

Furthering our understanding of early human development for the generation of stem cells

We would like to invite you to donate your frozen embryos for a research project that is focused on furthering our understanding of early human embryo development. All embryos donated will enable research to progress and your donation is a valuable contribution. Since all research builds on the findings of earlier research, please be assured that your donation will be a valuable contribution to this research, and to future research.

Embryos can be donated to this research project whether stored for your own use in the future or donated to help others conceive but are now no longer required or unable to be used. Before you decide, it is important for you to understand why the research is being undertaken and what it will involve. You are invited to take as much time as needed before making a decision on whether or not to participate in research focused on an important aspect of early human development. We very much appreciate you taking the time to read this document.

All research on embryos has been approved by Research Ethics Committees including Cambridge Central Research Ethics Committee, Newcastle and North Tyneside Research Ethics Committee, and by the Human Fertilisation and Embryology Authority (HFEA). Your embryos will only be stored for the length of time you have consented. Only licensed researchers will have access to the stored embryos.

1. Introduction to the research

Choosing the right embryo for transfer is one of the most difficult tasks faced by an embryologist during assisted reproduction treatment. In a group of embryos created after IVF or ICSI, we can grade an embryo based on its appearance and cell number, but this may not necessarily be the embryo that is most likely to lead to the birth of a healthy baby. Over the past decade, research has provided advanced new technological tools that have led to a deeper understanding of embryo quality, the factors involved in the differentiation of early embryonic cells that lead to the formation of tissues (stem cell differentiation), and how the embryonic tissues interact with the lining of the womb to establish a successful pregnancy. At present, these new tools are still under evaluation and are available only in academic research institutions that have the appropriate expertise and resources.

At Bourn Hall Clinic, all of our energy and resources are invested in providing the best possible care and prognosis for our patients; however, we recognise that we can only achieve this by keeping up to date with the latest innovations in research and technology. We therefore collaborate with leading academic centres and research institutes in Cambridge, and we make a significant contribution to their research by providing the teams with their most precious resource: embryos that are surplus to treatment, and whose storage as frozen embryos is no longer required.

2. What is the purpose of these studies?

One of the main reasons for the failure of IVF treatment is poor egg and embryo quality. To understand the causes of failure we need to study the genes, chromosomes and proteins that are important in regulating the early development of the embryo and its precursor cells, together with the placenta that supports it in the womb.

We hope that the results of these studies will benefit medical knowledge in a number of important ways, including:

- Improving our understanding of the conditions that are important for growing human preimplantation embryos within a laboratory. We hope that ultimately these insights could lead to improvements in the treatment of infertility and benefit other patients trying to have a baby through the use of IVF.
- Advancing our understanding of how early human embryo cells become more specialised during early development. The first critical step in this process is when a small subset of cells are set aside to form eventually the foetus, whilst another subset of early cells differ in their fate to become the placenta, which supports the development of the foetus throughout the pregnancy. We are interested in how these specialisation events occur and are regulated before implantation.

Understanding the genes that are essential for this first important specialisation process could provide insight into some causes of pregnancy failures and birth defects. Understanding this important switch in cell fate may also provide a deeper understanding of stem cell formation. Developing stem cell lines that can be established from the embryo and multiplied in the laboratory for many years. This can help us study and understand more fully devastating human diseases at the cellular level in the laboratory and potentially develop new drug treatments.

- Understanding the transformations that embryos undergo as they develop beyond implantation. As embryos implant in the maternal uterus, they grow and their cells reorganise to form different structures, such as the amniotic cavity, which will protect the future foetus throughout the pregnancy. Placental and yolk sac progenitor cells also become more specialised. Using a new method to culture human embryos up to day 14 in vitro, we would like to understand how these changes in embryo shape take place and which genes are involved in this process. These findings could explain why many human pregnancies fail shortly after implantation.
- Improving of our knowledge of how human embryos implant into maternal endometrium and subsequently develop up to 14 days is important for understanding of maternal and fetal health, pregnancy complications, developmental disorders and stem cells.

If you wish to contribute to this research, you may donate any of your surplus embryos that are currently kept in storage at Bourn Hall Clinic. Donating your embryos to these research projects will help to increase our knowledge of an aspect of human biology that is currently poorly understood.

3. Do I have to take part?

Taking part in the research is entirely voluntary. If you do decide to take part, you will be given this information sheet to keep and be asked to sign a consent form. You are free to decline to participate in this research, and to withdraw from participation, or to vary the terms of your consent, after you have consented to do so, without in any way affecting your subsequent medical care. You are free to withdraw your consent at any time. If you withdraw your consent, or vary the terms, after transfer of embryos to the research centres, any embryos remaining unused will be destroyed. They cannot be returned to the treatment clinic or transferred elsewhere. Once the embryos that you donate have come under the control of research staff and are being cultured/grown for use in research, they can no longer be withdrawn. It is important to point out, however, that the embryos might be used at any time up until their expiry date, unless you specify otherwise. Where consent is given to the storage of embryos for research purposes by different persons on different days, the reference to the day on which consent is given is to be taken as a reference to the last of those days. By consenting to donate your gametes or embryos to this research project, you are also agreeing to them being used and stored if you were to die or lose the ability to decide for yourself (become mentally incapacitated).

In order to withdraw from participation, or vary your consent, you must contact Dr Kay Elder (contact details below).

4. What will happen to our embryos if we take part?

The main laboratory procedures that your eggs or embryos will be used for include:

- A donated egg may be used, together with donated sperm, to create an embryo that can then be used in further research.
- Fertilising eggs with sperm and growing the resulting embryos for no more than 14 days to study the way that embryos divide and grow. We will look at different ways of growing embryos to find the best methods.
- Studying how different culture conditions affect embryo quality with the aim of improving culture methods and better understanding embryo development.

- Biochemical studies to understand the biological properties of the eggs or embryos.
- Studying the genetic composition of the eggs or embryos.
- Altering how a gene's coded information is converted into structures in a cell (gene "expression") to examine how this affects embryo quality with the aim of understanding how early human embryo cells become more specialised. This work may provide the research team with crucial information on the best conditions for developing stem cells.
- The resulting genetically modified embryos may be used to produce stem cells.
- If an embryo is used for the purpose of producing stem cells, the early embryonic cells will be separated so that the embryo is no longer intact. These separated cells may die naturally, or they may survive and multiply indefinitely as stem cells. These stem cells can be used to further study many types of diseases, which can be replicated in the laboratory to look at their cause and progression as well as search for treatments.
- Embryos may be co-cultured with uterine models of the endometrium to provide understanding of human implantation. This is foundational for human health, disease, and fundamental principles of human biology.

5. What do I have to do?

If you agree to participate, you (and your partner, if applicable) should sign the enclosed consent form, in front of a witness, who should also sign the same form.

6. What are the possible disadvantages and risks of taking part?

There is no disadvantage or risk to you in taking part in this study. The research performed on your surplus frozen embryos will not affect you or your subsequent medical care in any way.

7. What are the possible benefits of taking part?

It is important for you to know that this research will not lead to any direct medical benefits to you. However, the information we get from these studies may help us to treat other infertile patients by improving infertility treatment. This research could also lead to the development of cures for many serious disorders such as miscarriage, avoiding serious disabilities that may affect unborn children, and to the development of new research tools.

It is possible that discoveries resulting from research on donated embryos, or stem cells that may be generated from them, could result in patents or licenses being awarded to the researchers or to commercial organisations. You will not receive any financial benefit from research discoveries arising from the embryos you donate or from stem cells generated from them.

8. Will my taking part in this study be kept confidential?

Yes. The proposed research includes careful procedures to protect your identity. The research is done under a licence from the Human Fertilisation and Embryology Authority (HFEA) and with approval of Cambridge Central Research Ethics Committee and Newcastle and North Tyneside Research Ethics Committee. These organisations impose strict requirements about maintaining your confidentiality. The embryos will be coded and your identity and participation in the research will be kept strictly anonymous. This code will allow researchers to access clinical data on your embryos (i.e. parameters of embryo quality), as this information is potentially relevant for the research studies. The information identifying your embryos will be visible to a member of the research team when they verify that consent for the research has been obtained, but your identity will not be recorded by them. If stem cells are generated in the research, a sample of these will be deposited with the UK Stem Cell Bank. Its activities are overseen by the Steering Committee that supports stem cell research and ensures that this is conducted within an ethical framework that is transparent to the public. In this case only, it will be necessary for your treatment clinic to provide a copy of your consent form in

confidence to the Secretary of the UK Stem Cell Steering Committee. Your identity will not be disclosed to the staff of the UK Stem Cell Bank or to anyone else.

9. What will happen to the results of the research studies? Am I entitled to information on the outcome of the research?

Whenever possible we will publish the results of our studies in scientific journals. We will also present data at scientific conferences. You will not be identified personally in any way in any publication or presentation.

You will not receive any information from either the study or on the genetic testing of the embryos that you donate or about stem cells that may be generated from them. This is because the steps taken to protect your confidentiality will make your identity unknown to the researchers.

10. Some background on our research

Your donated embryos will make an important contribution to several research programmes. We would like you to understand the different areas of interest that are under active investigation at the research institutes and to give you an appreciation of the wider context in which your embryos are such a valuable resource. You can find out more generally about our research at the following website: <https://www.trophoblast.cam.ac.uk/embryo-donations>.

Points that you should know about the research

- Eggs and embryos are used in our research programme. These eggs and embryos (tiny clusters of cells not visible to the eye) are surplus to IVF and would otherwise be discarded.
- Your eggs or embryos will either be transferred immediately for use in research or may be stored for use in later experiments. The storage period from consent to research will not exceed 10 years (please indicate your preference in the consent document).
- No eggs or embryos used for research will ever be used to establish a pregnancy.
- Embryos used for research may be grown in the presence of uterine models of the endometrium to investigate aspects of implantation. They will never be grown for more than 14 days.
- No eggs or embryos used for research will ever be grown for more than 14 days. Any remaining embryos will be destroyed beyond this date.
- In addition to growing the eggs or embryos, we will perform a range of biochemical and genetic studies to help us to understand their biological properties.
- Some of our research involves 'genome editing'. This includes the use of specific techniques (such as CRISPR-Cas9) to alter the DNA sequence or to introduce a fluorescent label to visualise development. Changes to the DNA sequence may cause a gene to become active or inactive, thereby allowing us to study its function in the early embryo in greater detail. Some of our research involves interfering with transcripts or proteins encoding for specific genes. In this case a gene is not changed, but a product it makes is either eliminated or its level is increased to determine the function of a gene. This can lead to significant insights into the earliest stages of human development, prior to implantation.
- After the eggs or embryos have been genetically modified their development will be stopped prior to 14 days post-fertilisation. We will perform biochemical and genetic studies and derive stem cell lines from these embryos.
- None of the research using the human eggs or embryos will involve animal testing.
- Any stem cells lines derived in this research project will be deposited in the UK Stem Cell Bank. They may be made available to other research groups nationally and internationally.

- Some of the stem cell lines could be used in the future to develop new treatments for diseases. In this way, the stem cells could be used indefinitely in a wide variety of research projects, and it is not possible to foresee all the potential research opportunities they would provide. You will not be able to control any future use of the embryonic cells or any stem cell derived.

11. Who is organising and funding the research?

This research is carried out with approval from the Human Fertilisation and Embryology Authority (HFEA) and is funded by several independent research bodies, including the Medical Research Council, Wellcome Trust, Cancer Research UK, the Centre for Trophoblast Research among other public or private funding or philanthropic organisations. Further information about the specific research programmes, funding bodies, the researchers and their published research results can be found on the research group's websites:

More information about the research project R0162 can be found on the following web pages:
<https://www.trophoblast.cam.ac.uk/embryo-donations>

Please refer to the HFEA website for information about licensed human embryo research:
<https://www.hfea.gov.uk/donation/donors/donating-to-research/embryo-research-project-summaries/>

More information about stem cell research in the UK can be found on the web page of the UK Stem Cell Bank: www.UKstemcellbank.org.uk.

12. How will the embryos or eggs be stored prior to use in research?

Once you have signed the Consent for Research and Storage form, your donated embryos or eggs may be stored at the clinic for up to 6 months before transport to University of Cambridge. This is to minimise cost and environmental impact of transport between the sites. While the law allows for storage of gametes for research purposes for up to 55 years from date of storage, for the purposes of this research, your gametes will be stored for 10 years or a shorter time depending on your preference. There will be no cost to you. Once you have consented for storage and research, your donated embryos or eggs may be used for up to 10 years, or a shorter period, depending on your preference. Please indicate on the Consent for Research and Storage form your preferred storage limit.

13. Contact for further information

Access to counselling independent from the study team is available. If you have any questions or concerns and would like to discuss this further, please contact Dr Kay Elder. Dr Elder's role in the clinical team is independent of these research projects.

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Adequate provision is made for insurance or indemnity to cover liabilities which may arise in relation to the design, management and conduct of the research project.