SENTINEL

Sentinel Skin Flap in Lung Transplant

(Full Scientific Title: Efficacy and mechanism of sentinel skin flap reduction of solid organ (lung) transplant rejection: A randomised controlled trial)

PATIENT INFORMATION SHEET

Before you decide whether or not you wish 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 leaflet carefully and discuss it with friends, family and your GP, if you wish.

Please ask your clinical care team or the research team if there is anything that is not clear or if you would like more information. Take your time to decide whether or not you wish to take part.

Our contact details are at the end of this leaflet.

What is the purpose of the study?

The aim of the SENTINEL study is to evaluate whether lung transplant patients who receive a small patch of skin, transplanted onto their forearm (from the same donor as the lung), benefit from this. This patch of skin is known as a sentinel skin flap (SSF) because it stands guard (like a sentinel), potentially alerting the patient to rejection of the donated lung by displaying a visible rash. In this way, the flap may detect signs of transplant rejection earlier than the methods currently used. It may also help us to protect the lung transplant itself from rejection damage.

What is organ rejection?

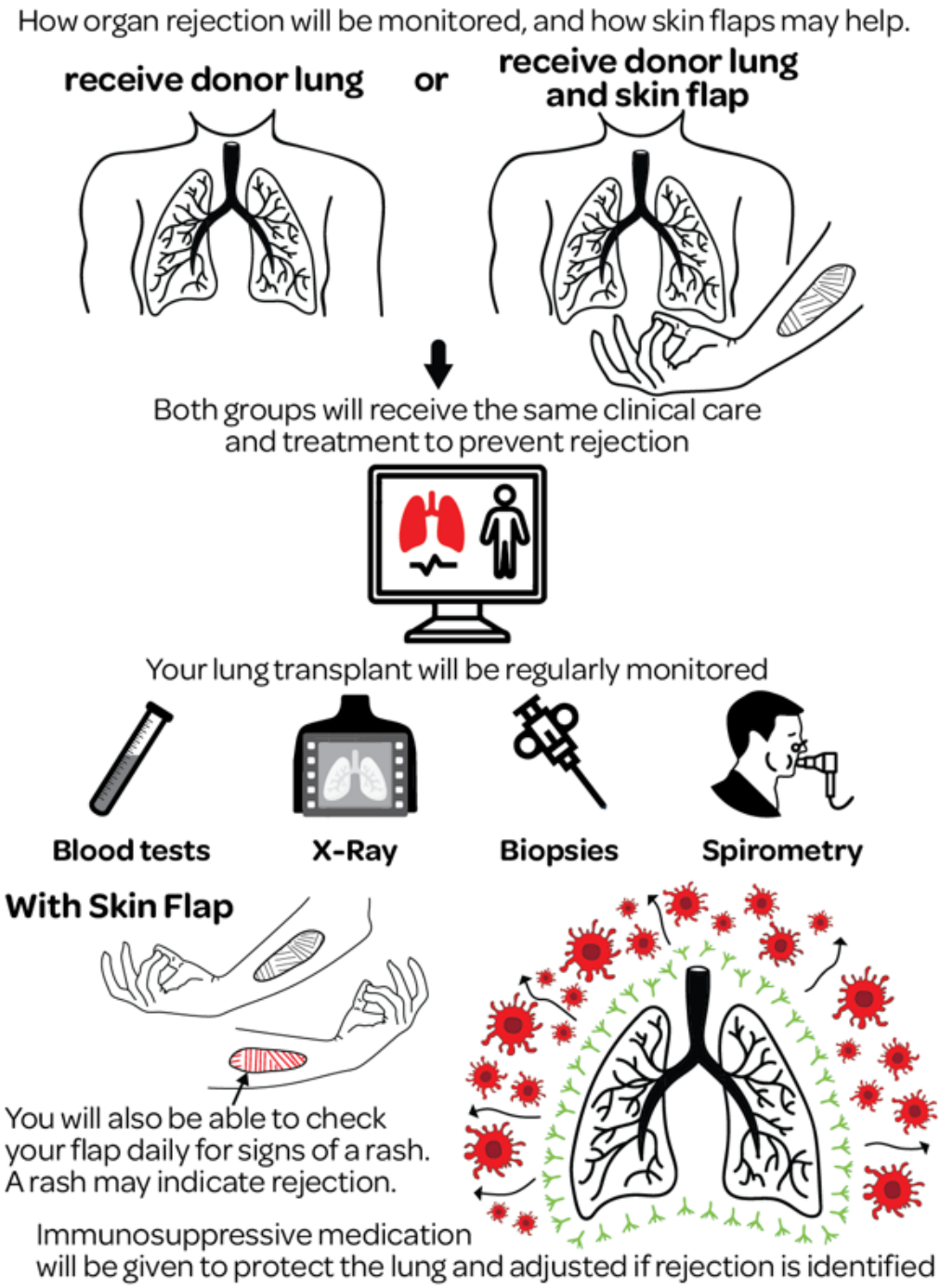
Transplanted organs including lungs are subject to attack by the immune system causing rejection of the transplanted organ. Rejection is prevented by immunosuppression medication that interferes with the body's immune system and hinders rejection. Despite these medications rejection may still occur. If rejection is not detected and treated early enough the transplanted organ is damaged and can eventually stop working.

How do we detect organ rejection?

Detecting lung rejection is difficult as it does not have specific features. In lung transplants attempts are made to detect rejection by frequent hospital visits for chest x-rays, lung function tests, blood tests and some times biopsies of the transplanted lung.

These tests can show if there is inflammation (which may be due to rejection) but there is no specific measure of rejection until the rejection is very severe.

Figure 1. Shows how Skin flaps may help to detect organ rejection



What previous studies have used Sentinel Skin Flaps?

Sentinel skin flaps (SSFs) were first used in a study involving intestinal transplants. In this study, we discovered that the skin displayed a visible rash between 1-10 days before the transplant was rejected. The skin also guarded against rejection. The risk of developing organ rejection dropped from 80% to 25% in patients who had a SSF. As the skin was always visible, there was no need routine biopsies or tests, performing these only when the skin indicated there was rejection.

SSF transplantation was also successful in guarding against rejection in a follow-up study involving pancreas and kidney transplant patients.

The SENTINEL study hopes to study the effect of a sentinel skin flap in patients receiving a lung transplant. All patients will receive the lung transplant as routine care with half also receiving a skin flap transplant. If the skin transplant can act as a rejection monitor for lung transplants, we can reduce the immunosuppression drug levels, and have earlier warning of possible rejection damage to the lungs and therefore avoid rejection injury to the lungs. This would also mean in the future we could reduce the number of hospital visits and tests patients would need to undergo.

Why have I been invited to take part?

The study is being conducted at the five lung transplant centres in the UK. We are looking for 152 people who will receive a lung transplant to take part. As you are on the waiting list for a lung transplant at one of the five centres, you are invited to consider participating in this study.

Doctors believe that either lung transplant alone or a lung transplant with a sentinel skin flap would be good options for you. As these treatments have not been directly compared before, doctors and policy makers do not know if the outcomes will be the same for both groups. This is why we are providing you with information so you can consider whether you would like to take part in the SENTINEL study.

The results of the study will provide detailed information to help patients, clinicians and policymakers decide the future care for lung transplant patients in the future.

Do I have to take part?

No. It is completely up to you to decide whether to participate in any aspect of the SENTINEL study. If you take part, you can later withdraw without giving a reason. If you do not want to take part or withdraw, this will not affect your clinical care in any way.

What will happen to me if I decide to take part in the SENTINEL study?

Below is a full description of what happens if you participate in the SENTINEL study (there is also a summary in the Study Flowchart on the page 5).

Informed consent and baseline measures

You will have the opportunity to discuss the SENTINEL study with a member of the clinical research team and ask any questions you may have. If you agree to join the SENTINEL study, you will be asked to sign the SENTINEL study consent form. This consent will be checked and confirmed just before any transplant surgery. You do not have to take part if you do not wish to and can change your mind at any time.

In order to take part in the study, you will be given a unique study identification number which will be used for all of the information we collect from you. This information will be transferred to, and stored at The University of Oxford, using a secure encrypted web-based system. Taking part in this study means that we will keep your details on file and if you are offered a lung transplant from a matched donor and the donor's skin is also available, then you can participate in the SENTINEL study. We will ask you to complete a questionnaire about your quality of life and how you feel. This should take about 10-15 minutes to complete.

SENTINEL is a randomised study. In this type of study, there is a direct comparison between people who have lung transplant only or lung transplant and sentinel skin flap. The only way we can compare these treatments fairly is by dividing participants into two groups that are as similar as possible by a process called randomisation. Randomisation means that patients who agree to participate in the study are randomly allocated to one of the treatment groups. If you agree to take part, this means that you would have an equal chance of having lung transplant only or lung transplant and sentinel skin flap. It is important that you only agree to take part if you are prepared to accept either lung transplant only or lung transplant and sentinel skin flap.

Randomisation will only happen on the day before or day of your transplant. By looking at everyone's care together, we can then improve our understanding about the best way to detect rejection in lung transplant patients in the future. **Your lung transplant takes priority at all times;** taking part in this study will not result in any delay to the timing of your lung transplant or affect your place on the waiting list. Both groups of patients will receive standard care after the lung transplant.

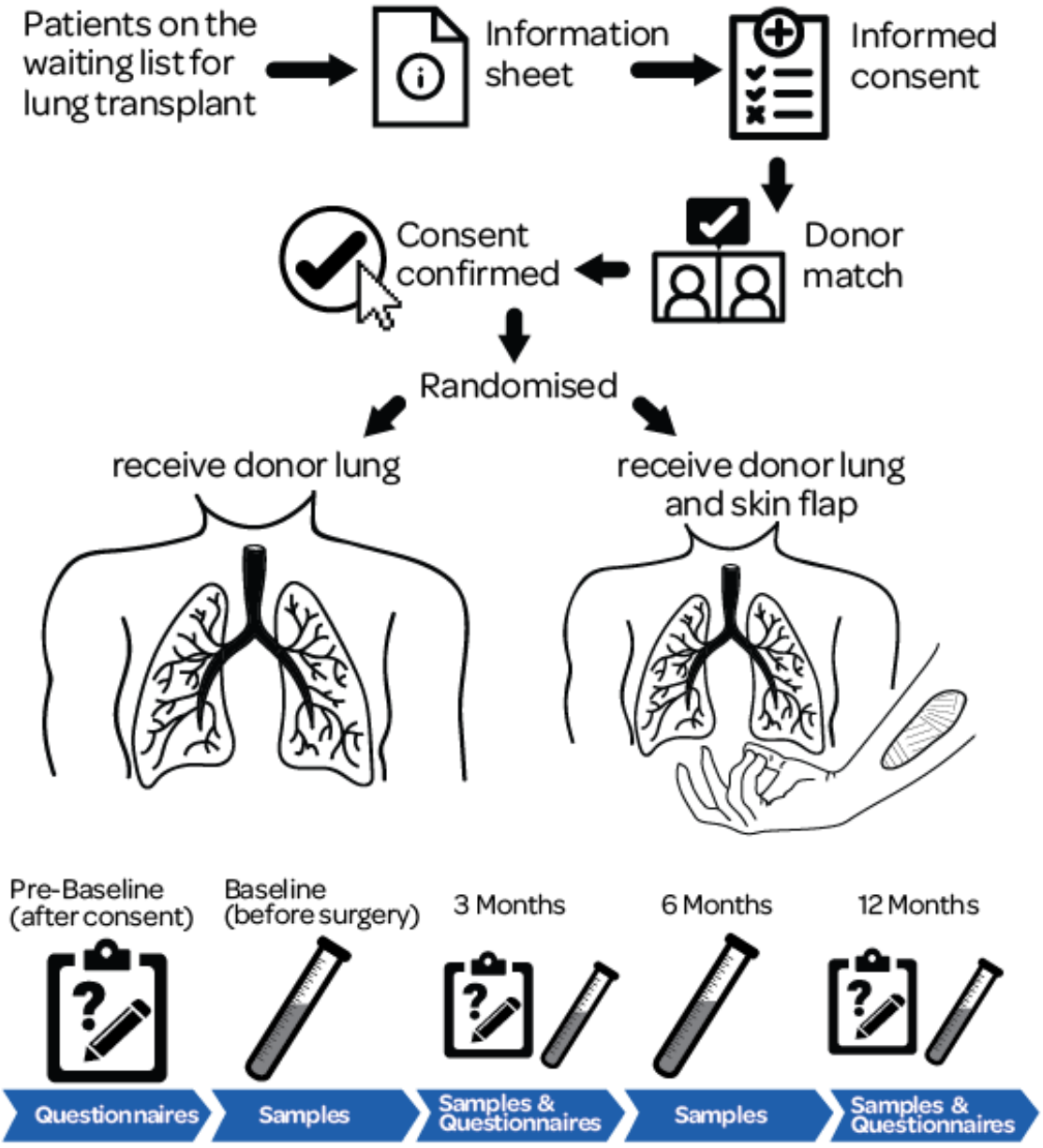
Randomisation is the only way to ensure that the groups are as similar as possible to each other. If you or your doctor choose a treatment, the groups would not be the same.

What if the donor does not offer a skin flap?

If a skin flap is not offered by your matched donor then you will proceed with the lung only transplant as planned but you will no longer continue with the study. Unfortunately, the randomisation process will not permit you to carry on in the study if the skin flap is not available at the beginning. However, we are grateful for your participation and you can keep informed of the outcome of the study via the study website.

Study flowchart

Figure.2. An outline of the processes involved in the SENTINEL study



How will the skin flap be transplanted?

The sentinel skin flap is a type of tissue transplant, composed of forearm skin and blood vessels. It is taken from the donor at the same time as the lung for transplant. The skin flap is stitched on as a patch, into the inside of your forearm and connected to the blood supply.

The small patch of skin is about the length of a finger (10cm) and the breadth of two fingers (3-4 cm) wide, and stitched to the undersurface of the forearm. The exact size may vary by 1-2 cm in length or width. Once transplanted onto the underneath of the forearm, the skin can be easily and continuously monitored for any signs indicating the start of rejection. Patients with the skin flap will be asked to check daily for any visible signs of rejection (rash, redness) and a painless biopsy of the skin flap may be taken if any signs of potential rejection appear.

The skin flap will be done at the same time as your lung transplant. You will not need to have a separate operation. The plastic surgeon who attaches the skin flap, will try to work at the same time as the transplant surgeons, so your operation duration will not be increased. The skin flap should not affect your recovery in any way. You will be able to receive the usual care after your lung transplant, with the addition of a dressing around your forearm. You may have some local pain around the site of the skin flap, for which you will be given pain medication if required.

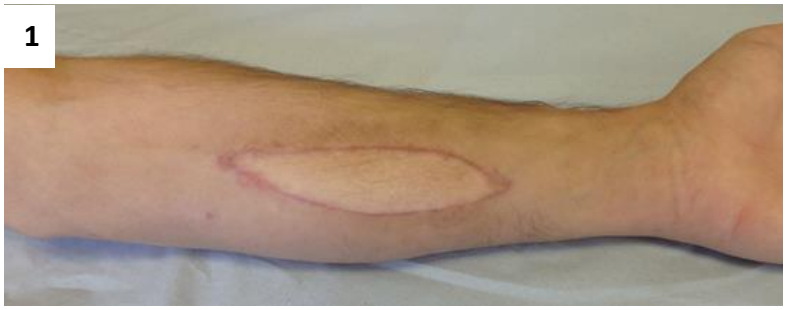
Post-operatively, the nurses and doctors will monitor the skin flap closely. Initially they will be assessing the blood supply via visual assessment (ensuring the flap looks pink) and touch (ensuring the flap is warm and that colour returns when the skin is pressed or lightly touched).

We will ask you to check the skin flap daily and teach you how to monitor it. A patient booklet will show you what to look for and who to contact if you have concerns. The sentinel skin flap does not require any special care. A moisturising cream, such as E45 can be used. It is advisable to protect the skin flap area from sunburn for the first six months by using long sleeves or SPF 50 sun cream. If you are concerned about the appearance of the skin flap, you can ask your surgeon about camouflage make up. However, we cannot guarantee skin tone match from the donor.

By taking part in the SENTINEL study, your skin flap could alert you to any early signs of transplant rejection in the form of a rash or redness. This would then require you to attend hospital for your transplant team to investigate. Our hope is that the skin flap will help with detecting rejection earlier, thus allowing your transplant team to treat rejection signs sooner, should they wish. Overall the flap should not increase the number of times you have to attend hospital for routine checks.

Figure 3. A sentinel skin flap on the forearm of a patient (1) three months after their transplant surgery and (2) 12 months later with biopsy scars (photographs with permission).

1



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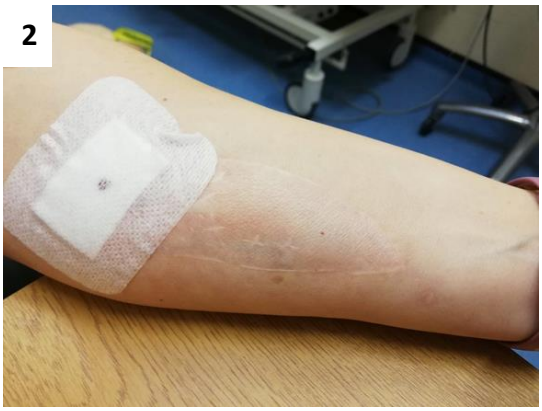

(3) As the picture shows, the sentinel skin flap is discreet, yet easy to check at any time (photographs with permission*).*

3

Should there be any reason that the forearm not suitable for the skin flap transplant alternative sites such as the groin, or armpit will be discussed with you and the most appropriate location chosen before the procedure.

If you develop a rash on your sentinel skin flap, your transplant doctor may ask you to send them a photograph. It is likely you will be asked to attend a follow-up appointment with your transplant doctor, so that they can do some further tests to check for rejection in the skin flap and in your lung. This will include a biopsy of the skin flap as described below. Any other investigations performed by your transplant doctor would be the same as your usual clinical care.

If you wish to have the sentinel skip flap removed at any point, we will make arrangements for this to be done. The removal would be performed under local or general anaesthetic by a surgeon who is part of the research team. The procedure would take around 45-60 minutes in total and would take place as a day case (no overnight stay in hospital required). Removal will leave a single scar on the forearm. Your usual clinical care would continue as normal afterwards. Only a small number of patients have elected to have their skin flaps removed primarily because of the visual nature of the skin flap. Removal has not resulted in any ill-effect that we can notice. Some of our patients whom have had skin flaps for over 10 years report benefit in being able to self-check their transplant health.

The length of time you are in hospital is individual to each patient receiving a lung transplant and the transplant team will be able to give you guidance on this. However, the addition of a skin flap should not increase your stay.

Follow up study tests and monitoring of the skin flap

We will be interested in how you are and how your transplant performs, and particularly interested in any rejection alerts that may occur with your transplants.

Monitoring of the lung transplant.

Following your transplant, you will attend hospital regularly to have check-ups and tests to ensure that your new lung is working properly. Your usual follow-up care will not be affected by you taking part in the study, you will still attend regular appointments. Your transplant healthcare team will check the function of your new lung, using a variety of different tests. These may include sputum and other samples or a biopsy of the lung; and will involve you having some blood tests. We will collect the results of these tests from your medical records and some of these samples will transferred to the research laboratory for research analysis. We will also collect and store an extra blood sample (10ml – around two teaspoons). This will be collected at the time of your transplant and 3, 6 and 12 months later; and if you develop rejection. The blood samples you give will be used to see whether there are any other signs suggesting rejection which can be detected in the blood.

At the 3 and 12 month routine visits after the transplant, a member of the research team will ask you some additional questions about your health for the purpose of the study. At each of these hospital visits we expect these questions to take an additional 10 - 15 minutes.

Monitoring of the skin flap transplant.

If you have a sentinel skin flap, then a small biopsy of the skin flap will be taken and stored at the time of your transplant as well as a small biopsy of the skin edge of the incision made to insert the skin flap. Further skin flap biopsies will be performed when you have your usual hospital visits 3, 6 and 12 months after your transplant. A small sample of skin will be taken using a skin punch biopsy tool. This is usually a painless procedure, not requiring any local anaesthetic, as the skin flap does not tend to regain sensation after the transplant operation. However, if you prefer, we do offer a local anaesthetic injection or spray to make sure you will not feel the biopsy.

Half of the biopsy will be sent to the laboratory at your hospital and the results will be reported back to your transplant doctor who will use these to help decide whether further investigations for transplant rejection are needed. The other half of the biopsy will be analysed in our laboratories in Oxford to help us understand more about how the body's immune system responds after a lung transplant and during rejection. This will help us improve the treatment of future transplant patients. For comparison, we hope to collect a small biopsy of your lung after it has been removed in the transplant operation.

We will also swab the skin on your forearm and from the flap to collect some surface skin cells and bacteria as part of this analysis in Oxford.

What happens the skin flap shows a rash?

If the sentinel skin flap shows signs of rejection (i.e. a skin rash), a skin biopsy will be taken. This will help your doctor to decide whether further investigations are needed. All other investigations carried out would be part of your usual care after a lung transplant and would be performed at your transplant centre even if you were not taking part in this study. The skin rash is easily seen on all skin types but redness and mild inflammation is most easily seen on paler skin.

When will I be asked to complete questionnaires?

You will be asked to complete a questionnaire when you give consent to the study. You will complete a further questionnaire either on paper or electronically at 3 and 12 months following your transplant. It will include questions regarding your symptoms, emotions and activities. It will help us to measure overall quality of life in study participants. If you prefer, you can ask for a paper questionnaire to be posted to you at your address. We will send you an advance notification that a questionnaire will be on its way, and reminders if it is not completed. If we have any queries about the information you have already provided, we may contact you by your preferred method.

Can I ask about the donor?

As the recipient of a donated organ you are entitled to know the following:

- Age range of the donor
- Gender of the donor
- Type of death (such as a head injury) unless this might compromise the donor's confidentiality

- Whether the donor poses a greater risk to you of spread of infection or cancer

What will happen to me if I decide not to take part in the SENTINEL study?

If you do not want to be part of this study, this will not change the level of care you will receive. You can change your mind about participating at any time without giving a reason, and can contact the research team at any time .

What are the possible benefits of taking part in the study?

We cannot guarantee that participating in this study will be of direct benefit to you. We do not know whether using a sentinel skin flap will help us to detect or prevent rejection in lung transplantation. This is why we are carrying out this study.

If you receive a sentinel skin flap transplant we might be able to detect rejection and treat this sooner than it would have normally been detected and treated.

The results of the study will help us find out if the sentinel skin flap transplantation can be used in the future to monitor the lung transplant for rejection. If the study shows that the sentinel skin flap does help with detecting rejection earlier than the current methods used, this technique may be incorporated into routine clinical practice for future patients receiving a lung transplant.

Further information can be found at:

https://www.nihr.ac.uk/patients-carers-and-the-public/i-want-to-take-part-in-a-study.htm www.nhs.uk/Conditions/Clinical-trials/Pages/Introduction.aspx

Are there any possible disadvantages or risks from taking part?

Sentinel skin flaps have been used in previous studies and have been well tolerated by the patients that have had them.

The initial concern about adding a sentinel skin flap was the possibility of increasing the risk of rejection, increasing the level of immune suppression, and the development of antibodies. However, results suggest that this may be the opposite, with reduced risk of rejection, reduced immunosuppression and the same risk of developing antibodies, and this inspired us to conduct this trial.

Initially the skin patch will feel numb and does not feel any sensation or pain. Over time (months to years) some sensation may return. There is a very small risk that the skin flap may need to be removed for medical reasons. There is a risk that you may have some wound problems, infection or some skin dying at the edge of the flap leading to scabbing and delayed healing. The swelling associated with the skin flap procedure on your forearm may lead to temporary compression of the nerves to your hand giving you some pins and needles, numbness or weakness.

Although it is as hidden as possible on the under surface of your forearm, the sentinel skin flap will be a visible reminder of your transplant. It may lead to questions from other people when they see it. Some people in previous studies have considered this a

disadvantage, others have found it reassuring to be able to monitor their transplant and made them more aware of the gift of transplant they had received.

It is important for you to understand that we cannot guarantee a skin tone match with the donor, and rarely some donors' skin may be tattooed. The skin may have a different colour and texture or hairiness and will have no sensation except to deep pressure. However, over time the patch of skin changes to look and feel more like the patient's own. Your transplant doctor will discuss any important differences in skin matching with you before your transplant (if you are randomised to receive the skin flap) and you may withdraw from the study at any time if you wish. This would not affect your lung transplant or usual clinical care in any way.

In our experience, most participants elect to keep the sentinel skin flap after the research period of 12 months. However, you can opt to have the sentinel skin flap removed as detailed earlier.

You may experience minor discomfort and a minor bruise, with a very small risk of bleeding or infection during the taking of skin biopsies or blood samples. All research blood samples will be taken at the same time as routine clinical blood samples. Skin biopsies will be taken under sterile conditions by trained staff.

Will my General Practitioner (GP) be informed of my participation?

It is standard practice to inform your GP about your participation in a research study, and we will ask your permission to do this. If you get a donor match that is willing to provide a skin flap as well – on randomisation we would inform your GP.

Will my taking part in the study be kept confidential?

Yes, all the information that is collected about you during the course of the research will be kept strictly confidential. You will be given a unique participant ID number and all data and results will be stored using this, instead of your name or any other identifiable personal information, and under password protection. A document linking identifiable personal information (including names, addresses, email addresses and telephone numbers) to ID numbers will be stored separately, on a secure password-protected University of Oxford network database only accessible by the study team. It will not be possible for anyone else to identify the results as yours. Responsible members of the University of Oxford, appropriate regulatory bodies and relevant NHS Trusts may be given access to data for monitoring and/or audit of the study to ensure that the research is complying with applicable regulations.

What will happen to the samples I give?

Laboratory tests will be performed to see what genetic markers of rejection and inflammation are stimulated, as well as other inflammatory and immune markers. The results of the investigations on the samples are exploratory and are not intended to influence your routine medical care. Findings will not be reported routinely to the responsible clinician.

We will ask your permission to retain any donated samples once the study has ended. Your samples will be anonymised, labelled with your trial number , and will be used mainly by local researchers but ethically approved research projects may take place in hospitals, universities, non-profit institutions or commercial laboratories worldwide.

What will happen to my data?

We will need to use information from you and your medical records for this research project. This information will include:

- your name,
- your NHS number and date of birth
- your contact details

Data protection regulation requires that we state the legal basis for processing information about you. In the case of research, this is 'a task in the public interest.' The University of Oxford is the sponsor for this study, based in the United Kingdom, is the data controller and is responsible for looking after your information and using it properly.

We will be using information from your medical records, the information held and maintained by the NHSBTand other managing organisations (such as, the national registries and other datasets and databases for data collection) may be used to help contact me or provide information about my health status to the study team. The shared data may include my NHS number and SENTINEL Trial Number. We will keep identifiable information (contact details) about you for 3 years after the study has finished to allow us to send you the website links when the study results are available. This excludes any research documents with personal information, such as consent forms, which will be held securely at the University of Oxford for 25 years after the end of the study. If you agree to be contacted about future research we will keep your contact details for longer. We also need to keep your consent form but the consent form and your contact details will be kept separate. If you agree to your samples being used in future research, your consent form will be held until the samples have been depleted or destroyed
Your treating hospital will collect and hold information about you and or your medical records for this research study in accordance with our instructions and local trust policy.

Data protection regulation provides you with control over your personal data and how it is used. When you agree to your information being used in research, however, some of those rights may be limited in order for the research to be reliable and accurate. Further information about your rights with respect to your personal data is available at

https://compliance.web.ox.ac.uk/individual-rights

You can find out more about how we use your information by contacting:

- Through the Health Research Authority - www.hra.nhs.uk/information-about-patients/
- At the SENTINEL website - <insert study URL>

- By asking a member of the research team : <insert local research team contact details>
- ssftrial@nds.ox.ac.uk

What will happen if I want to withdraw from the study?

If you participate in the study, you are free to withdraw at any time and without giving a reason. Withdrawal from the study will not affect the standard of care you receive. If you would like to withdraw, please contact the Trial Manager at ssftrial@nds.ox.ac.uk or using the electronic forms that you receive. A member of the SENTINEL team will discuss your withdrawal options with you – you will need to have your study ID (this can be found at the top of the consent form that you signed). If there are certain parts of the study that you no longer wish to continue with (e.g. completing follow-up questionnaires) you can just let the study team know and they will ensure that you are withdrawn from the appropriate parts of the study. Your data and samples are valuable to our research and we would like to use the data and samples already collected up until the time you withdraw, as well as continuing to collect data from your hospital. If you do not want this to happen, please tell us and we will stop. All results will be anonymised so no-one can identify you from the results.

We need to manage your records in specific ways for the research to be reliable. This means that we won't be able to let you see or change the data we hold about you.

If you agree to take part in this study, the information collected about you may be used to support other research in the future, and may be shared anonymously with other researchers.

What will happen to the results of this study?

We intend to publish the results of the SENTINEL study in medical journals, and to present the results at conferences. Please note that it will never be possible to identify you or your individual data from any report or publication placed in the public domain. Your contact details will be retained until the website link (SENTINEL.octru.ox.ac.uk) publishing the results of the study can be sent out.

What if there is a problem?

The University of Oxford, as Sponsor, has appropriate insurance in place in the unlikely event that you suffer any harm as a direct consequence of your participation in this study. NHS indemnity operated in respect of the clinical treatment which is provided.

If you wish to complain about any aspect of the way in which you have been approached or treated, or how your information is handled during the course of this study, you should contact Professor Henk Giele who is the overall study lead on 01865 223223 or email henk.giele@nds.ox.ac.uk; or you may contact the University of Oxford Research Governance, Ethics and Assurance (RGEA) office on 01865 616480, or the head of RGEA, email: RGEA.Complaints@admin.ox.ac.uk

The Patient Advisory Liaison Service (PALS) is a confidential NHS service that can provide you with support for any complaints or queries you may have regarding the care you

receive as an NHS patient. PALS is unable to provide information about this research study.

If you wish to contact the PALS team please contact <insert relevant NHS site phone number and email from the PALS website http://www.ouh.nhs.uk/patient-guide/pals.aspx>.

Who is organising and funding the study?

SENTINEL is funded by the Health Technology Assessment Programme of the National Institute for Health Research (part of the Department of Health & Social Care). The study is sponsored by and led by the University of Oxford. The Chief Investigator devised the study with transplant surgeons and respiratory specialists across the UK. The research team is qualified to do this study because they have the specialist skills required. The day to day running of the study is being performed by the Surgical Intervention Trials Unit (SITU), a research group working with the Oxford Clinical Trials Research Unit (OCTRU).

Who has reviewed the study?

Transplant patients, including other patients who have received a sentinel skin flap, have also been involved in the development and management of this study.

All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee, to protect participants' interests. This study has been reviewed and given a favourable opinion by the Queen's Square Research Ethics Committee. It has also been reviewed and approved by NHS Blood and Transplant.

Participation in future research:

All contact regarding future research will come from the research team at the University of Oxford in the first instance. Agreeing to be contacted does not oblige you to take part in future research, and you can be removed from this register at any time if you wish.

Further information and contact details

General information about taking part in research can be found here: www.nhs.uk/Conditions/Clinical-trials/

If you have any concerns or wish to discuss the study further, please contact:

XXX, Research Nurse Tel: Email: Address:	XXX, Local Principal Investigator Tel: Email: Address:

SENTINEL Trial Manager Email:ssftrial@nds.ox.ac.uk	**Chief Investigator** Professor Henk Giele

Tel :07407876298 Surgical Intervention Trials Unit (SITU) Nuffield Department of Surgical Sciences, University of Oxford Botnar Research Centre Nuffield Orthopaedic Centre Windmill Road Oxford OX3 7HE	Email: henk.giele@nds.ox.ac.uk Tel: 01865 223223 Nuffield Department of Surgical Sciences, University of Oxford Old Road Campus Research Building Oxford OX3 7DQ

Thank you for considering taking part in the SENTINEL study.