

**Parent/Guardian Information Leaflet, Version 1.1 – 02/03/15**

## **Generation of induced Pluripotent Stem (iPS) Cells and Rare Diseases**

### **Induced Pluripotent Stem (iPS) Cells and Rare Diseases**

Many people in the UK are said to be living with a Rare Disease. Living with a Rare Disease can have a major impact on a person's quality of life and on their close relatives. There are an estimated 7000 different Rare Diseases and most of these are inherited. Many genes causing these diseases have been discovered with the help of thousands of NHS patients and healthy volunteers. The next step in the journey to better help individuals and their close relatives is to improve our understanding as to how the genes identified cause ill-health.

We would like to invite your child to take part in the above research study. Before you decide whether or not your child can participate, you need to understand why the study is being done and what it will involve for your child. Please take time to read the following information leaflet carefully. Ask us if there is anything that is not clear or if you would like more information. Talk to others about the study if you wish. Participation is entirely voluntary.

### **Why has my child been invited?**

Your child has been identified as someone who has a Rare Disease, and may have already joined the NIHR BioResource – Rare Diseases (NIHRBR-RD). We hope that you/your child are interested in taking part.

### **What will happen to my child if they take part?**

If you are interested in your child participating, a member of their NHS Clinical Care team or from the NIHR BioResource - Rare Diseases team will contact you via phone, text, e-mail or letter to arrange an appointment. This generally will be at the NHS hospital where your child receives clinical care. A nurse, doctor or another appropriately trained and qualified healthcare worker will see your child when you attend to explain what will happen in detail and you will have the opportunity to ask further questions. If all questions have been answered to your satisfaction and you agree for your child to take part in the study, you will be asked to sign a consent form.

### **Does my child have to take part?**

It is entirely up to you and your child to decide whether or not your child should take part. If you/your child decides to take part you will be asked to give informed consent for your child to take part by signing a consent form. You are free to withdraw your consent at any time without giving a reason. This decision will not affect your child's future medical care.

### **What is the purpose of the study?**

Researchers would like to use iPS cells made from your child's donation to make many different types of cells in the laboratory. iPS cells are believed to have the

same properties as embryonic stem cells but they have the advantage of not being derived from human embryos. Another benefit of using iPS cells is that it allows for the creation of cell lines that are genetically customized to an individual and their DNA code is almost identical to the DNA code of the person who has given the sample. Therefore, researchers can use iPS cells to study the relationship between the genetic make-up (genotype) of individual cells and their characteristics or traits (phenotype). The behaviour of these cells can be investigated to gain better insights into the causes of diseases.

### **How are iPS cells created?**

iPS cells are generated in the laboratory from donated cells by a process called genetic reprogramming. Genetic reprogramming refers to changing the fate of your child's donated cells to become (convert to) another type of cell. At a first stage they are turned into iPS cells, which are immortal and can be stored indefinitely at low temperatures for later use. The iPS cells will be stored in a repository, and copies can be made in the future by cloning for use in a wide range of research studies. At a later stage the iPS cells can be grown under different conditions to generate cells which can become any type of tissue, e.g. muscle, blood, liver, depending on the conditions under which they are grown.

### **What is cell cloning and what can we achieve with it?**

Cloning refers to the process of making identical copies of a cell in the laboratory, giving a large number of identical cells which can be stored at low temperatures for later recovery and use.

With cell cloning, copies of the iPS cells and of other cell types can be stored indefinitely and used in the future for a wide range of research studies.

### **What samples are required for this study?**

We can produce iPS cells from several cell types present in the donated samples, e.g. skin cells, blood cells, cells from hair roots and even the small number of cells present in urine. We will discuss with you the most suitable source of cells considering your child's Rare Disease, but generally cells obtained by skin biopsy (a very small piece of skin) are the preferred option.

This study involves the donation of a small skin sample, a blood sample or in some cases, a sample of urine or several root hairs, for the generation of Induced Pluripotent Stem (iPS) cells for use in research studies..

For this study we will ask you to donate:

1. a small skin sample\*
2. a blood sample of up to 50 ml (three tablespoons),
3. on some occasions, we may also ask your child to donate a sample of urine (about a cup full) or several plucked hairs
4. surplus cells from a scheduled diagnostic or biopsy test (e.g. to take a sample of breast tissue, lymph node, kidney, liver, cerebral spine fluid, etc.); usually there are some cells left over after the test is completed and these could be used to produce iPS cells.

5. surplus cells from tissues that may be removed during a scheduled operation and which, similarly, can be used for research
6. finally; cells may be harvested from the blood or bone marrow and stored for future treatments but, in the harvesting system, some cells remain and these can be made into IPS cells.

*\* if there are medical reasons to not take a skin sample then a blood sample may suffice and this will be discussed with you; also in some circumstances we may require a blood sample of up to 75ml (five tablespoons) in total.*

Generally, we will try to arrange that samples for research are collected when your child already has an appointment to come to the hospital. The research appointment will last approximately 30 minutes. On occasions we may ask your child to come especially to the hospital to donate these samples for research, but we will pay travel expenses then.

### **What does a skin biopsy involve?**

A skin biopsy is usually taken from the upper arm. Alternatively, it may be taken from the inner lower thigh or upper calf areas. A local anaesthetic is used to numb the biopsy site so usually you do not feel any pain when the skin sample is taken. A special small needle is used to take the biopsy. The needle is gently inserted into the skin and rotated so that a small circle of skin can be carefully removed. The biopsy size is 2-4 mm in diameter (i.e. up to half the size of a small pea).

### **What happens after the skin biopsy and blood sample is taken?**

The biopsy site occasionally bleeds slightly immediately after the procedure, but stops when pressure is applied to the site. The skin biopsy site is closed with steri-strips (a type of sticky plaster) and covered with an adhesive dressing and your child will be able to go home. Steri-strips will need to be kept on the biopsy site and the area kept dry for at least 2 days. A blood sample will be taken in the usual way from one of the veins in your arm. A small plaster will be placed on the site where the blood was collected; this can be removed after 3 hours.

### **What are the possible disadvantages and risks involved with a skin biopsy and the taking of a blood sample?**

In some instances people may experience

1. light-headedness and fainting during or just after the procedure,
2. bruising and some bleeding,
3. increased tenderness,
4. localised infection which can follow any invasive procedure,
5. minute scarring.

Every precaution will be taken to minimise the chances of these risks occurring. If you have concerns for your child following the test when you are back at home then please contact the research team which collected the samples.

### **How will my child's samples be used?**

Samples your child provides will be used for a wide range of research studies either in the UK or overseas. Researchers overseas, just like the researchers in the UK, will have to follow the laws and guidelines that apply to research in their country.

We will use your child's donated samples to generate iPS cells. If the cells are generated from the skin biopsy then the first step is to isolate a specific type of cell, known as a fibroblast and in a second step iPS cells are generated from the fibroblasts. Because the process of generating clones of iPS cells is not simple we may not always succeed. If we succeed, the cloned iPS cells will be stored indefinitely for future use in research and shared with researchers around the world. Other cells, e.g. the fibroblasts (a type of skin cell) will also be stored indefinitely and may also be shared with other researchers.

We will isolate, amplify (chemically copy), and store:

- Cells (e.g. blood cells, fibroblasts, iPS cells, etc.) derived from your child's donated tissues,
- DNA and RNA from your child's donated cells and from other bodily fluids (e.g. urine, etc.),
- Blood plasma, serum and other bodily fluids (e.g. urine, etc.).

Researchers will analyse these materials for research purposes and perform all sorts of measurements on protein, lipid, carbohydrate and other molecules and other tests, which may include the deciphering of your child's DNA or RNA code in its entirety. Genes are made out of DNA and that is why we want to analyse your child's DNA in order to find out what genes may have contributed to them having a rare disease. RNA is also analysed as this is the version of the DNA code that the body uses to direct how proteins are made.

Data will be collected by making measurements and performing other tests on your child's donated tissues and the derived iPS cells, and on other cells and fluids. The information gleaned from your child's DNA (or RNA) will be deposited in a research database, which is not accessible to everyone. Researchers can ask for access to your child's DNA (RNA) code by completing an online request and they have to explain why they want the data, e.g. which research question are they trying to answer. Genuine researchers will be given access to the data for their research and they will be reminded of their obligation to keep your data safe by accepting the conditions of a data transfer/access agreement. It is important that you understand that the DNA code of iPS cells is near-identical to your child's DNA taken from other samples (e.g. blood, hair, skin).

### **How will my child's iPS cells be used in the future?**

There are about 200 different types of cells in the body, any of which researchers may want to generate from the stored iPS cells or from your child's other stored cells. The type of cells which may be generated from your child's donated cells may be for example, endothelial cells which line the inside of your blood vessels, stem

cells that make all of your blood cells, neuronal cells like the ones present in brain, or liver cells. The majority of these cell types are generally inaccessible and iPS technology provides a powerful alternative to create and study cells from certain organs for use in research.

The iPS cells and other cells derived from your child's donated tissues will also be deposited in a repository, from which they will be made available to other research and healthcare groups in the UK and overseas. These groups may be in the public or non-profit sectors, or commercial companies and industry, and the cells may be used for research or commercial purposes.

The iPS cells and data will be available for use for many decades; for example clones of cells which were generated during the early Sixties and related data are still being used across the world by thousands of researchers and their work with these lines has resulted in many benefits for patient care.

### **Will my child's information be kept confidential?**

We will protect your child's personal information at all times. Their skin, blood and other samples, including the iPS cells, will be labelled with unique sample identifier numbers before being transferred to the research repositories. Your child's name and contact information will never appear on the samples that are stored for the long term and/or are distributed to researchers.

### **Are there risks associated with placing data from my child's cells in a research database?**

We will place anonymised data from your child's samples and cell lines in a managed access database, which means that researchers would need to complete an online request form explaining why they wish to have access to the data. No personal data about your child other than their gender, ethnicity, approximate year of birth (in 5 year bands) and their type of Rare Disease will be available from the database. This means that neither your child's name, nor contact details nor other data from their medical and other health records will be available.

As each person's DNA sequence is unique, it would be possible in principle, for someone who already has genetic data from your child to make a match. This would not be permitted as part of this study using the iPS cell lines or DNA derived from your child's sample. It would also be possible to make a match to genetic data from a close relative. Because the Y chromosome is inherited through the male line, genetic data from the Y chromosome can in some cases be used to guess a surname from a more distant relative. The chance of this happening is small as only *bona fide* researchers are allowed to use your child's DNA data, but in theory, a dishonest person may decide to not adhere to the agreements and policies. However even if a match is made, the information about your child that a user can access from the data made available in this study would be their gender, ethnicity, approximate year of birth (in five year bands), type of Rare Disease and data derived from their iPS cells and the results of the scientific analysis of their donated samples. Although extremely unlikely, such a person could attempt to identify your



child, by linking information about their DNA code with genetic information taken from genealogical databases.

### **How can researchers invite my child to take part in another study in the future if they do not have their personal identifiers?**

If a researcher would like to approach you/your child for another study or ask for another sample as part of this study then they will contact your child's Clinical Care team or the NIHR BioResource team and provide the unique sample identifier number. The information from the consent form, which contains your child's personal details will be entered into a database that also contains your/ your child's contact information (address, phone and mobile numbers, email address, information about your Clinical Care team, etc.). This database can only be used by designated members of the NIHR BioResource or Clinical Care teams for the purpose of contacting you/your child for future studies or sending you additional information. If you are contacted for a further study you/your child are free to decline without giving a reason.

### **Is there something wrong if my child is asked to give another sample?**

No. There are many reasons why researchers may want to ask your child to give another sample. They may want to reproduce former results or may wish to invite you to join another study.

### **What will happen to the results obtained from my child's samples?**

Results of this study will be made available to the public through scientific publications, including placing information on a research database (data about your child's samples will require a special access request, see above), in press articles, in project leaflets and through social media. Under no circumstances would your/ your child's personal information be disclosed in any publication without your explicit written permission.

### **Can I know the results obtained from my child's samples?**

As outlined above, for protection of your/your child's privacy, your child's samples will be kept completely separate from their personal details and contact identifiers. It is not planned to feed back any research results to participants as it would be of no direct benefit to them. The only occasion that any laboratory test results would be communicated back to you/your child would be in the event that something is discovered that has an immediate impact on your child's healthcare (e.g. severe anaemia, a very high white blood cell count which may point to a serious illness, etc.), but you will not receive the results of any genetic testing on your child. If we wish to feedback laboratory test results (but not genetic test results) to you/your child researchers will contact your Clinical Care team or the NIHR BioResource team. Feedback of results will only happen if you have granted permission for feedback of research findings at the time of consent.

You may wonder if a clone of your child's cells has been established from which all different cell types in their body can be generated, whether this could be of benefit to your child, a relative or someone else with the same Rare Disease. It is hoped that

in future we may be able to use this for the treatment of some Rare Diseases, but we must be clear that we cannot use the iPS clones generated from your child's cells for this purpose. This is for several reasons. Firstly, we don't know yet whether cells derived from iPS cells are safe. Secondly, we don't generate the iPS cell clone under conditions of culture which are suitable for possible future applications in treatment. Research is being performed in many laboratories around the world to address these important questions.

### **Who will work with my child's samples?**

The primary laboratories working with your samples are NHS Blood and Transplant, the NIHR Biomedical Research Centres and Units, their associated NHS Hospitals and research institutes. These centres are in Cambridge, London (Imperial College, Guy's, King's and St Thomas', University College London Partner Hospitals), Newcastle and Oxford. Many of these centres work closely with the Wellcome Trust Sanger Institute which is one of the locations where iPS cells are generated and the European Bioinformatics Institute in Hinxton (Cambridge), and the University of Dundee. The Clinical Care teams also work with Genomics England, a not-for-profit company established by the Department of Health. The NIHR BioResource – Rare Diseases aims to expand the number of UK hospitals and affiliated research institutes that make use of the BioResource; therefore the number of collaborating centres in the UK will continue to grow. Furthermore, as described above, iPS cells and other components derived from your child's donated samples will be available to other research and healthcare groups in the public and commercial sectors, including industry in the UK and overseas, via repositories in which we deposit the iPS cells and other components derived from your child's donated samples.

### **Expenses and payments**

We will cover reasonable expenses for travelling to the sample collection point if you/your child is especially attending for research. If samples are taken during your child's routine NHS care visit then we are not able to provide these expenses.

### **What is the benefit of being involved in this project?**

There will be no direct financial or medical benefit to your child if they choose to participate. However, there may be a benefit to the future development of healthcare provision, and the long-term understanding of Rare Diseases and of many other diseases. It is hoped by making the biological material obtained from your child available to many researchers across the world that research towards a treatment, or even a cure, for some Rare Diseases will be better facilitated. We would however like to be clear that efforts to develop a treatment or cure may take decades and there is no guarantee of success.

### **What happens if the funding for this project stops?**

This study is currently funded by the Medical Research Council, National Institute for Health Research (NIHR), Wellcome Trust, and from time to time by other funders of research. The research repositories will distribute iPS cells and other cells and materials derived from your child's donated samples to researchers. They will be charged a fee for the service provided and this fee will include the costs of

maintaining the collection of donated materials, including the iPS cells. The results of analysis and research data generated on the donated samples and the iPS cells will be deposited at the European Bioinformatics Institute in Hinxton, south of Cambridge. This institute maintains many of the large datasets of biomedical interest. If funding for the research repositories ceases then all samples will be discarded following normal procedures.

### **Who has reviewed this study?**

All research in the NHS is reviewed by an independent group of people called a Research Ethics Committee to protect your safety, rights, wellbeing and dignity. This study has been reviewed and was given a favourable opinion by the East of England- Cambridge [Central](#) Research Ethics Committee.

### **What happens if an invention is made using my sample?**

You/your child are giving your child's samples and related data as an absolute gift. An "absolute" gift is a gift which is given as a donation, i.e. without receiving a payment and without conditions. In the future, your child's sample may help us or others to make an invention, e.g. develop a new product to diagnose or treat your child's disease or other diseases. If an invention results from the research undertaken with your child's sample, you/your child will not receive any compensation or payment. The inventors may work together with commercial companies and industry to develop inventions for the benefit of patients and we hope that such products are brought into use by the NHS to improve healthcare.

### **Can I withdraw consent for my child after participating?**

Study participants can withdraw from the study at any time and without giving a reason. If you wish to withdraw your child, please contact the NIHR BioResource – Rare Diseases team on Freephone 0800 0853650 and a withdrawal form will be sent to you. Please note that we will not be able to remove results from the study or any tests and measurements already obtained using your child's sample from the databases and laboratory notebooks and we would also not be able to remove your child's samples, cloned cell stocks, including the iPS cells and any materials derived thereafter. We will take care however that your child will not be contacted anymore by the NIHR BioResource or your Clinical Care team in relation to any follow-up studies for this research project.

### **What arrangements have been made regarding insurance?**

The Cambridge University Hospitals NHS Foundation Trust & University of Cambridge are joint sponsors of this study and therefore cover is provided under the NHS and University indemnity schemes.

In the event that something does go wrong and you are harmed during the research and this is due to someone's negligence, then you may have grounds for a legal action for compensation against NHS CUH, but you may have to pay your legal costs. The normal NHS complaints mechanisms will still be available to you



**What if there is a problem?**

Any complaint about the way you/your child have been dealt with during the study or any possible harm your child might suffer will be addressed. If you have a concern about any aspect of the study, you should ask to speak to the researchers who will do their best to answer your questions [Name of PI & contact details inserted here-local for each participating site]. If you remain unhappy and wish to complain formally, you can do this by contacting the NHS PALS (Patient Advice and Liaison Service) [insert contact details].

**Whom do I contact if I have further questions?**

If you have any questions or wish to comment about any aspect of this study, please contact Sofie Ashford (Research Manager) of the NIHR BioResource – Rare Diseases on Freephone 0800 0853650 or email

[rarediseases@nihrbioresource.org.uk](mailto:rarediseases@nihrbioresource.org.uk) or contact a member of your Clinical Care team.