How research can benefit patients and professionals

Annual conference 2018 workshop

Chair: Bobbie Farsides
15 March 2018

www.hfea.gov.uk
The current research landscape

St Mary’s Hospital, Manchester
Research using donated embryos, eggs and sperm

Research using data held on the HFEA register
Reasons to be Cheerful - about Research!

Patients like to be involved in Research

97% of public want NHS to do research
MORI, 2011

630,000 patients in research studies in 2016 [www.nihr.ac.uk]

Clinical centres doing research have better results

“Research-active trusts have better patient outcomes, study shows”
NIHR, 2015

Research involvement is a badge of honour

Meets patient expectations
IVF Embryo Research

But isn’t IVF different?

Should we really be asking patients to donate their embryos to research?

Only surplus eggs/embryos are used. Fresh poor quality. Long term frozen.

Embryo creation and use 1991 - 2012

• 3.5 million embryos created in the UK (The Telegraph Dec. 2012 FOI Lord Alpine)
• 1.4 million embryos transferred
• 235,480 clinical pregnancies
• 1.7 million embryos created, unused & discarded

ART patients and professionals do not like wasting embryos!

Tope Adeniyi
I have remaining embryos
What are my options?

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If you have embryos in storage that you no longer need for your own treatment you may find it difficult to decide what to do next. Whether or not your treatment was successful, letting go of your frozen embryos can be hard to do. This leaflet guides you through the options for your remaining embryos, and where you can find more information and support to help you when making your choice.

What are my options?

The options for you to consider will depend on what your clinic is able to offer, and could be to:

- **donate your embryos to a research project.** Embryo research is crucial for developing fertility treatments, and without this IVF would not have been possible. Embryos can only be used for medical research that addresses specific purposes and that we have authorised. This option may only be possible if your clinic has a link with a research project.

- **donate your embryos for training purposes.** Training is vital for all embryologists to improve or learn new techniques.

- **donate your embryos to another person or couple for treatment.** This option will help realise others’ dreams of becoming parents. If this is something you would like to do your clinic can talk you through the process, including meeting the eligibility criteria for being a donor.

- **allow the embryos to perish.** If you decide to take this option, the embryologist will complete this process with respect and sensitivity.

Where do I start?

If you decide that you no longer need your embryos for your own treatment, you might be given the option to donate them to research, training or to other patients for their treatment. However, if these choices aren’t right for you, you might decide that it’s time to allow your embryos to perish. This could be a difficult decision for you to make and you may need to consider all your options very carefully.

If you feel you’d like extra support, counselling could help and your clinic may offer this to you. Alternatively, you can organise this yourself. Your GP can give you advice about getting counselling on the NHS or if you’d prefer to go private, the British Infertility Counselling Association (BICA) has a directory of accredited therapists with various options including telephone and Skype counselling. Or, you can contact a patient organisation, such as Fertility Network UK, for support.
Establishing embryo research partnerships on the Clinic Portal

List of projects

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<td>In-vitro development and implantation of normal human preimplantation embryos and comparison with uni- or poly-nucleate embryos</td>
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<td>Wellcome Trust-Medical Research Council Cambridge Stem Cell Institute</td>
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<td>Derivation of pluripotent human embryo cell lines</td>
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<td>Centre for Reproductive Medicine, Coventry</td>
<td>Geraldine Hartshorne</td>
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<td>Indicators of Oocyte and Embryo Development (R0155)</td>
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<td>The Francis Crick Institute, London</td>
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<td>Derivation of stem cells from human surplus embryos: The development of human embryonic stem (hES) cell cultures, characterisation of factors necessary for maintaining pluripotency and specific differentiation towards transplantable tissues - R0162</td>
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<td>Improving methods for preimplantation genetic diagnosis of inherited genetic disease and predicting embryo quality - R0075</td>
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Researchers rely on treatment clinics to help recruit egg, sperm or embryo donors for their projects. This is only possible if researchers and clinics establish partnerships.

This section of the Portal contains a list of research projects that are actively looking for clinic partners, to help identify potential donors for their research. It includes details about the projects, the types of research materials needed and any support or resources available to help recruit donors. If you are a treatment centre and are interested in establishing a partnership with one or more of these research groups, please contact the project lead directly.

https://portal.hfea.gov.uk/knowledge-base/embryo-research/
St Mary’s system

Project R0026 ‘In-vitro development and implantation of normal human preimplantation embryos and comparison with uni- or poly-pronucleate embryos’
University of Manchester and St Mary’s Hospital since 1993

Network of Patient Identification Centres (PICs)

“A PIC is a site where participants are identified and referred to a different centre specifically to take part in a research study. The receiving centre is the research site and is responsible for... taking informed consent to enter the participant into the study.”

Gives clinics ethical approval status and useful NIHR kitemark?

Lucy Dwyer
St Mary’s system

Network of Patient Identification Centres (PICs)

Research Nurse posts
Clinical Embryologist co-ordinator

Funded by
Clinical Research Network/
CRN Portfolio

- Obtain PIC approval and handle all research consenting directly with patients
- Arrange transport of embryos by courier to St Mary’s
- Close involvement of Embryologists (STP projects, Postgraduate (MSc, PhD) degrees)
- Grant funding - Tope Adeniyi NIHR doctoral (PhD) fellowship
Aims of human embryo research?

Increase basic scientific understanding
Improve the success and safety of ART

Molecular biology of human embryo development

Impact of ART lab environment on embryo development
e.g. EmbryoScope

Improving ART success rates
e.g. EmbryoGlue and implantation

Validation of technology
e.g. Oocyte vitrification – Tope Adeniyi
Register Research

- Background
- Update
- Future developments

Caylin Joski-Jethi
Head of Intelligence

www.hfea.gov.uk
Background

• The Register: largest database on fertility treatments in the world

• Until 2009/10: ‘patient identifiers’ could not be disclosed

• Law changed for research in 2009

• Research Regs 2010: provide ethical and legal safeguards for disclosure of register information for research

https://www.hfea.gov.uk/choose-a-clinic/how-we-manage-your-data/

Key facts
Researchers are allowed to request identifying information from us
They can only use information that would identify you with your consent
Research using your data is incredibly valuable to medical science
Only reputable applicants can request data from us
HFEA Register Research

Historical problems  HFE (1990) Act:

• Register not originally designed for research
• Missing key data fields such as parent and baby unique identifiers e.g. NHS numbers
• Specific patient consent for research was not considered

This changed in the HFE (2010) Act, with changing public attitudes to patient confidentiality and monitoring of safety from medical treatments.

1991-October 2009 – Presumed Consent to research for 110,000 children whose health outcomes can be tracked.

October 2009 onwards – Consent to disclosure (CD) required.

HFEA Information for Quality (IfQ) programme - Data quality improved and key fields added such as NHS number

For register research, only CD to non-contact research is required!
HFEA Register Research

1991-2009 cohort projects approved by RRP

Cancer (UCL)

EpiHealth: ART child growth and health (Manchester)

Health, hospital admissions (UCL +)
HFEA Register Research

1991-2009 cohort projects approved by RRP

Cancer (UCL)

EpiHealth: ART child growth and health (Manchester)

Health, hospital admissions (UCL +)
Mark Hann, Stephen Roberts, Nick Macklon, Daniel Brison

David Moysen, Nick Jones, Suzanne Hodgson
James Chalmers, David Clark

**EpiHealth**

**HFEA Data**
- 106,243 IVF Cycles
- 132,392 Births

**Scottish Morbidity Record (SMR02)**
- N Records
- Interested in Births in Scotland from Fresh/Frozen IVF Cycles

**Births in Scotland:**
- approx. 9,000 from approx. 7,700 IVF Cycles

**Scottish Delivery Records**
- 7,306 IVF Cycles Matched

**NRS Birth Register**
- 7,108 IVF Cycles Matched
- 8,775 IVF Births
- 5,220 Singleton IVF Births
  - 4,127 from Fresh IVF Cycles
  - 1,091 from Frozen IVF Cycles
  - 2 unknown

**4 Matched Naturally-Conceived ‘control’ Babies for each IVF Baby**
- N=20,879 (1 x 3 controls only)

- Fresh IVF babies low birthweight and show catch up growth by age 5
- Risk factors for cardiometabolic disease
- FET babies similar to naturally conceived
HFEA Register Research

1991-2009 cohort projects approved by RRP

Cancer (UCL)

EpiHealth: ART child growth and health (Manchester)

Health, hospital admissions (UCL +)

Challenges and hurdles to register research:

Funding. Expertise. Lack of identifying information on the register. Patient awareness,

*Rate of patient CD in clinics - now crucial for future funding*
Challenges and hurdles to clinical embryo research

Funding

Independent patient consenting/research organisation – NIHR CRN

Involving Embryologists in embryo research
  Time! Research facilities and training STP programme

Embryo freezing
  Frozen/thawed embryos may behave differently to fresh...

Numbers of embryos is critical to designing meaningful studies and obtaining funding
Discussion

What can clinics do to help embryo research?

What can HFEA and researchers do?

What can HFEA do to help with Register Research (data quality, CD forms?)
40 years of clinical IVF: celebrating the birth of Louise Brown in 1978

Conference to be held in Manchester, July 2018
The effect of Hyaluronan on human embryo implantation and gene expression

Chelsea Buck, Phoebe Babbington, Pete Ruane, Daniel Brison

Does Hyaluronate improve implantation rates by improving embryo development (YES), or acting as an implantation “glue” (NO)?

Figure 4- Average gene expression levels across all EmbryoGlue treated embryos vs. controls relative to expression of housekeeping reference gene β-Actin.
Who decides what happens to my embryos?

This depends upon how your embryos were created. If they were created using both your eggs and sperm then it’s the decision of you and your partner. However, if your embryos were created using donor sperm or eggs, the consent of those donors would be needed.

How long can I keep my frozen embryos for?

You can keep your embryos frozen for up to 10 years (although if you or your partner have premature infertility, you can store them for longer).

However, your embryos can only be frozen for the length of time you consented to, which could be less than the maximum of 10 years. Once they reach the end of their storage period, they will be allowed to perish. So, if you do decide to donate your embryos, let your clinic know as soon as possible, so there is time to use them.

What happens if I don’t make a decision?

If you are unable to reach a decision, or feel you don’t wish to donate your embryos, they will be kept for the period agreed with your clinic. After this, your embryos will be allowed to perish.

Can I change my mind?

Yes, you are free to change your decision to donate your embryos at any stage up until they have been used. You can withdraw your consent via your clinic.

For more information about embryo donation options and support, go to

https://www.hfea.gov.uk/donation/donors/donating-your-embryos/
https://www.hfea.gov.uk/donation/donors/donating-to-research/
https://www.hfea.gov.uk/treatments/explore-all-treatments/getting-emotional-support/
Who to contact: Professor Daniel R Brison
Clinical Embryologist/IVF Scientific Director
St Mary’s Hospital
Email: Daniel.brison@manchester.ac.uk
Telephone: 0161 701 6966

Our team:

Research Nurses: Claudette Wright, Katie Swindells

Clinical Embryologist Research co-ordinator: Kate Goulding/Anna Burdina

Clinical Embryologist researcher: Tope Adeniyi (NIHR PhD fellowship)

PhD students: Maribel Montufar, Liam Hanson

Postdocs: Dr Peter Ruane, Dr Helen Smith, Dr Adam Stevens
1st day after IVF - tPNf (n=4 conventional culture)

1st day after IVF - tPNf (n=10 time-lapse culture EMBROSCOPE)

5-6 days later

Collection of Hatched blastocysts (n=4+10)

RNA
cDNA
polyA PCR
hybridization

Affymetrix® Gene Profiling Array cGMP U133 P2

Conventional Screening

Time – lapse parameters monitoring

Hui Xiao
Helen Smith

Good embryo viability

poor embryo viability

tPNf - the time of the pronucleous fading, known also as syngamy
The importance of research

Professor Daniel Brison
15 March 2018

www.hfea.gov.uk
Deriving clonal pluripotent stem cell lines and understanding mechanisms of early development

Austin Smith and Jennifer Nichols
Embryonic stem cell derivation and tissue production

ES cells come from the **epiblast**, the precursor of the foetus

- Muscle cells
- Blood cells
- Neurons
- Intestinal cells
- Liver cells
- Pancreatic Islet cells

**Blastocyst**

**Inner cell mass**

**ESCs culture**
D6 and D7 embryos show segregation of ICM into epiblast (Nanog+) and primitive endoderm (Gata4+)
Single cell transcriptional profiling of human embryos

Giuliano Stirparo
Isolation of inner cell mass cells

Blastocyst
d6

Trophoblast lysis

Discarded trophoblast

Isolated inner cell mass

Single cells ready for plating

Guo et al., 2016
Single cell profiling to determine the changes occurring during ES cell derivation

What changes occur in gene expression and its control?
Derivation of clonal ES cell lines

• Many (~60%?) of human embryos tested are a mixture of normal and aneuploid cells
• The most common aneuploidy is trisomy 21 or 22 (Downs Syndrome)
• Having lines of both normal and abnormal karyotype from the same embryo would provide a valuable tool to study the effects of a particular defect on differentiation
• Tissues derived from these lines could be used for drug testing
Deriving clonal ES cell lines from human embryos

Produce both normal and aneuploid ES cell lines from the same individual
PrE formation in human embryos cannot be blocked by inhibiting FGF signalling

Roode et al., Dev. Biol. 2012
Human embryos cultured from morula stage in inhibitors of FGF and Wnt signalling
Progress and future plans

• Further improve culture regime to generate stable ES cells
• Track the transcriptional and epigenetic properties during ES cell derivation
• Derive clonal lines from the same embryo, some of which may have medically relevant aneuploidies
• Devise improved protocol for transfer to other clinics using epiblast expansion
Acknowledgements

Patients and staff at Bourn Hall, Barts, Leeds, Woking and East Sussex ACUs

Mila Roode
Ge Guo
Ken Jones
Austin Smith
Paul Bertone
Giuliano Stirparo
Thorsten Boroviak

Charlotte Hall
Research collaborations at
Sussex Downs Fertility Centre

Dr Charlotte Hall
Sussex Downs Fertility Centre, BMI Esperance Hospital, Eastbourne
Sussex Downs Fertility Centre

- Small IVF centre on South Coast
- Approx 300 Fresh IVF/ICSI cycles (NHS & Private)
- 120-140 Frozen cycles
- Clinical team - 2 consultants, 4 embryologists (2 full, 2 part-time), 4 nurses (part-time)
2004

- Only option to couples was to discard or donate to another couple
- Very few couples feel they are unable to donate to another couple (particularly around this time when donor anonymity was removed - 2005)
- Couples don’t like the idea of embryos going to waste
- Embryologists don’t like throwing good embryos away.
2006

- Started a collaboration with Guy’s and St. Thomas’, London
- Allowing patients with existing frozen embryos to opt to send embryos for research
- Patients were sent paperwork detailing choice of projects to be involved with (fertility-based or stem-cell research)
- Provided access to research nurse
- HFEA consent forms updated to indicate use in research
- Advised can withdraw at any time up until point of donation
- Collected by research nurse (10-12 sets accumulated)
Embryo Freezing at SDFC

Number of patients with frozen embryos

Number of patients

<table>
<thead>
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<th>Year</th>
<th>Number of Patients</th>
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<tbody>
<tr>
<td>2005</td>
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<tr>
<td>2016</td>
<td>130</td>
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<td>2017</td>
<td>140</td>
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</table>
Embryo Freezing at SDFC

Number of patients with frozen embryos

Number of cycles

Number of patients

Number of cycles


0 20 40 60 80 100 120 140 160 180 200 220 240 260 280 300 320 340 360 380 400

0 10 20 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180 190 200 210 220 230 240 250 260 270 280 290 300 310 320 330 340 350 360 370 380 390 400

The Esperance Hospital

Serious about health. Passionate about care.
Changes in Embryo Freezing Practices

Availability for freezing based on change in policies/practices

- 2006 – 2008 mostly day 2/3 embryos – needed at 3 embryos to freeze (slow)
- 2009 – routinely freezing as blastocyst - min 2 to freeze (slow)
- 2010 - freezing single blastocysts = more patients freezing (slow)
- 2011 – started vitrification – frozen multiple times/later in the day
- 2014 – only blastocysts frozen (even for freeze all)
- 2015 – started using single step culture medium – more on time blastocyst available
SDFC Embryos donated to Research

- Between 2006 - 2015 - 60 patients donated 248 embryos

- 2015 – Project Funding ceased
- 2016 – Attempted new collaboration
- 2017 – HFEA Workshop “Establishing Embryo Research partnerships”
HFEA Workshop – Establishing Research Partnerships

Oocyte Kinetochore to explore female ageing
Requirement: GV and MI oocytes frozen after egg collection

Gene Inactivation in Embryos
Requirement: Frozen embryos (Pronculeate stage)

Embryo Metabolism Project to identify viable embryos
Requirement: Spent medium or embryos

Creation of stable cell lines from Embryonic stem cells
Requirement: Frozen embryos

Which Project?
- Discussed requirements for the project
- Suitable for both parties
- Involvement mirrored our existing process
  - Cambridge supply paperwork for us to give to patients
  - Collect embryos when a group are ready
  - Ensure collection of the embryos personally
Where are we now?

- Submitted an acknowledgement to be a participating centre to HFEA
- Agreed to:
  - Displaying the cover page of our research licence in the clinic;
  - consenting the couples
  - providing the consented embryos to CSCI at agreed time points in advance of their expiry date
  - maintaining the original consent forms securely and confidentially

- Update our patient letters/paperwork to show we can now donate to research
- Provide interested patients with information leaflets (CSCI/HFEA)
- Already have embryos waiting
- Looking forward to being involved and eventually hearing how the research progresses
ACKNOWLEDGEMENTS

- HFEA
- Jenny Nichols & Austin Smith CSCI
- SDFC Team
Supporting patients to take part in research

Laura Riley
Head of regulatory policy
15 March 2018

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Our strategy 2017-2020

Improving the quality of patient care and treatment relies on encouraging more research.

**We are supporting:**

- clinics to be more proactively research-focused, and to report research consent more accurately,
- patients to understand why research is needed and what research they could take part in,
- easier patient donation of embryos for research, and access to those donated embryos by more research centres.
Research consent: barriers to participation?

HFEA data shows:

• Significant variation in HFEA consent rates between licensed centres to any research participation.
• Significant variation in consent rates between licensed centres, to ‘contact’ research model, vs. ‘non-contact’ model.
• Informed patient choice is key: ‘non-contact’ consent doesn’t support recontact with research invitations by clinics or HFEA, nor some research using patient data.

Consent for embryo donation

• is only permitted to be given to specific research projects (not to embryo research biobanking)

Others?
Next steps: 2018-19

Supporting world class research at licensed centres, by:

2018: continue to

- improve patient information about embryo donation for research,
- streamline HFEA research applications process,
- support clinic-research project collaborations.

2019: new Embryo research landscape review, evaluating potential impact of this work on research participation

- numbers of embryos donated
- numbers of clinic-research project collaborations.

Dependent on these outcomes, we will consider also reviewing the patient research consent process.
Thanks and over to you