NRG
March 2017

RINTAG/ Research update

1. Executive Summary

In instances where approval is given for removal of organs solely for research purposes and there are the necessary licenses etc in place, it would be helpful if NORS teams were able to undertake the retrieval. This is particularly relevant for cases where the research team lacks the necessary skills/ expertise or resources to undertake the retrieval themselves.

The Research, Innovation and Novel Technologies Advisory Group (RINTAG) secretariat have been approached by a number of researchers asking for support in this area (details at Annex A).

It is suggested that in instances where the NORS team is already attending and where the necessary research licences/ approvals/ consent are in place, NORS teams undertake the retrieval of organs for research purposes. The cost of any additional consumables and transport for organs would need to be met by the research team.

In addition, the NRG is asked to advise on whether the current process for liaising with NORS teams via NRG and the Clinical Retrieval Forum is sufficient.

2. Actions Required

The NRG is asked to:

1. Advise what more NORS teams could/ should do to facilitate research by removing organs for research purposes.
2. Should NRG agree to remove organs for research purposes, what (if any) changes should be made to the current RINTAG approval process for new research requests.
3. Building on the outcome of this discussion, what response should be given to the current research proposals/ requests at Annex A.
4. Advise on the best approach for ensuring NORS teams are kept up to date with developments regarding relevant research proposals.
5. Note progress with the research proposals previously discussed at RINTAG, provided at Annex B.

3. Background

Contractual situation

The current NORS contract states: *Members of the NORS team may agree to retrieve organs or tissues for research purposes but this is **not** part of the NHSBT commissioned service and the researcher must engage separately with the retrieval teams and NHSBT will accept no responsibility for the actions of the Retrieval Team.*

This is slightly unaligned with the MOU between NHSBT and research teams, which states**:**

The retrieval personnel are responsible for ensuring that:

- *Any removal of relevant material for research does not interfere with the retrieval for transplantation.*
- *Appropriate consent/ authorisation have been obtained.*

- *The retrieval takes place in licensed premises (not required in Scotland) and in accordance with all current regulations.*
- *Prior agreement will need to be in place with the researcher (if not the researcher or deputy undertaking the retrieval) regarding an appropriate time and location for the collection of samples removed by NORS teams for research purposes.*
- *The retrieved material, if removed for the purpose of research, is transferred to the custodianship of the research team.*
- *Recording the retrieval of relevant material for research according to current legislation and local governance arrangements.*
- *Members of the National Organ Retrieval Service may agree to retrieve relevant material for research purposes but this is not part of the NHSBT commissioned service and the researcher must engage separately with the retrieval teams and NHSBT will accept no responsibility for the actions of the Retrieval Team.*

NRG is asked whether any amendments should be made to the MOU regarding the role of NORS in retrieval for research purposes.

Approval process

On receipt of a research proposal, the RINTAG secretariat and ODT Research Project Team undertakes an initial assessment of the potential impact of the study on the organ donation, retrieval and transplantation process. Where appropriate, the team will contact key stakeholders, such as the relevant SNOD team etc to explore this in more detail. The proposal is then sent to the RINTAG Executive Group (membership of which includes the Chairs of the NRG and the solid organ Advisory Groups) for advice before being formally presented to RINTAG for a decision regarding approval.

NRG is asked whether this process is sufficient, or whether any amendments are required when considering requests for support in organ retrieval. For example, should there be a more formal process for liaising with NORS teams directly regarding these requests and if so, what is the best forum to undertake this?

Disseminating information to NORS teams

Currently the ODT Research team and RINTAG secretariat liaise with NRG regarding projects that may impact on NORS teams. They will liaise with specific NORS teams if advised to do so by the NRG or RINTAG. In addition, updates on progress/ hot topics are provided by a number of routes, such as the BTS Congress, RINTAG annual stakeholder meetings, ODT website and AMD Bulletin.

NRG is asked whether this process of information dissemination is sufficient.

4. Research proposals

There are currently 3 new research proposals where NORS teams help is sought in retrieving organs for research purposes. Details of these are provided at Annex A.

NRG is asked whether the CT-related proposals should also be presented to CTAG for comment (next meeting is 26th April).

In addition, there are 3 studies that have been raised with the NRG and approved by RINTAG subject to a number of conditions being met. Details of these are provided at Annex B for information.

5. Next steps

Subject to NRG advice, the ODT Research Project Team and RINTAG secretariat will liaise with stakeholders to make amendments to their current processes and documentation to clarify the role of NORS in retrieval of organs for research purposes and if necessary, improve the sharing of information with NORS teams.

Maria McGee
ODT Research Project Manager

Claire Williment
Head of Transplantation Development

Annex A – Research proposals seeking NORS support for retrieval

There are currently 3 proposals received by RINTAG, where NORS support for retrieving organs solely for the purpose of research is sought.

The NRG is asked for advice on what, if any, support should be offered to these proposals. Any other comments would be welcomed.

1. Newcastle, Andy Fisher (Bill Scott) - EVLP - RINTAG approved.
   Please see attached information sheet for NRG consideration. Initial agreement between researchers and Newcastle retrieval team to be sole retrievers of lungs for research initially.

Project application lay summary:
The shortage of suitable donor lungs for transplant has a major impact meaning that about 1 in 4 people listed for a lung transplant will not survive long enough to receive a suitable organ. New technology that allows the donor organ to be treated outside the donor before a decision on its suitability for transplant, offers the potential to address the shortage of donor lungs. The technique called ex-vivo lung perfusion or EVLP involves passing a nutrient solution through the lungs and also giving them oxygen via a ventilator machine. The decision about which donor lungs should be placed on EVLP could be improved if we had a better way to identify the lungs that will improve their function. In this study, with permission of the next of kin, we will use lungs from donors that would not otherwise be used for transplant to better understand what happens to the lungs during EVLP and to assess if we can better predict if they could have been used for transplant. In addition we will test a number of new treatments that might improve the way the lungs work so that in future these could be used to help increase the availability of donor lungs for those on the waiting list.
This work is a very important way in which we might make a difference to those dying on the waiting list and mean more organs can be used when families agree to organ donation.

2. Scotland, Kevin Dhaliwal (Annya Smyth) - EVLP - RINTAG approved.
   Please see attached information sheet for NRG consideration.
   Please be aware agreements are in place between the researchers and Edinburgh Abdominal team and Glasgow/Newcastle Cardiothoracic teams for only these retrieval teams to retrieve lungs initially and this is for awareness only of this project initially.

Project application lay summary:
Our main aim with this project is to develop and deploy novel methods that will assist in increasing the numbers of lungs available for transplant in the future and also help to monitor lungs once transplanted. The study will develop novel techniques to image and sense infection, inflammation and

physiological indices in the human lung. This will enable more accuate assessment of lungs for transplantation. We aim to retrieve lungs deemed not suitable for transplant from organ donors whose families consent to use of the lungs for research. The lungs will be connected to a breathing and circulation system which will keep the lungs alive for a day. This is called ex vivo lung perfusion (EVLP). During his time we will study the infection and inflammation in the lungs and deliver new agents we have developed to be able to detect certain types of infection (e.g. bacteria) and disease processes and also deliver treatments to the lung to see how well such treatments work. Optimising these lungs will improve the rates of lung transplantation. These methods will help teams around the world to improve the way they monitor and assess lungs both in patients and also in centres that perform EVLP. The lungs will be imaged just as they would be if they were in a patient. This provides the best model system for us to rapidly tailor therapies and imaging agents to take back to the intensive care and to investigate possible lungs for transplantation in the future.

3. Southampton - Oliver Harrison - Ascending aortic tissue and blood samples from DBD donors – RINTAG application yet to be completed.
   Please see attached information sheet for NRG consideration.

Project application lay summary.

Bicuspid aortic valve disease is one of the commonest congenital cardiac defects, affecting 1-2% of the population. It is caused by partial or complete fusion of two of the normal three aortic valve leaflets and often results in early progressive thickening and hardening of the aortic valve (aortic stenosis). It is also associated with dilatation of the main blood vessel that leaves the heart (aorta). The cause of this dilatation is, however, poorly understood. If left untreated, dilatation of the aorta can result in fatal rupture or tearing. This study aims to describe the molecular changes in the cells of the aortic wall, associated with this congenital condition. If successful, this study would provide an insight into one of the causes of aortic wall cell loss (apoptosis) and suggest ways in which this could be prevented.

ANNEX B – Update on proposals previously raised with NRG and RINTAG

The following proposals have previously been raised to NRG's attention, but are not yet live:

1. Birmingham, Graham Flint, Olfactory Bulbs.

RINTAG approved this study to proceed for 3 cases, subject to a number of further reassurances being given regarding the protocol and clarification or and liaison with the proposed donor centres and SNOD teams. This work is still ongoing and the study is not anticipated to go live for several months. Progress will be discussed at the next meeting of RINTAG in May. This team are proposing the removal of olfactory bulbs via trans sphenoidal route post organ retrieval.
NRG Information sheet not yet received.

Project application lay summary.
Recent publicity surrounding the para-olympics has brought home to those of us who are able-bodied just how devastating it must be for somebody to have their life completely changed by a spinal cord injury. We can only admire the victims of these injuries, be they sustained on the sports field, in a road traffic accident or on the battlefield. These people pick themselves up, get on with their lives and, as we have seen in London and Rio, sometimes achieve more than the rest of us do. There is, then, a general acceptance that a spinal cord injury is often a permanent, life-changing event. Treatment, to date, has consisted of rehabilitation and social support with, beyond about two years after the injury, little hope of any further recovery. This, it would seem, is the price that we have to pay as a mammalian species, being warm-blooded and fast-moving animals. Birds are subject to the same "curse" and yet cold-blooded vertebrates, i.e. fish, amphibians and reptiles, retain the capacity to regenerate a severed spinal cord. Further, close inspection of a damaged mammalian spinal cord reveals that attempts to repair the damage are made but that they are frustrated by the inability of regrowing nerve fibres to cross the area of injury. It therefore seems very likely that even mammalian and avian species retain the capacity to regenerate their central nervous systems and that it is a question of "unlocking" this potential. The rewards, to individuals and to society, if we could achieve this end, would be tremendous. Over the past three-quarters of a century, since the end of the Second World War, increasing efforts have been made to induce regeneration of central nervous system "axons" - these being the individual fibres that conduct nerve impulses within the spinal cord. Efforts have focused in particular in modifying the local environment through which the axons are attempting to re-grow. Success has been achieved only relatively recently, by the use of what are called olfactory ensheathing cells. These cells normally exist in the nerves of smell, within the head. The ensheathing cells, whilst not conducting any nerve impulses themselves, do support the olfactory nerve fibres. Further, they do seem to be able to permit re-growth of axons, something which other "support cells" in the central nervous system are unable to do. Laboratory experiments have demonstrated recovery of lost function in rodents which have undergone grafting of cultured olfactory ensheathing cells into the region of a spinal cord injury. Most recently of all, a human victim of

spinal cord injury received a graft of olfactory ensheathing cells, derived from one of his own olfactory bulbs. He has since recovered some function in his previously paralysed lower limbs. This case was the subject of a BBC Panorama programme in 2015, as well as a follow-up BBC news item more recently.
Clearly, this work needs to be explored further but two issues arise. Firstly, the patient needs to undergo several, separate surgical operations, on the brain, on the spinal cord and on a nerve in one of the legs. Secondly, there is a limit to the amount of olfactory ensheathing cells that can be cultured from one olfactory bulb. Happily, recent laboratory work, in rodents, has shown that olfactory ensheathing cells can be harvested successfully from one rodent species, cultured and then grafted into the injured spinal cord of another rodent species. With immunosuppressant, continued over a limited period, the donor cells allow host axons to regrow successfully across the site of spinal cord injury, with resultant recovery of function. After an interval the immunosuppression can be withdrawn, leading to death of the donor cells but survival of the regenerated axons. There is an other, unfortunate consequence of spinal cord injury, which is that victims quite often go on to develop a complication known as post-traumatic syringomyelia, which sometimes requires surgery to be carried out upon the spinal cord. If such surgery is required, in an individual patient, and if there were then available a source of olfactory ensheathing cells, from a human tissue bank, the opportunity could then be taken, at the same time as the "necessary" surgery, to perform a tissue graft that might permit regrowth of spinal cord axons, across the original site of injury, with some resulting recovery of neurological function. The proposed study has two stages. The first is to establish whether or not a suitable tissue bank of viable human olfactory ensheathing cells can be established. If it can then a pilot clinical study could follow, whereby banked human olfactory ensheathing cells are grafted into the damaged spinal cord of human spinal cord injury victims, who are undergoing surgery for their post-traumatic syringomyelia.

2. London, Marios Papadopoulos, Olfactory bulbs.
NRG Information sheet not yet received.

RINTAG approved this study to proceed for 3 cases, subject to a number of further reassurances being given regarding the protocol and clarification or and liaison with the proposed donor centre and SNOD teams. This work is still ongoing and the study is not anticipated to go live for several months. Progress will be discussed at the next meeting of RINTAG in May. This team are proposing removal of olfactory bulbs via a craniotomy post organ removal.

Project application lay summary.

Spinal cord injury is a devastating condition. Most patients are young men who will remain paralysed or wheelchair bound. There is no treatment that improves outcome. This is because any spinal cord neurons that die are not replaced and do not regenerate. Our objective is to remove olfactory bulbs from brain stem dead donors. We will culture olfactory ensheathing cells

(OECs) from these olfactory bulbs. There is evidence from several animal models and from a human study that OECs, transplanted at the injury site, promote neuronal regeneration and improve outcome after spinal cord injury. In PHASE 1, we would like to study the human OECs in the lab. We will devise a protocol to maximise the yield of these cells and optimise storage conditions. In PHASE 2, We will create a bank of OECs in a GMP facility. Cells stored at this bank will be transplanted into patients with spinal cord injuries to assess improvement in outcome. We have designed the olfactory bulb removal process to avoid any interference with standard organ donation. The scalp incision will be inconspicuous to the family.

3. Imperial, Richard Smith, Uterine Transplantation

Issues raised regarding the approach to retrieval and use of iliac vessels have been addressed. RINTAG and the ODT Senior Management Team have approved this study subject to a number of requirements being met. This includes confirmation being provided regarding the final approach for donor centres, retrieval teams and transplanting centres. Once this has been received, the team will need to liaise with the relevant CLODs etc to agree the final protocol. This will need to be approved by SMT before going live. This team are now aligned with Oxford and have proposed to perform retrieval with this team only and will be transplanting in Oxford. We are awaiting formal agreement for this programme from Oxford Trust.