MRC National Survey of Health and Development

Neuroimaging sub-study (Insight 46)

Invitation to participate for a follow-up visit

Some time ago, you kindly came to UCL to have a variety of cognitive and other tests, and a brain scan. As you may recall from this visit, the study plan involved seeing all participants again for follow-up at two years.

We are writing to invite you for this second visit, and to provide you with an update on what we are requesting of you. Details are provided below, but in brief, the first day of assessments will be very similar to those that were performed during your first visit. The study now also includes an optional additional half-day visit the following day for some further testing.

As with the first visit, this follow-up visit complements the regular home visits and postal questionnaires.

Before you decide if you would like to participate, it is important for you to understand why the research is being done and what it will involve. Please take whatever time you need to discuss the study with your family and friends. Your participation is voluntary.

For this clinical sub-study, the research team responsible for the MRC National Survey of Health and Development (NSHD) is collaborating with neurologists who work at the National Hospital of Neurology and Neurosurgery, and Institute of Neurology at University College London (UCL).

UCL
UCL Bloomsbury Centre for Clinical Phenotyping

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What is Insight 46?

For most people, health changes gradually with age, often in subtle ways that we scarcely notice. We have already studied those changes by comparing the measures of health taken throughout your early life, and in adulthood, most recently at the 68–69 years home visit. From that we learned a lot about the processes of ageing, building on our knowledge of how factors across life influence health and function. Now we would like to measure health again, with a particular focus on memory and thinking, using a variety of measures to look at brain structure and function.

The specific aims of the Neuroimaging sub-study, also known as Insight 46, are firstly to identify the brain changes that accompany healthy ageing; and secondly to see if we can detect brain changes that in due course might help predict who is at risk of developing dementia, and Alzheimer's disease in particular.

We will then explore the genetic, environmental and lifestyle factors that contribute to this increased risk. We aim to be able to identify preventive measures to maintain good health and activity for as many years of later life as possible, and so to influence national health policy. We hope also to gain valuable biological information about early cognitive (memory and thinking) decline, which may in due course help determine how best to design drugs to prevent Alzheimer's disease and other forms of dementia, and how best to conduct drug trials aiming to see if these therapies are effective.

Why have I been invited to participate?

Insight 46 is a clinical sub-study of the MRC National Survey of Health and Development (NSHD), the British 1946 birth cohort study. You have been invited to participate because you are a member of this cohort study and kindly previously attended a baseline visit.

Do I have to take part?

No, your involvement is voluntary and it is up to you to decide if you would like to participate in this sub-study. You do not have to participate in all assessments that are being offered, and you can opt out of some or all of the assessments at any time. If you decide not to participate, this decision will not in any way affect your ability to continue to participate in the main NSHD data collections or any other NSHD clinical sub-study. It will not affect any NHS treatment you receive if you do not take part.

What will I have to do if I take part?

Participating in Insight 46 will involve you making a trip to London for a series of assessments and a scan, which are very similar to those that you participated in previously. We would additionally like to invite you to take part in an optional second day of assessments that will last for about half of the day.

We will find dates that suit you, reimburse you for any travel expenses, provide meals and refreshments, and will arrange for up to three nights' stay in a hotel. We would encourage you to bring a partner or someone who knows you well. The person accompanying you would also have all their travel and accommodation expenses reimbursed.

At the visit we would like to:

1) ask you about your health, medications and any concerns you have about memory; perform a neurological examination; and test your walking;
2) perform some tests of memory and thinking;
3) take blood and urine samples; and
4) perform a brain scan.

If you decide to stay for a second day of testing, we would like to:

1) perform ultrasound scans of your heart and the arteries in your neck (repeating the measures that were performed in 2006–2010);
2) ask you to wear a cap to measure blood flow to the brain while you do some tests of thinking and memory; and/or
3) perform a lumbar puncture.

You can opt to have some or all of these tests.

In addition to the tests above, we would like to ask you to wear a monitor on your wrist, which is the same size as a watch, to measure your sleep over a 7-day period.

More detail concerning what is involved with each of these investigations is provided below.

Pre-visit discussion

If you are interested in taking part, we would first give you the opportunity to discuss what is involved with a member of the research team by telephone. He or she will explain what the study involves, answer any questions you have, and will ask you some questions about your health and your medical history to ensure you are eligible to participate (e.g., make sure there is no reason why you cannot have an MRI brain scan). If, following this discussion you are eligible and willing to take part, we will arrange convenient dates for you to come to London.

A few days before your visit takes place, we would like to speak with someone who knows you well over the phone. We would prefer this to be the person who we spoke with when you came to the neuroimaging sub-study visit two years ago, but it can be any family member or friend who knows you well. We would like to ask this person a few questions about your memory, problem solving, hobbies and personal care. We would also like to ask them whether you have any previous history of delirium following a medical illness. This phone call will take approximately 15 minutes.

The visits

On the day of your visit you will be asked to come to the Bloomsbury Centre for Clinical Phenotyping. This is a new facility, owned by UCL, that has been specifically designed for studies of this kind. The building is located very close to the scanner. You will have the opportunity to discuss any questions or concerns you have about participating at that stage. If you decide to continue with the assessments, you will be asked to complete and sign a research consent form. We will give you a copy of the consent form to keep. If you have not already provided this information, you will also be asked to nominate a family member or friend who you would like to act as your consultee in the future, should you lose the ability to provide consent.

A typical overview of Day 1 is as follows:

DAY 1

Arrive at Bloomsbury Centre for Clinical Phenotyping
Greeting and tea or coffee

↓

Consent and history
approximately 15 minutes

↓

Tests of memory and thinking
approximately 1.5 hours

↓ Break 20 minutes

Physical examination
approximately 1.5 hours
(This will include a blood sample if you are not attending day 2)

LUNCH
approximately 1 hour

Additional tests of memory and thinking
approximately 1 hour

↓ Break 20 minutes

Transfer to Macmillan Cancer Centre
2 minute walk

↓

Walking test
approximately 20 min

↓

Brain scanning
approximately 1 hour

END OF DAY 1

Clinical assessments

We will ask you to update details of your family tree including familial history of dementia, Alzheimer's disease and Parkinson's disease and any medications you are taking. We will ask you some questions about your memory and thinking skills. With your permission, we will discuss other relevant research studies, which you may wish to consider or receive further information about. This part of the study will take no more than one hour, with suitable breaks.

With your permission, we will measure your height, weight and blood pressure; we will test your grip strength; and we will perform a standard neurological examination, which we will video. The videos will be used for research purposes only and all original recordings will be destroyed; digitised copies will be stored on a secure server at UCL. We will ask you to take off your shoes and socks and allow us to examine your arms and legs, but you will not need to undress. We would like you to do some walking tests while wearing an accelerometer, which is a small device attached to your waist, and a step test. These assessments will together take no more than 90 minutes, with suitable breaks.

Tests of memory and thinking

We will perform a variety of tests of memory and thinking. Some of these will be paper and pen assessments; others will be computer based. These assessments will take about two hours, with breaks if necessary. With your permission, we would like you to wear a wrist band during these assessments that measures your heart rate and skin conductance.

When we schedule your visit, we would also like to schedule a phone call with you exactly seven days after your visit. During the call, we will ask you to open an envelope that you will be given on the day of the visit. We will then ask you to provide some answers based on the content of the envelope. This call will take no more than 15 minutes of your time.

Donating blood, DNA and urine

With your permission, we will take a non-fasting blood sample (55mls, equivalent to 4 table spoons), and collect a sample of urine. Some of the blood will be sent to laboratories to derive cell lines that will be used to generate different types of cells (for example, nerve or muscle cells); and some of the blood and urine will be stored in the Institute of Neurology and used to try to develop new tests for detecting early dementia. The remainder of the blood will be used to extract RNA, which will be sent for sequencing. This sequenced information will then be safely and securely stored by the study team, and used to try to understand the genetic causes of early dementia.

What are the risks of having a blood test?

Blood taking is a routine and very safe procedure and will be performed by trained personnel. Some people can feel faint during the procedure, which will therefore be performed sitting or lying down. There is a small risk of bruising.

Sleep monitor

We will ask you to wear a small device on your wrist for 24 hours each day for 1 week. This device, which is about the size of a large watch, will monitor your wake and sleep patterns. The device is waterproof so it does not need to be removed at any time, and it should not interrupt your daily living.

Brain scanning

The brain scan will be identical to the scan you had done previously.

What type of scan will I have?

At the end of the day, we will invite you to have a brain scan on a special PET/MRI scanner housed at University College Hospital. You will either be accompanied there on foot or by taxi as required. This scanner allows PET and MRI scanning to be done at the same time. PET stands for Positron Emission Tomography. A PET scan can be used to demonstrate if certain proteins are building up in the brain. MRI stands for Magnetic Resonance Imaging and produces an electronic picture of brain structure created using a strong magnet instead of an X-ray.

Before you have a scan, the researchers will ask you some questions to make sure it is safe for you to have the MRI. Metal items may interfere with the MRI and some can be potentially hazardous.

These include but are not confined to: cardiac pacemaker, aneurysm clip(s), implanted insulin/drug pump, neurostimulator (TENS unit), hearing aid/cochlear implant, surgical clip or staple(s), heart valve prosthesis, dental braces or any type of removable dental items. It is essential that you tell the study team if there is any possibility that you might have metal in your body. You will be asked to remove any dentures, hair clips, combs, earrings, and necklaces just before you enter the scanner. You can eat and drink as normal before a PET/MRI scan.

Why am I having this scan?

In this study we are using the PET scan to look at the levels of a protein (β amyloid) that occurs in the ageing brain and Alzheimer's disease. The scan will use a very small amount of radioactive substance called Florbetapir to show up the protein (β amyloid). The MRI scan allows us to assess brain structure, connections and blood flow, and to see if there have been any damage to the blood vessels.

What will happen before, during, and after the scan?

Before you enter the scanner, a small cannula (tube) will be inserted into one of the veins in your hand or arm. When you are ready to go into the scanner you will be asked to lie flat on your back on the scanner bed, which will then slide into the scanner. A small dose of Florbetapir will be injected through the cannula just as the scan starts. You will be able to press a button when you are in the scanner to tell the study team if you feel uncomfortable or want the scan to stop. You will need to lie as still as possible during the scan as this helps to ensure that the images we collect are of a good quality.

The scanner makes loud knocking noises during the scan; we will provide you with earplugs which will help to reduce the level of noise for you. The scan will take no more than one hour to complete. Before you leave the scanning department, you will be given time to rest and ask any questions you may have about the study. The day after the scan we will telephone you to see how you are and to answer any further questions you may have. We will give you a telephone number for you to call if you have any problems or concerns and wish to speak to one of the researchers in the interim.

What are the risks of the scan?

Many thousands of people have been imaged using Florbetapir, which has proven to be very safe. Florbetapir was licensed for clinical use in Europe in January 2013. A side-effect, affecting approximately 1 in 100 people, is headache. There have been no known harmful reactions to Florbetapir compounds. Despite this, there is still the possibility of a rare allergic reaction. Venous cannulation is a routine medical procedure that has minimal risk when performed by trained personnel. A cannula is a flexible tube containing a needle that is inserted into a vein in your hand or arm. The Florbetapir will be injected through the cannula. Some people feel lightheaded following insertion of a cannula and there is a risk of fainting.

To minimize these effects, the cannula will be inserted in the vein while you are sitting down. Having a cannula inserted can cause some discomfort and there is a very small risk of blood clots, bruising and infection.

Florbetapir is a radioactive substance and you will receive a radiation dose from it. The total amount of radiation that you will receive will be 7mSv, which is 3 times the normal radiation to which people living in Britain are exposed to naturally over one year (2.5mSv), and is equivalent to driving an extra 7000 miles in a year. The additional risk of death from cancer if you were to live another 30 years is extremely low (estimated to be ~1 in 3000). As with all studies involving radioactivity, specific permission has been obtained to ensure that the levels of radiation to which you will be exposed are safe, and a nominated expert nuclear medicine doctor at the Institute of Nuclear Medicine will oversee this part of the study. We have previously performed research scans using this tracer on healthy volunteers without any complication. You may feel claustrophobic or uncomfortable lying in the PET/MRI scanner. You can ask to stop the scan at any time.

Please inform one of the researchers if you have had any research or clinical scans in the last 12 months as this may affect your eligibility to take part in Insight 46.

Additional measures on Day 2 (optional)

We would like to invite you for a second day of additional measurements. You may choose to have all, some or none of these tests. Please only have a light breakfast without caffeinated drinks before arriving for your visit on day 2. A typical overview of day 2 is as follows:

DAY 2

Return to Bloomsbury Centre for Clinical Phenotyping
Greeting

↓

Consent
approximately 10 minutes

↓

Lumbar puncture procedure
approximately 45 minutes
(This will include blood and urine collection)

↓ Break 10 minutes

Assessments of cardiovascular health (heart imaging) and functional near-infrared spectroscopy (blood flow testing)
approximately 2.5 hours

↓

Spoon taste assessment
approximately 15 minutes

END OF DAY 2
(around lunchtime)

Assessments on Day 2

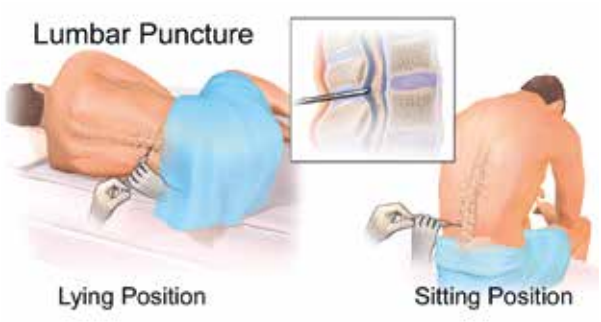
Lumbar puncture

What is a lumbar puncture?

This is a procedure in which a small amount of cerebrospinal fluid is removed by inserting a needle in the lower back. Cerebrospinal fluid is a clear and colourless liquid produced in the brain that circulates around the brain and spinal cord. As it is in direct contact with the brain, it can provide unique and invaluable information about brain chemicals. We will use the fluid to look for biological markers of ageing and very early dementia and we may share this fluid, in anonymised form, with other specialist centres (academic and commercial collaborators) within and outside the UK.

What happens during the procedure?

You will be asked to have a light breakfast and then change into a gown and to lie on a bed curled up on your side, enabling the clinician to clean your lower back with antiseptic. Alternatively the trained specialist performing the test may decide that it will be easier for you to have the lumbar puncture in a sitting position leaning forward. The person performing the test will then inject a local anaesthetic



Blausen.com staff (2014). *Medical gallery of Blausen Medical 2014.* WikiJournal of Medicine 1(2). DOI:10.15347/wjm/2014.010. ISSN 2002-4436.

(lignocaine – similar to the injection used for dental procedures) into the skin of your lower back. When the area is numb, a very thin needle will be inserted into the spinal canal in the lower back below the level where the spinal cord ends. 20ml (2 tablespoons) or less of spinal fluid will be removed for analysis and storage. Your body will replace this spinal fluid within 1-2 hours. The procedure, from start to finish, will take no more than one hour. We will ask you to rest for up to one hour. Please refer to **http://tinyurl.com/Insight46LP** to see a video of someone having a research lumbar puncture for a related study.

What happens afterwards?

After the procedure, you will sit or lie flat for about an hour to decrease the risk of headache. You will be given something to drink after the procedure. You should not do any strenuous physical activity for 24 hours after the procedure. This includes lifting, bending, doing housework, gardening, or doing exercise such as jogging or bicycling. The study team will contact you the day after the lumbar puncture, and subsequently as required, to ensure you are well.

What are the side effects?

The most common side effect of a lumbar puncture is a headache which is worse on standing/sitting but improves significantly on lying down. About 1 in 10 of those receiving a lumbar puncture (for any reason) report a headache. Such headaches are usually mild and last 0-2 days. If you experience a typical post-lumbar puncture headache, you will be advised to take bed rest, and painkillers if needed. In rare cases (less than 1 in 250 of all individuals) the headache may be persistent for more than 7 days despite simple

painkillers and bed rest. In such cases the headache can be treated by a blood patch, which involves a specialist injecting a small amount of your own blood into the spinal canal, under local anaesthetic. On the remote chance that this was required, we would arrange for this to be done either at the National Hospital for Neurology and Neurosurgery in London, or at your nearest appropriate neuroscience centre where it can be performed.

Mild backache following the lumbar puncture may occur. Nerve damage after a lumbar puncture is extremely rare. Sometimes during the procedure the nerves that float in the spinal fluid can touch the sides of the needle causing them to be stimulated and when this happens a feeling like an electric shock or tingling may occur lasting for a few seconds.

The risk of bleeding and bruising following a lumbar puncture is very small and you will not be offered a lumbar puncture if you are taking certain medications, including warfarin or clopidogrel, or if you are known to have a bleeding disorder or a clotting problem. The risk of infection being introduced by the lumbar puncture needle is extremely rare. Other extremely rare complications (reported by fewer than 10 individuals in the world) are mild double vision or mild hearing loss, which come back to normal after few days. All precautions are taken to anticipate potential problems and minimize these risks.

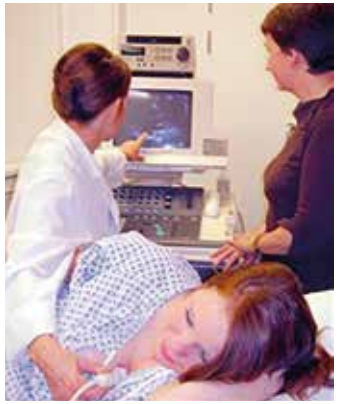
We have previously performed many research lumbar punctures on patients and healthy volunteers in several other studies. You can ask to stop the lumbar puncture at any time.

Cardiovascular tests

We will look at your heart function by doing an electrocardiogram (ECG). The ECG is a tracing of the electrical activity produced by the heart while it beats. For this test, we will place a few small, sticky sensors called electrodes on your chest. The test will only last a few minutes.

We will also look at your heart and artery function by using a small hand-held ultrasound scanner across your chest and neck. These assessments will be the same as you had at age 60–64. Ultrasound scans do not use radiation and are safe and painless. In total these scans will take about 60 minutes to perform.

For the ultrasound of your heart, you will be asked to lie on your left side while a probe and a small amount of gel are placed on your chest. The probe will be moved to different positions to allow for moving images to be taken of the heart from different angles. The ultrasound of your heart shows the thickness of the walls of the heart and the size of the heart chambers. It tells us how well your heart is working.



For the ultrasound of your arteries, the probe and a small amount of gel will be placed on your neck and chest. As with the heart ultrasound, the probe will be moved to different positions to be able to see different angles of your arteries. This ultrasound looks at the health of your arteries.

We will also measure the speed of blood flow by applying a cuff around your leg and a small Velcro band (like a necktie) around your neck. This assessment will be the same as you had at age 60–64.

If you choose to do the lumbar puncture, we will do the ECG and the ultrasound while you are resting after the lumbar puncture. If you choose not to do the lumbar puncture, these tests will be done on their own on day 2 of your visit.

Functional near-infrared spectroscopy (NIRS)

We will perform a test that looks at oxygenation of your brain during a few memory and thinking tests. This will involve you wearing a cap that is embedded with multiple optical fibres that examines changes in the reflection of near-infrared light from your brain. It is completely safe and painless, and it will last for about 60 minutes.

Spoons test

We will perform a taste test using spoons that are made of different types of materials. You will be asked to taste each spoon and to place the spoons in an order based on how you find each taste. This test will only last for about 15 minutes.

Credit: Zoe Laughlin, Institute of Making, UCL

Ending involvement in the Neuroimaging sub-study

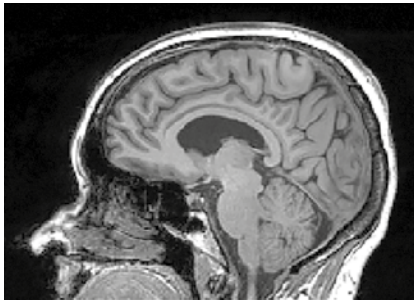
You can decide to end your involvement in this sub-study at any time. A decision to withdraw would not affect any ongoing care, or stop you from continuing with the main NSHD data collections. Information about you that has already been collected as part of your involvement in Insight 46 may be retained. If at any point during your participation, the Chief Investigator or the study sponsor or the director of the study determines that it is not in your best interest to continue the study, or if it is determined that no further valuable data can be obtained, they will stop your participation in the study, with no cost or consequence to you. This would be explained to you at the earliest possible opportunity.

Involvement of your General Practitioner (GP)

If you consent to participate in this follow-up visit of Insight 46, we will again ask for your consent to inform your GP of your involvement in the study. If you are not happy for your GP to know that you are participating in this study it will not be possible for you to take part.

What are the possible benefits of taking part?

If during the course of Insight 46 we determine that you do have significantly elevated blood pressure, with your permission we will inform you and your GP. We will also inform your GP if the neurological examination reveals any significant abnormalities that



the investigators consider it would be in your interests to know. We will not routinely provide you or your doctor with the results of the brain scans as they are for research purposes only, but will let you and your doctor know if there are any major abnormalities on the MRI scan (e.g. the presence of a tumour or a large aneurysm) which might affect your clinical care. You should be aware that being in a research study does not take the place of routine physical examinations or other appointments with your doctor, and should not be relied upon to diagnose or treat medical problems. The heart and carotid ultrasound artery scans are being taken for research purposes. However, if the technician notices anything that requires further investigation, the test may take slightly longer so that a clinical report can be sent to your GP. In that case, you will be advised to discuss the results with your GP.

New Information

New information acquired during the course of the research that may affect your involvement in Insight 46 will be discussed with you as soon as possible after the findings become available to the study Chief Investigator.

Confidentiality and use of information

Any information collected during Insight 46 will be kept strictly confidential. Assessment and test results will be stored on a secure, confidential, computer network on the UCL system, accessible only to members of study team. We shall collaborate in our studies with research and clinical scientists in other centres in Britain and overseas, and they will have access only to anonymous computer-based information. Only members of the research and clinical team will have access to identifiable information. We shall keep the information for the foreseeable future in order to continue our studies of ageing. We will protect your personal information in accordance with UCLH NHS Trust Information Governance policy; the handling, processing, storage and destruction of data will be conducted in accordance with the UK Data Protection Act (1998) (and any amendments thereto) to ensure that confidential information is safeguarded.

Expenses and Payments

You will not receive any payment for participating in this study. However, travel and hotel costs and the costs of meals/drinks during your visit, for you and the person accompanying you, will be reimbursed. We will discuss your travel arrangements with you and either arrange or help you to arrange travel and hotel bookings for you and the person accompanying you.

What if there is a problem?

If you or your relatives have any concerns about Insight 46 you can speak to a member of the research team who will do their best to answer any questions. Contact details are at the end of this information sheet.

If you wish to complain, or have any concerns about any aspect of the way you have been approached or treated by members of staff you may have experienced due to your participation in the research, National Health Service or UCL complaints mechanisms are available to you. Please ask a member of the research team if you would like more information on this.

In the very unlikely event that you are harmed by taking part in this study, compensation may be available to you. If you suspect that the harm is the result of the Sponsor's (UCL) or the hospital's negligence then you may be able to claim compensation. After discussing with the research team, please make the claim in writing to Prof Jonathan Schott who is the Chief Investigator for Insight 46 and is based at the Institute of Neurology. The Chief Investigator will then pass the claim to the Sponsor's Insurers, via the Sponsor's office. You may have to bear the costs of the legal action initially, and you should consult a lawyer about this. NHS Indemnity does not offer no-fault compensation i.e. for non-negligent harm, and NHS bodies are unable to agree in advance to pay compensation for non-negligent harm.

What will happen to the results of the research study?

We shall, as in the past, continue to publish the results of our research in medical and research journals, and let you know each year (with the birthday card) what we have published and where. References to all the publications will continue to be available on our web site (www.nshd.mrc.ac.uk). No one in the study will be identifiable in any report or publication.

Who is organising and funding the research?

Insight 46 is being organised by researchers at the MRC National Survey for Health and Development, the Institute of Neurology and the Institute of Nuclear Medicine, UCL. It is sponsored by UCL. Funding for the study is from the Wolfson Foundation, Alzheimer's Research UK, and the Medical Research Council. AVID Radiopharmaceuticals (a subsidiary of the pharmaceutical company Eli Lilly) are supplying the Florbetapir tracer at no cost, but have had no part in the design of the study, and will have no influence over the way in which results are published.

Who has reviewed the study?

This research project has been reviewed by the London Queen Square Research Ethics Committee.

What happens next?

If you are interested in taking part, a member of the research team would like to talk to you on the phone and answer any questions you may have about the study and to discuss any medical conditions that may affect your participation. Following this discussion, and if you agree to participate, a member of staff from the research unit will contact you to arrange a mutually convenient time for your first visit and organise travel and overnight accommodation if needed.

If you have any queries about your appointment please contact:

Ms Heidi Murray-Smith
Institute of Neurology
London
WC1N 3BG

Telephone: 020 3448 3853
Mobile: 07557 393419
Fax: 020 3448 3104

If you have any queries about the NSHD please contact:

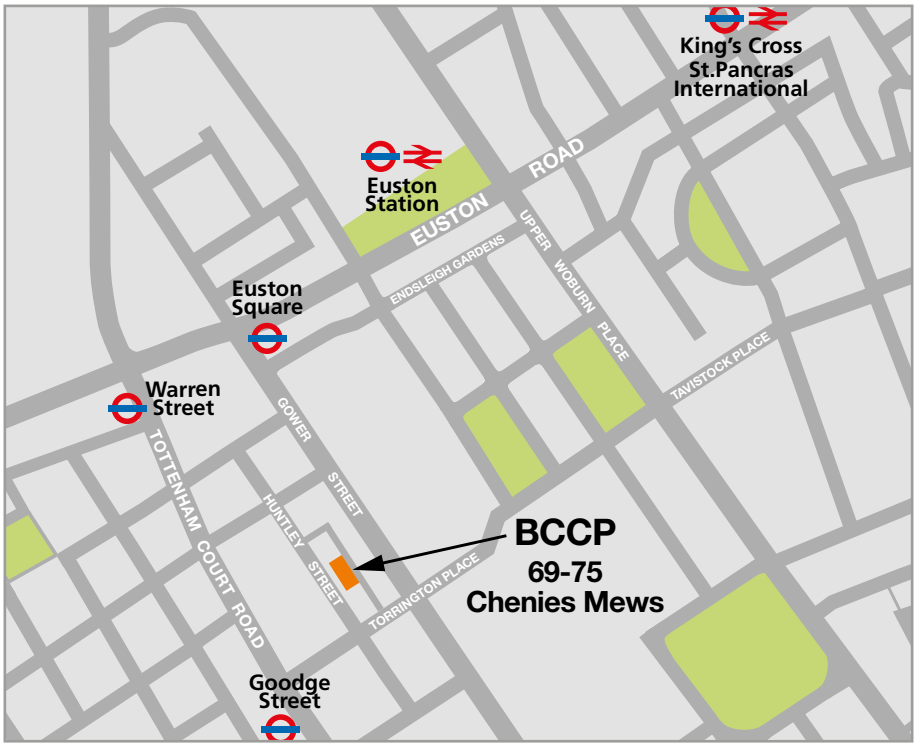
Dr Andrew Wong
MRC National Survey of Health and Development
MRC Unit for Lifelong Health and Ageing
33 Bedford Place
London
WC1B 5JU

Telephone: 020 7670 5700
Fax: 020 7580 1501

E-mail: **andrew.wong@ucl.ac.uk**
Web: **www.nshd.mrc.ac.uk**

Location of the Bloomsbury Centre for Clinical Phenotyping

The Bloomsbury Centre for Clinical Phenotyping is located at 69–75 Chenies Mews (WC1E 6HX).



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Nearest tube stations are Goodge Street (Northern line), Euston Square (Northern line), and Euston Station (Circle, Hammersmith & City, and Metropolitan lines).

Buses 14, 24, 29, 73, 134, and 390 serve the Centre.

Nearest mainline train stations are Euston (0.5 miles), King's Cross and St. Pancras International (1.0 mile).

MRC Unit for Lifelong Health and Ageing

UCL

National Survey of Health and Development, 2017