PRINT ON FERTILITY CENTRE HEADED PAPER

Hyaluronic Acid Binding Sperm selection for ICSI (Intracytoplasmic Sperm Injection)

COUPLE INFORMATION SHEET AND INFORMED CONSENT FORM

We invite you to take part in a research study called HABSelect

Before you decide to take part, it is important for you to understand why the research is being done and what it will involve.

- Please take time to read the following information carefully and discuss it with friends and relatives if you wish.
- It is entirely your choice whether or not to take part in this research study. If you decide not to take part, this will not affect the care you are receiving from your doctors.
- Ask us if there is anything that is not clear or if you would like more information.
- Thank you for reading this information. If you decide to take part you will be given a copy of this information sheet and your signed consent form.

Important things that you need to know

- We want to find out the best way to select an individual's sperm for in vitro fertilisation by ICSI (IntraCytoplasmic Sperm Injection) treatment.
- We are comparing sperm selected by the currently used method or using Hyaluronic Acid Binding (HAB) before ICSI is performed. We will then determine the effect of the different procedures on pregnancy and live birth rates.
- The study is called HABSelect – 'HAB' stands for Hyaluronic Acid Binding and 'Select' for sperm selection.
- This study will compare two sperm selection methods. Regardless of which sperm selection group you are in, you will receive the usual follow up care from the Fertility Centre.
- The study fits into your normal fertility treatment schedule, so there are no extra hospital visits.
- We will also ask you to donate any residual sperm following the ICSI, which would normally be discarded, so it can be used for further tests to understand sperm characteristics and the causes of male infertility.
- You can stop taking part in the study at any time, without giving a reason. Your treatment and care will not be affected in any way.

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If you have any questions about this study, please talk to your doctor or another member of your clinical team:

<<Enter PI, nurse name>>
<<contact details for site>>

Before you decide if you would like to take part in this study, we would like to tell you why the research is being done and what it will involve. Please read the following information carefully and discuss it with others if you wish. Please ask if anything is unclear or if you would like more information (contact details above).

1 Why we are doing this study

Problems with male fertility account for almost half of all referrals to the infertility clinic for help in having a baby. In many cases, the man's sperm are present but unable to fertilise his partner's egg. There are numerous reasons why this might happen but assisted selection of good quality sperm allows us to inject the best one directly into the egg using Intra Cytoplasmic Sperm Injection (ICSI) and for pregnancies to be achieved as a result. Although ICSI is very successful at achieving fertilisation of the egg and pregnancy, it is estimated that less than a quarter of all fertilised eggs, once transferred into the womb, will result in a live birth. The reasons for this are not obvious but evidence suggests that we are still not very good at choosing the best sperm for injection.

Recently, a new method for sperm selection has been developed and preliminary results suggest it may help pregnancy outcomes. The method relies on selecting sperm by their ability to stick to a naturally occurring substance 'hyaluronan' that is normally found close to the surface of the egg. This material can be coated on to a special plate and if the man's sperm is allowed to swim or flow over the material, the 'best' sperm will bind to the coating and can then be easily picked for injection.

Scientists are not sure why this method works or indeed what it is about the sperm that makes the ones which stick to material better than those that don't. The purpose of this research is therefore twofold.

Firstly, we want to test this new Hyaluronic Acid Binding (HAB) sperm selection method for ICSI compared with the current standard sperm selection practice that relies on the embryologist choosing the best sperm by appearance before injecting it into the egg. This bypasses the normally occurring process where the egg itself selects the successful sperm for fertilisation. Hence, ICSI could be more vulnerable to a poor choice of sperm, resulting in fewer successful pregnancies. We are trying to find out if we can improve pregnancy outcome by selecting sperm using the Hyaluronic Acid Binding (HAB) method. This will allow us to advise UK Infertility clinics in the future on the best way to select sperm with the aim of improving the success rates for couples where male fertility is affected.

Secondly, we want to find more about the Hyaluronic Acid Binding (HAB) sperm and how they are different to those that do not bind hyaluronan. We want to find out if sperm selected by hyaluronan have lower levels of DNA damage. It is possible that simple changes in the way we pick sperm like the one being tested in this study could improve the couples' chance of achieving a successful pregnancy. If this method is successful it may help to improve the live birth rate and lead to a correspondingly lower miscarriage rate in the couples seeking fertility treatment.

2 Why are we being asked to take part?

You are being asked to take part in this research study because the Fertility Centre has recommended that you undergo ICSI treatment to help you conceive.

This study is taking place in at least 10 Fertility Centres across the UK and plans to recruit 3730 couples.

3 What will happen to us if we take part?

Your scheduled ICSI treatment will not differ from any other patient, except that just before ICSI takes place you will be put into one of two groups that will

determine how your sperm will be selected for the ICSI treatment:

- **The Intervention Group** – where the embryologist or andrologist (specialists in human sperm and eggs) will select the sperm using hyaluronan binding for the ICSI procedure.

  or

- **The Control (non-intervention) Group** – where the embryologist or andrologist will select the sperm using the standard practice i.e. by looking at the appearance of the sperm for the ICSI procedure.

All the sperm samples from couples participating in the study, regardless of the intervention group they are put into, will have a test performed on their sperm sample to measure their Hyaluronan Binding Score (HBS). This will allow us to record how many sperm bind to hyaluronan and together with other laboratory tests will help to describe the quality of the sperm in each sample.

All other parts of the ICSI procedure remain the same as in the standard practice, as does the way your treatment is followed up afterwards.

How is it decided which couple gets which sperm selection method?

The best way of finding out whether the new sperm selection using HAB works as well as or better than the standard treatment (using a visual selection), is in a randomised clinical trial. 'Randomised' means that a computer will allocate each couple randomly (as if by the roll of dice) to receive ICSI using sperm selected by HAB or conventional visual selection. Neither your doctor nor you will choose which treatment you receive. In this way, a fair comparison can be made. You will also be unaware which group you were allocated into until the end of study.

What will we have to do?

The study does not involve any extra procedures once you've had your ICSI treatment. We will follow the outcome of the ICSI using routine data collected by the Fertility Centre. The Fertility Centre where you received treatment is obliged to inform The Human Fertilisation Embryology Authority (HFEA) about **the outcome of your pregnancy** following the HFEA Code of Practice. That is why you will be encouraged by the Fertility Centre to contact them once your pregnancy comes to the end. This data is also essential for our research.

Analysis of sperm samples

We will also ask for your permission to take the residual sperm leftover **after** performing ICSI that would normally be discarded unless there are specific contraindications to collect these samples. We would use these sperm samples to undertake laboratory tests to help us better understand the sperm properties of those sperm that bind to hyaluronan and those that don't. The same tests will be performed regardless of the trial group you were entered into. These sperm sample will be labelled with a unique number that the researchers cannot use to identify you. These samples **will not** be used for clinical (fertility) treatment of any kind.

The laboratories will handle your samples with the same duty of confidentiality as they would for any clinical sample. The University of Leeds will have overall control over what happens to the samples.

What will happen to the residual sperm used in the research?

A series of additional tests will be performed by specialist laboratories; each of them using different techniques to investigate the 'quality' of the sperms' DNA (its genetic material) which we think is a key requirement for producing a healthy embryo. All the tests performed are established techniques used to research DNA structure and damage in sperm cells.

Initially samples will be frozen stored in the local Fertility Clinic and then transported to a central

storage facility in Birmingham. The samples will be coordinated for further testing across four UK research laboratories. The **samples are for research only** and stored in such a way that they **CANNOT** be used for your or someone else's fertility treatment.

Once we have finished the laboratory testing of your sperm sample, anything remaining at the end of the study will either be destroyed or with your additional consent will be banked (long term storage) in Human Biomaterials Resource Centre (HBRC) in Birmingham. The banked samples will be available for use in further studies by the wider scientific community; requests for use of the banked samples are reviewed carefully by an advisory group to ensure that only the best research will be undertaken to advance our understanding of male infertility. Your identity will not be known to any researchers making use of these remaining banked samples and results of their research will have no bearing on your current treatment or its outcome. Having any surplus sperm banked in this way is optional, if you do not wish your sample to be banked and made available in this way, it will be disposed of safely at the end of the study.

4 Is it safe?

Yes, we are only testing sperm selection methods for the ICSI procedure. Hyaluronan selection equipment we are using has been extensively tested and has obtained all necessary approval for clinical use within European Union (EU). All other parts of the ICSI procedure remain the same as in the standard practice, as does the way your treatment is followed up afterwards

5 What are the possible benefits of taking part and will the research study have any significance to us?

It is very unlikely that any information which would change the course of your clinical management will be generated by this study. This research may, however, in time improve general ICSI treatment for male infertility.

What are the risks?

ICSI is routinely performed and as might be expected from a naturally occurring substance that is present throughout the body, there have been no reported risks with using hyaluronan. There are no other trial-specific risks and ICSI related risks beyond those were explained in the HFEA consent forms you signed at the very beginning of your fertility treatment.

6 What happens to the information you collect about us?

What data is recorded about us for the study?

If you agree to take part in the study we shall:

- Collect some general data about both of you (i.e. weight, height, smoking history).
- Ask about your medical history including any gynaecological disorders and surgical operations of the female partner.
- Ask about any previous pregnancies and their outcome.
- Ask about any past fertility treatment for both of you
- Record the level of female hormones and assess the semen profile, which are both routinely measured as a part of fertility assessment prior to ICSI procedures.
- Record the number of embryos transferred into your womb.
- Record the outcome of the pregnancy (including baby's sex and birth weight if available).

Will our taking part be kept confidential?

Yes, if you decide to participate in HABSelect, the information collected about you will be handled strictly in accordance with the consent that you

have given and also the Data Protection Act 1998. Your treatment centre is also registered with the Human Fertilisation and Embryology Authority (HFEA) and we are bound by their Code of Practice.

The information collected is used for research purposes only. The information needed for study purposes will be collected electronically (where possible) and stored in a secure database designed by Pragmatic Clinical Trials Unit (PCTU) supporting this trial in accordance with Data Protection Act 1998 and accessed only by authorised staff members. You will be allocated a study number, which together with the site code will be used to identify you on each study form. Your full names will only be included on your consent form and this will be retained in your hospital records. Only your direct clinic team will have access to it. Every effort will be made to ensure that any information about you, which leaves the hospital, will have identifiable information about you removed and your study number will be used instead so that you cannot be recognised from it.

By consenting to this study, you agree that your relevant information can be collected from the hospital notes and other medical records and entered into a secure study database. This will allow your pregnancy outcome to be followed up by a member of the study team. Your healthcare records may be looked at by authorised individuals from the research team, the University of Leeds (the study Sponsor, or their delegate), the study funder (NIHR EME), or the regulatory authorities to check that the study is being carried out correctly.

Your identity will not be made known to the research laboratories analysing sperm samples. You will not be identified in the publication of any results following the end of the study.

Any procedures implemented for handling, processing, storage and destruction of your data will be compliant with the Data Protection Act 1998. You have the right to check the accuracy of the data held about you and correct any errors.

Informing your General Practitioner.

It is normally expected that we tell your GP of your participation in HABSelect, and we shall ask for your consent to do this. But if you would prefer us not to inform your GP, please let us know. All information about you and your treatment will remain confidential.

7 What do I do if I have any concerns?

How is our fertility treatment monitored?

Your fertility treatment will be monitored in the same manner as your usual clinical care and there will be no need for additional appointments for follow up.

What if there is a problem?

This study does not involve any extra risk to you. If you experience any adverse consequences of treatment then please contact your local Clinical Lead – please insert contact details for local Principal Investigator.

Any complaint about the way you have been dealt with or any possible harm you may have suffered should be addressed to the HFEA Person Responsible at your clinic, please insert name of HFEA responsible person at the centre, Telephone please inert contact phone number.

If you remain unhappy and wish to complain formally, you can do this through the NHS Complaints Procedure. NHS Direct can advise on NHS complaints on 0845 4647. Independent advice or support can be accessed by contacting the Patient Advisory Liaison Service (PALS). For more information on PALS or to find your nearest office visit their website at www.pals.nhs.uk .

If you have a concern about any research aspect of this study, you should contact the Trial Coordinator on the contact details at the end of this leaflet.

If you have private medical insurance, you should tell your insurer that you are taking part in research. They will let you know if it affects your policy.

What will happen if I don't want to carry on with the study?

You may choose to withdraw at any time, without giving a reason from: 1) the main study; 2) the sperm sample laboratory testing or 3) the long-term sperm biobanking (if you agreed to it in first instance). Your decision will not affect the future medical care you receive. You should contact your doctor or a member of the clinical team if you change your mind and decide that you no longer want to take part and you will be asked to complete a withdrawal form indicating exactly what aspects of the study you wish to withdraw from. You will be also asked about your preferences in regards to the data we already collected about you for the study purposes. Similarly if you do not wish any sperm to remain in storage you will have the opportunity to indicate this to the clinical team.

At the end of the study your data will be archived In line with Research Governance Framework guidelines and Trust policy of each participating centre.

8 More information about taking part

Who is organising and funding the research?

The study is organised as a collaboration between the University of Leeds and its partners and (organisationally) supported by Pragmatic Clinical Trials Unit, Queen Mary University of London. It is funded by the National Institute of Health Research Efficacy and Mechanisms Evaluation (NIHR-EME) grant EME 11/14/34.

Do we have any rights to the research?

Taking part in this project will not give you any rights to any results of the research. In the event that the results of certain parts of the research are patented and have commercial potential, you will not receive any financial benefit from this.

What will happen to the results of the research study?

When the study is complete the results will be published in a medical journal, but no individual participants will be identified. We will also make results of the study publicly available on HABSelect website

On your request, we shall also tell you, how the sperm used in your ICSI was selected but only after the end of the trial. No information identifying individual patients will be published.

Who has reviewed the study?

To have obtained funding by the NIHR, the study had to go through review by experts who felt this study to be of relevance and importance to couples undergoing ICSI treatment for male infertility. The study has also undergone a thorough ethical review through the Intergrated Research Approval System (IRAS). The Data Monitoring and Ethics Committee (DMEC) and Trial Steering Committee (TSC) will be supervising the study data on a regular basis.

Additional research

Not all the samples we collect will be in a condition allowing them to be used in research tests we perform in our laboratories. That is why we created the opportunity to donate remaining sperm samples to Human Biomaterials Resource Centre (HBRC) Biobank in Birmingham. At the end of the study these samples will be made available to the scientific community for projects unrelated to this study. If you wish to consent to donating your samples to Birmingham Biobank a member of your clinical team will provide you with a separate consent form and participant information sheet which are specific to this. Participation in the additional research is entirely optional, and your decision to participate will not affect your participation in the rest of the study.

Your samples will **not** be used for commercial purposes or for fertility treatment.

Will any genetic tests be done?

Genetic tests will not be performed in any of the samples you have provided **as part of** this study.

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If you agree to donate the remaining samples to Birmingham HBRC Biobank, please note genetic testing may be performed as part of the studies using its tissue samples supply (please see the specific participant information sheet for more details).

9 Where can I get more information?

If you have any **specific queries** regarding your fertility treatment or eligibility to the study please contact your local Research Team on the contact details on the front page. They will answer any questions you may have and arrange to discuss the project further with you in the clinic when you attend for your next consultation.

With any **general queries** regarding this study you may also contact the Trial Coordinator:

Ms Karolina Witt
Pragmatic Clinical Trials Unit
Queen Mary University of London
58 Turner Street
Whitechapel, E1 2AB
Tel: 0207 882 2526
HABSelect@qmul.ac.uk

The UK Clinical Research Collaboration has produced a guide entitled, 'Understanding Clinical Trials'. This can be downloaded from their website: www.ukcrn.org.uk and could be useful if you require general information about research.

Association of Research Ethics Committees (AREC) is an independent, self-governing body which promotes excellence in ethical research in human beings. It publishes a leaflet entitled 'Medical Research and You'. This leaflet gives more information about medical research and looks at some questions you may want to ask. A copy is free to download from their website www.arec.org.uk .

Another source of independent advice or support is the Patient Advisory Liaison Service (PALS). For more information on PALS or to find your nearest office visit their website at www.pals.nhs.uk or ask your doctor.

Local organiser

If you want further information about the study, contact your local organiser/doctor whose details are given on the front page.

Thank you for taking the time to consider taking part in this study.

Hyaluronic Acid Binding Sperm Selection for ICSI (Intracytoplasmic Sperm Injection)

Couple Informed Consent Form

Chief Investigator: D Miller Principal Investigator: INSERT

Site code: ☐☐☐☐ Couple ID: ☐☐☐

	Please INITIAL in the boxes below	
	Female	**Male**
We confirm that we have read and understand the information sheet (version 2.1 dated 10Oct2014) for the above study and we have had the opportunity to ask questions and these have been answered satisfactorily.		
We understand that our participation in the study is voluntary and that we are free to withdraw at any time without our treatment or legal rights being affected. We understand that even if we withdraw from the above study, samples that have already been used for the research may be included in the final study analysis.		
We understand that relevant sections of our medical notes and data collected during the study may be looked at by individuals from the research team, from regulatory authorities or from the NHS Trust, where it is relevant to our taking part in this research. We give permission for these individuals to have access to our records.		
We agree our General Practitioner(s) to be informed about our participation in HABSelect study.		
We understand what is involved in HABSelect trial and agree to take part in the study.		
We agree that any residual sperm samples left over from the ICSI can be used for laboratory testing to characterise the quality and structure of sperm DNA in our laboratory analysis.		
We agree that at the end of the study, any remaining samples left over from this research can be retained at the Birmingham HBRC Biobank for use in medical and scientific research. We understand that no link to our identifiable information will be maintained in this regard (***Please note**: full consent to the donation of remaining samples for medical research is subject to signing an additional consent form which will be provided by the research team member once you initial this section*)		

Print Name - Female Partner	**Signature**	**Date**
Print Name - Male Partner	**Signature**	**Date**
Print Name - Researcher	**Signature**	**Date**