, in the previous US study, the sleep patterns of the children who participated in the study became better and not worse. We think this was due to the reduction in ADHD symptoms with the treatment. Your child could be randomised to the sham eTNS device, and we would therefore not expect there to be any benefit.

Potential delay of medication treatment: If your child is not taking medication, but is planning to start taking medication, this will have to wait until after the four weeks of the research treatment before they can start taking medication.

Personal information in assessments: Some of the questions seem personal and can cause distress (if for example you have mental health problems or epilepsy). These are similar to when your child was first diagnosed with ADHD.

Side effects: No serious side effects or adverse events have been reported in studies with eTNS and we do not expect any side effects. However, we cannot guarantee that your child will not have any side effects, and some have complained about headache (that quickly goes away) or skin irritation (that goes away with cream). Other potential side effects could be fatigue and increased appetite. Some participants with darker skin can also show some discolouration on the skin which is related to the patch removal and goes away with sun exposure and time.

The National Institute for Health and Care Excellence (NICE) issued guidance regarding this treatment in January 2023 based on the USA trials. Their guidance mentions additional side effects such as negative effects on cognitive function and worsening of symptoms. However, it should be pointed out that this was reported more within the group who had the sham device than the group

who had the real device. Given that the sham device is not doing anything, such side effects are then thought to be more likely to be related to ADHD itself rather than the device.

Scanner anxiety: MRI is a safe imaging method and there are no reported side effects. However, some people can sometimes be anxious about the scanner, which can be seen as noisy, unpleasant, and uncomfortable. We are sensitive to this possibility and will stop testing sessions at your child's request or at the first signs of their distress or discomfort. Your child will be informed that they are free to terminate the scanning session whenever they want to. There is a microphone in the scanner through which your child can easily communicate with the radiographers. Additionally, the radiographers will constantly check that your child is content to remain in the scanner.

The research team will inform you if the device is an effective treatment for ADHD after the end of the study, but this is not likely to be until 2026. Unfortunately, it is not possible currently to purchase this device if you feel that it has benefitted your child. However, the device is likely to be available in the UK in the future.

What is good about your child taking part in the research?
We hope that the information we get will establish whether eTNS is a suitable treatment for ADHD and therefore help treat other young people with ADHD with eTNS in the future. It is likely that your child's behaviour improves with the eTNS treatment (if they are in the active group). However, we cannot guarantee that your child gets better as this is a research study and there is no guarantee that every child gets better with the eTNS treatment.

In addition, you will also get some information about 1) your child's intellectual performance which could be useful for school planning 2) about your child's clinical profile (i.e. we can give you the results of the questionnaires we ask you to fill in which will be an indicator of the severity of your child's symptoms) and 3) your child will get a picture of their brain if they want to.

Can the researchers remove me from the study?
The researchers aim is to keep you and your family in the study and they will only remove you from the study if there are any welfare and safety concerns for either your family or the researchers. If this is the case, we will ask that you return for one final visit so that you can return any equipment and supplies and so that we can check and be sure your child's health is OK.

What happens when the research stops?
At the end of the study, we will send you and your child a letter about the results of the study if you are interested.

Who will access the medical records of my child and why?
The immediate care team for your child has access to the medical records and referred your child for this research because it was thought to meet the inclusion criteria for this study. With your permission, as part of the research, we also request that the research team can access the clinical records for your child. This is so that we can check that they meet the inclusion and exclusion criteria for the study and so that we can find out what medication or other forms of treatment they may have received. This will not be possible if you have been recruited through a support group or flyer, but only if you have been recruited through a clinic or clinical records.

Will the information that is collected about my child in this research be kept confidential?
Anything we find out about your child will be kept to ourselves. Any information we have collected from your child or about your child will be saved in computer files but will be coded and have your child's name removed so that no one can tell it is your child. This applies to any data, including the behavioural questionnaires you have filled in, the cognitive performance data, the physiological data, the eye-tracking data, or the IQ data that your child has given us.
In the data system where we will input all information about your child and which we use to analyse the data, we will use your child's initials and month and year of birth but nothing else that can identify your child. Later this information will be removed and only a code number will be kept.

In extremely rare circumstances, information that is discussed during the assessment may raise concerns about your child's safety or the safety of others; in these cases, we are required by law to share such information with the appropriate authorities.

How will we use information about you?
King's College London and South London and Maudsley NHS Foundation Trust are the sponsor for this study. We will be using information from you and your medical records to undertake this study and will act as the data controller for this study. This information will include your name and contact details. People will use this information to do the research or to check your records to make sure that the research is being done properly. People who do not need to know who you are will not be able to see your name or contact details. Your data will have a code number instead. We will keep all information about you safe and secure. King's College London will keep identifiable information about you for 3 years after the study has finished.
Once we have finished the study, we will keep some of the data so we can check the results. We will write our reports in a way that no-one can work out that you took part in the study.

What are your choices about how your information is used?
You can stop being part of the study at any time, without giving a reason, but we will keep information about you that we already have. We need to manage your records in specific ways for the research to be reliable. This means that we won't be able to let you see or change the data we hold about you. If you agree to take part in this study, you will have the option to take part in future research using your data saved from this study.
You can find out more about how we use your information at https://www.kcl.ac.uk/research/support/rgei/research-ethics/kings-college-london-statement-on-use-of-personal-data-in-research or by contacting Mrs Lena Johansson at lena.johansson@kcl.ac.uk

What will happen to my child's brain activation images?
All brain imaging data from your child will be kept for 10 years, but it will be completely anonymous.

Will my child get anything for taking part?
To thank your child for their participation we will give your child:

- £50 for the initial assessment (this may be done on more than one occasion and may be at the research centre)
- £50 for each of the three research visits totalling £150
- £150 for the four weeks of using the eTNS device while sleeping
- If your child participates in the fMRI scan, they will receive £50 for each scan (i.e., £100)

We will give your child tokens for each visit that are exchangeable for money. At the end the four weeks of using the device your child will receive the money for the study participation so far (i.e., £300). The remaining £50 will be paid 6 months later at the last visit. The money for the fMRI scans will be given after the second scan. We will also reimburse you any bus, taxi or train fare or some petrol money if you came by car, so that you have no costs. However, we are not able to reimburse any hotel costs.

What if my child feels distressed or has any complaints about the study?
If you or your child have any complaints about the study, you can contact the research team on attens@kcl.ac.uk or the chief investigator, Prof Katya Rubia (email: katya.rubia@kcl.ac.uk; Tel: 02078480463). If you want to contact someone outside the research team at the Institute of Psychiatry, Psychology & Neuroscience, , please contact the Joint R&D Office of South London and Maudsley NHS Foundation Trust and Institute of Psychiatry, Psychology & Neuroscience (IoPPN), Contact via: R&D Office (PO Box O5) , IoPPN Main Building, King's College London, De Crespigny Park, London SE5 8AF; Email: slam-ioppn.research@kcl.ac.uk. You can also contact the local Patient Advice and Liaison Service (PALS) of the South London and Maudsley NHS Trust at the freephone 0800 731 2864 or by email at pals@slam.nhs.uk.

What will happen to the results of this research?
The results of this study will appear as articles in special magazines that medical doctors and scientists read. If you would like to read the results you can have copies of these articles sent to you by asking Prof Katya Rubia. However, your name will not be in any of these articles, and we will only report the

effects of the eTNS treatment on the group of ADHD children and not mention any individual people. In addition, we will also provide you with a summary of the research results in lay language.

Who is managing and paying for the research?
The Chief Investigator is Prof Katya Rubia, Department of Child and Adolescent Psychiatry, Institute of Psychiatry, King's College London. This study is being funded by National Institute of Health Research and the Medical Research Council, both UK government funding agencies that fund research.

Is there insurance in place for this research?
In the event that something does go wrong, and you are harmed during the research you may have grounds for legal action for compensation against King's College London and/or SLaM NHS Foundation Trust, but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you (if appropriate). King's College London has obtained insurance which provides no-fault compensation, i.e., for non-negligent harm, you may be entitled to make a claim for this.

Who has reviewed the study?
All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and granted a favourable opinion by the West Midlands – Solihull NHS Research Ethics Committee (REC) (Ref: 21/WN/0169).

Who can I contact for more information?
You can write to the ATTENS project team at the Department of Child and Adolescent Psychiatry, PO85, Institute of Psychiatry, Psychology & Neuroscience De Crespigny Park, London, SE5 8AF for any more information or you can telephone: 07923-881937 (email: attens@kcl.ac.uk).