NHS BLOOD AND TRANSPLANT
ORGAN DONATION AND TRANSPLANTATION DIRECTORATE

MINUTES OF THE RESEARCH, INNOVATION AND NOVEL TECHNOLOGIES (RINTAG) MEETING
HELD AT 10.30 A.M. ON MONDAY 9TH OCTOBER 2017
THE COUNCIL CHAMBER, THE ROYAL COLLEGE OF ANAESTHETISTS, 35 RED LION SQUARE, LONDON WC1R 4SG

PRESENT:

Mr Gabriel Oniscu	GO	**Chair**
Mrs Hazel Bentall	HB	Lay Member
Mr John Casey	JC	Chair, Pancreas Advisory Group
Mr Anthony Clarkson	AC	Assistant Director for Organ Donation & Nursing, ODT
Prof John Dark	JD	National Clinical Lead – Governance, ODT
Prof Andrew Fisher	AF	NIHR BTRU
Ms Victoria Gauden	VG	National Quality Manager, ODT, NHSBT
Ms Sally Johnson	SJ	Director of Organ Donation & Transplantation
Mrs Maria McGee	MMG	ODT Research Project Manager
Mrs Jennifer Mehew	JM	Statistical & Clinical Studies, NHSBT
Dr Gail Miflin	GM	Medical & Research Director, NHSBT
Mrs Elizabeth Murphy	EM	Lay Member
Ms Karen Quinn	KQ	Assistant Director for Commissioning, ODT
Dr Nick Watkins	NW	Assistant Director – Research & Development, NHSBT
Prof Chris Watson	CWa	Chair, Kidney Advisory Group
Mrs Claire Williment	CWi	Head of Transplant Development, ODT

In attendance:

Ms Oluwayomi Adebaju	OA	National Research Manager, NHSBT
Mrs Kathy Zalewska	KZ	Clinical & Support Services, NHSBT

Apologies:

Dr Rebecca Cardigan	RC	Head of Components Development, NHSBT
Prof John Forsythe	JF	Associate Medical Director, ODT, NHSBT
Prof Peter Friend	PF	Chair, Multi-visceral & Composite Tissue Advisory Group
Dr Rachel Hilton	RH	British Transplantation Society Representative
Mrs Rachel Johnson	RJ	Assistant Director of Statistics & Clinical Studies, NHSBT
Mr David Metcalf	DMe	Divisional Finance Director, ODT, NHSBT
Dr Paul Murphy	PM	Chair, National Organ Donation Committee
Prof John O'Grady	JOG	Chair, Liver Advisory Group
Prof Rutger Ploeg	RP	Chair, National Retrieval Group, Director of QUOD
Ms Maggie Stevens	MS	Specialist Nurse Research & Service Delivery
Ms Rachel Stoddard-Murden	RSM	Service Delivery Manager, ODT
Mr Michael Stokes	MSt	Hub Operations Manager, ODT, NHSBT
Mr Steven Tsui	ST	Chair, Cardiothoracic Advisory Group

ACTION

1 WELCOME

The Chair welcomed J Mehew to her first meeting of RINTAG.

2 DECLARATIONS OF INTEREST IN RELATION TO THE AGENDA

There were no declarations of interest in relation to the agenda.

3 MINUTES OF THE RESEARCH, INNOVATION & NOVEL TECHNOLOGIES ADVISORY GROUP MEETING HELD ON 15TH MAY 2017 – RINTAG(M)(17)1

3.1 **Accuracy**

The minutes of the previous meeting were agreed as a correct record. There was a request not to embed files (QUOD reports) into the minutes as embedded files can't be opened on a MAC.

3.2 **Action points: RINTAG(AP)(17)1**

All action points were either in hand, completed or on the agenda for discussion.

3.3 **Matters arising, not separately identified**

There were no other matters arising.

4 RESEARCH ACTIVITY – STATISTICS & CLINICAL STUDIES UPDATE

4.1 **Impact of changes to research consent/authorisation questions – RINTAG(17)9**

Members received a paper summarising the impact of changes to research consent/authorisation questions from 6th January 2016. This paper will be repeated when more data from 2017 is available and submitted to the next RINTAG meeting. In relation to figure 3, J Mehew also agreed to explore the reasons why so many organs with research consent were still disposed of in 2017. **JM**

4.2 **Progress Report Update and Publications - RINTAG(17)10**

All active research studies registered with NHSBT ODT were detailed in the paper and will be displayed on the ODT website in due course, together with lay summaries of each study as a drop-down box. Data is collected on a 6-monthly basis and members were asked to comment on the update. As of August 2017, there were 39 studies active on the ODT Research Registry, excluding three registered Research Tissue Banks. Three of the active studies aim to transplant organs into recipients. It was noted that some studies had exceeded the number of organs originally requested and had therefore resubmitted requests for further organs. Resubmissions to be considered later in the meeting.

5 ALLOCATION POLICY

5.1 **Two month review of the research allocation scheme – RINTAG(17)11a**

A paper presenting the results of a two-month review of the research organ allocation scheme was received. The following headline conclusions were noted:

- 95% of organs with consent for research were offered for research; 32% of these organs were not subsequently used for research and were disposed of
- 20% of organs used for research were not offered through the ranking system
- 5 studies were unable to use organs due to geographical issues
- Long cold ischaemia times may occur due to the length of the offering process
- Organs that went for research and were successfully transplanted are not distinguished from other routine transplants on the database and are therefore not included in the data for research organs.

Members discussed the fact that not all organs which are offered for research are being used, mainly due to a lack of response to offers which are outside of the 9am to 5pm weekday timeframe. This was felt to be a major issue and a breakdown of offering times would be useful for RINTAG to get sight of. Two suggestions to address this were:

- The possibility of offering to tissue banks further down the offering sequence when this situation arises; however Hub Operations does not have the capacity to do this given the additional resources required to deliver, amidst competing clinical priorities. Hub Operations have however expressed an interest in establishing a working group to look at how to incorporate the research scheme into the IT Hub development to establish a Research Matching.
- Look into the possibility of QUOD expanding its activities in this area without any extra funding
- Reinstate the requirement for studies, when submitting their application, to state what arrangements are in place for accepting and utilising organs.

5.2 **RINTAG Allocation Scheme: Recommendations & Survey Outcomes – RINTAG(17)11b**

Members received a paper outlining the impact of the new allocation scheme and recommending that the scheme be fully adopted into ODT standard practice as well as continuing with work to improve the transparency of the process and policy.

Arising from discussion at minute 5.1 above, the Group agreed to endorse these recommendations.

6 NOVEL TECHNOLOGIES

6.1 **Uterine Transplants**

The research team have submitted a REC and HRA amendment. The current proposal submitted to RINTAG is to undertake five cases of dry run retrieval to remove the uterus, then bench it and return it to the body. The team anticipates that a 45 minute warm dissection phase will be needed. Members supported the approach with specific consent for up to 5 cases when abdominal only NORS teams are mobilised. Members agreed the dry run will be subject to adherence to the current protocol; meeting the expectations of families and on the proviso that the procedure does not unduly delay the last offices. Assurance is also needed that the team is available to undertake the retrieval when consent is obtained then. The dry run will require REC amendment and licensing considerations in donor hospitals. NHS England should be updated on this amendment.

6.2 **Olfactory bulbs**

M Papadopoulos and colleagues joined the meeting to resubmit the application for the research study and to discuss the possibility of including a further recruitment group of non-organ donors (contraindicated and non-proceeding). RINTAG original issued support for the pilot project involving the retrieval of olfactory bulbs from three DBD donors post solid organ retrieval. Work has been taking place to address the issues raised by NHSBT/ RINTAG. HTA support has been verbally obtained at St George's hospital. It was confirmed that retrieved cells will only be characterised at the research facility and then disposed of at the end of the project. This is a feasibility study to ascertain whether viable tissue can be retrieved. The updated media policy in the study protocol is to be finally confirmed by NHSBT communications.

There was unanimous support to take the pilot project forward, including the amendment presented, with a request to report back via M Stevens.

7 SUB-GROUP UPDATE: INCREASING THE NUMBER OF ORGANS AVAILABLE FOR RESEARCH (INOAR) – RINTAG(17)12

7.1 Members received an update report including recommendations from the INOAR sub-group for endorsement. RINTAG agreed to endorse the recommendations which included:

- Extension of the QUOD licence to support removal of specific organs for generic research purposes. The removal of 'specific' consent would not be detrimental to the process as there is a clear and transparent process for consenting for research purposes.
- A list of all live studies should be accessible by SNODs to inform discussions. The ODT website should include data on all live studies and families made aware of the website in order to access more information.
- Those studies in centres which have their own HTA licence for removal of organs should be supported during an interim period of one year to allow those studies to seek REC amendment approval.

INOAR also suggested two further changes to support the ODT research infrastructure:

- Continue work to establish a number of RECs with interest/ expertise in organ donation
- Researchers should be encouraged to write to donor families and guidance could be provided to researchers on what should be included in the letter.

The need for a robust governance process around the extension to the QUOD licence was highlighted. This would be necessary to ensure that the licence would only cover organs that the NORS teams have agreed to and are currently trained to remove. Each study would need to be ranked with an identifying number by NHSBT for traceability as some organs could be used for more than one study. Studies will also need to have formal REC approval or confirm that approval is not required. M McGee and M Stevens will need to ensure that researchers are aware that they are responsible for ensuring that they are authorised to transport human tissue. **MMG/MS**

RINTAG agreed to support the proposal in its current format for submission to ODT SMT for approval.

8 STUDIES FOR APPROVAL AND INFORMATION – RINTAG(17)13

8.1 M McGee submitted a paper summarising the outcome of the first six-monthly re-scoring and re-ranking exercise. The paper showed the current and previous ranking whereby nearly all studies were affected by the re-ranking. RINTAG approved the new ranking list and MMG will notify all studies of the change. Details on all approved activated studies, including their ranking and lay summary, will be made available on the website.

A list of full submission and re-submission requests were displayed, together with study protocols and application forms giving further details for the former. RINTAG members involved with these studies left the room during discussion on a decision.

Request 1: *Does the introduction of a national pre-implantation biopsy histopathology service increase numbers, and improve outcomes, of kidney transplants performed in the UK? (The PITHIA Trial)*
Project was initially presented to RINTAG in May 2017 for information. Amendments in this submission primarily relate to operational agreements. Increased level of involvement for Hub Operations with a much greater role in determining where samples go for scanning. M Stokes has confirmed that should not be an issue. Submission supported.

Request 2: *Investigation of genetic and epigenetic marks in cancer:* Access is required to 10 discarded adrenal glands for chromaffin cell isolation. In each case the research team will need to obtain confirmation from Hub Operations that specific consent is in place. The ODT Hub change request is being processed with an 8 week timeframe (from 2nd Oct), pending RINTAG approval. The project was supported although concerns were expressed on the small number of glands required. RM confirmed support.

Request 3: *Correlation of cellular behaviours in Venous Intimal Hyperplasia to haemodynamic parameters using ex vivo living human vein tissue:* This two-year AVF failure study requires 100 discarded human gonadal veins which is proposing to taken when retrieved kidneys from deceased donors arrive at recipient centre in Belfast. The tissue would be transported to the study centred at the University of Limerick. This would require specific consent by SNODs in the donor hospital. No HTA licences are required. The proposal is classed as sharing material internationally.
There were no objection to this study being supported but it was felt that this should not be formally offered at present as there is no reciprocity from ROI which had reportedly declined the project. It is likely that the numbers required will not be achieved without this support. Assurance is also needed that these veins can be collected at any time of day, particularly out of hours.

Request 4: Collection and characterisation of human olfactory ensheathing cells: Refer to minute 6.2 above.

Request 5: *EVNP of kidneys for transplantation (no. 48):* Re-submission for access to18 additional kidneys with a 3 year study extension. Revised study objectives to include investigation of he impact of additional cell therapy products (MAPCs) during EVNP. Revision of inclusion/exclusion criteria to include paired kidneys for simultaneous EVNP (control vs treatment). REC amendment, now covered under BTRU REC approval 16/NE/0230. This is a generic research study which requires no further input from SNODs. Re-submission supported.

Request 6: *Process development for islet isolation targeted at enhancing islet yield and viability (no.20):* Newcastle has requested a change to the REC status, now covered under BTRU REC: 16NE0230. The study has been suspended at one site (Darling & Durham) until further notice from the local R&D reg. BTRU REC. This will accommodate SNOD activities, as specific research consent is required. Members were happy to support the re-submission.

Request 7: *Establishment of cultured human glomerular cells for the glomerular function in vitro (no. 19):* This Bristol study is seeking up to an additional 15 kidneys per year for 2 years. The original study duration has lapsed and an extension to 2021 has been requested. M McGee was asked to clarify the dates detailed on the re-submission. Changes to inclusion criteria were also noted. The study will include elements of the commercial sector/ cost recovery (tissue banks). All paperwork has been submitted apart from HRA approval which is awaited. Re-submission supported in principle, pending clarification of the above mentioned changes. **MMG**

Request 8: *Studies of factors influencing the structure and function of human pancreatic islets for transplantation (no.45)*: This Oxford study requires 20 additional samples to enable more robust statistical analysis following earlier protocol amendments. Additional approaches include genetic testing as part of this research. Members asked to see evidence of output implications of the study so far as well as the impact of this additional work on the existing study before approving this re-submission. **MMG/MS**

Request 9: *Establishing ex-vivo normothermic and hypothermic perfusion of livers for transplantation (no. 52):* This project is moving under the BTRU REC (16NE0230) and access is requested to an additional 24 livers for this project with same objectives. An extension to the study duration of three years is also requested to reach target. Re-submission supported.

Request 10: *A study utilising tissue from deceased organ donors to investigate regenerative cellular therapies and related physiological and developmental processes (24):* Access requested to 50 additional organs donors. Revised study inclusion/ exclusion criteria to include appendix and blood vessels. REC revision,15/EE/0152 REC amendment provided. The study will include the commercial sector/ cost recovery (tissue banks). All required documentation has been supplied, with the exception of DI support letter in progress. Re-submission supported.

Additional request:
Members were informed of an additional full submission request, and details were displayed as following:

RE Study: *Generation of patient specific stem cells towards cell based therapy for disease of the liver* - King's College Hospital, Denmark Hill, London, Institute for Liver Sciences

Requesting access to samples form an initial 20 livers (excess cells from RINTAG approved project). Propose to access tissue via:
1) Retrospective samples accessed via existing isolated hepatocytes from the freezer at King's
2) Prospective samples accessed by excess cells from Dhawan/Fitzpatrick allocated organs for research (King's Hepatocyte project already approved via RINTAG)

The purpose of this project is to evaluate the differences between hepatocytes isolated straight from human organs and those generated from the same starting cells but reprogrammed into Induced Pluripotent stem cells (iPSCs) then converted to hepatocytes. Obtain hepatocytes from donor material and reprogramme to iPSCs then convert back to hepatocytes and

characterize differences between the starting cell population and subsequently generated cells. In this manner we will improve quality of iPS derived cells making them more suitable from human transplantation.

Please note that this study does not require additional tissue from NHSBT but propose using samples from already allocated livers from King's hepatocytes group. Please note that this study has been active since 2008, operating without NHSBT approval. The King's hepatocytes team have agreed to give access to both retrospective and prospective samples to this research Group. REC approval is in place. RM and operational support gained for generic consent. Members highlighted the importance of re-using samples while R&D and QA reps. raised the need for consent process agreement and good traceability processes, as it involves generation of cell-lines. The proposal gained support in principle, pending adequately addressed aspects, such as consent and traceability.

General discussion:
It was recommended that the number of organs requested, offered and accepted should be incorporated on the re-submission sheet presented to RINTAG in the future. This data will aid the review, before a decision is made on whether to support re-submissions.

9 OPERATIONAL ISSUES

9.1 There are operational challenges across regions to facilitate requests for research studies. A Clarkson reported that SNOD teams are requesting guidance on which region takes on responsibility for particular studies, especially when a study requires specific consent. A UK wide map was displayed, showing the number of studies in each region requiring specific research consent. It was also discussed that the consent decision is not up to individual SNODs as this does not align with the RINTAG oversight and could have a detrimental impact on other studies. Operational oversight is the responsibility of RINTAG which should make this decision based on an internal process to look at what is operationally achievable. This would be best approached via the INOAR sub-group and should include a process for warning when issues occur after a study has been approved. The INOAR report will be submitted to SMT with a view to those recommendations helping to streamline the process.

10 SERVICE EVALUATION UPDATE

10.1 **EVLP** – The first EVLP was undertaken almost a year ago but recruitment has been overshadowed by concerns raised through the DEVELOP-UK study and therefore stopped. An update on any further developments will be given at future meetings.

10.2 **NRP** - Progressing well in both Cambridge and Edinburgh. There have been approximately 60 donors in the UK so far and a business case is being developed primarily based on liver data. The business case was not ready for submission to SMT and therefore not tabled at
10.3 RINTAG.

Discarded pancreas audit - Completed in so far as analysing organ discard over ten years and discrepancy in organ appearance between centres. There is huge variation between centres in the rates for organs discarded and interpretation of organ appearance and injury. Further discussions to be held with C Callaghan about how to take forward the findings of this audit and consider imaging at the time of retrieval.

11 QUOD – RINTAG(17)14

11.1 J Dark reported that QUOD had successfully applied for funding to extend its remit to retrieve and store whole organs, particularly heart, lung and pancreas. These organs will be retrieved by the NORS teams and a meeting is due to take place on 3rd November to discuss the practical issues involved. Members were encouraged by this development and the possibility of extending the INOAR remit to oversee this work.

One advantage of having non-transplant related researchers involved is the increase in general cardiac usage of these hearts and lungs increasing the possibility of cost recovery in the future.

12 DCD HEARTS

This will be a standing item on the RINTAG agenda. The remit for oversight of this programme has now been transferred to RINTAG

12.1 **Clinical status: Current level of activity – RINTAG(17)15a**
Members noted a paper looking at DCD heart activity and patient outcomes from 1 February 2015 to 31 August 2017.

J Mehew agreed to incorporate further analysis in the next report: **JM**

- Further detail on the reason for non-use recorded by Manchester in June 2017 currently reported as 'function'
- Paragraph 9 – two recorded deaths due to 'organ failure' – further detail/ reasons were requested
- Kaplan-Meier patient survival function - split for NRP and non-NRP
- Compare organ utilisation rates in Table 5 to national averages

12.2 **Clinical protocols – RINTAG(17)15b**
Members also received a tabled paper providing an overview of the process that NORS teams should follow if they wish to establish a DCD heart retrieval programme. This includes the requirement for the centre's DCD heart retrieval protocol to be presented to NRG. Records of accredited individuals performing DCD heart retrieval will need to be added to the training and accreditation process as part of the oversight.

The importance of the clinical protocols being available to RINTAG was emphasised, particularly with the extension of NRP to include cardio-thoracic organs.

12.3 **Update on use of allogeneic blood**
The protocol for blood utilisation for donor organ retrieval, ex situ perfusion and preservation technologies has now been finalised with references to allogeneic blood now changed to donor bank blood. This protocol will be incorporated in the next revision of the NORS standards. V Gauden added that the accompanying paper would also need to be updated.

12.4 **Identify data for the TA-NRP and DCD procedures**
Abdominal NRP takes priority over direct procurement and perfusion (DPP) of the heart unless thoraco-abdominal DPP can be provided. J Asher had previously asked for a steer on the data to be collected, particularly for thoraco-abdominal NRP to enable this to be built into protocols. It was decided that this should be agreed off line.

13 LEAN PROCESS

13.1 Survey outcomes – RINTAG(17)16

In mid-August 2017 an online survey was launched to seek user feedback on the ODT/RINTAG application process. Feedback confirmed that the improvements to the application and approval process have been successful. The results will be used to inform the lean process underway for ODT research. Response to the survey was low but most respondents felt their study was given the correct level of priority and accepted the basis on which the decision was made.

Key findings of the survey:

- A lack of understanding of RINTAG's aims and objectives.
- Lack of surety of the level of support offered by RINTAG
- Some dissatisfaction over the length and bureaucracy of the application procedure

Next steps:

- Continue to promote awareness of RINTAG and its role/remit eg via ODT website, AMD Bulletin, attending meetings, and building links with researchers.
- Review survey responses as part of the current lean process for the ODT research application system and use these responses as a baseline for measuring future service user satisfaction.

RINTAG members advised:

- Communication strategy: Present at BTS Congress as part of the NHSBT session or at RTSM/ equivalent workshops; run a horizon type workshop to raise awareness and inform of the mechanisms involved; present at Advisory Group meetings
- Dragons Den option: Not felt to be feasible due to the number of applications involved. Consider a dial-in option for researchers during RINTAG discussion, if required.
- Update reporting system: Change to short on-line updates highlighting key changes every 6 months and a more detailed progress report submitted annually.

13.2 Next steps: Application timeline - RINTAG(17)17

A paper was received outlining the application process timeline to RINTAG together with the key findings of analysis undertaken to identify trends and areas for improvement within the process. Responsibility for the primary delays lies with:

- NHSBT – internal consultation
- Researchers – submission requirements
- External organisations – local approvals

It was noted that corrective action has already been taken to prevent recurrence for most issues within NHSBTs remit.

M Stevens and M McGee were thanked for their involvement in setting up the survey, which it is intended to repeat annually to provide baseline data.

14 UTILISATION OF ISLETS FOR RESEARCH

Islet isolation utilisation for research is possible via two routes:
1. Islets isolated from organs for the primarily purpose of research
2. Islets isolated from organs for the primary purpose of clinical use; with insufficient yield once prepared and; subsequently made available for research.

The utilisation of islets in the 2nd category is most common and will not be allocated onto a research programme in another unit due to isolation costs by the local clinical unit.

The use of islets for research requires further decision from RINTAG and the islet community, including UKIC. There may be instances where RINTAG makes decisions for some projects, but is unaware of others. While it is important that these projects are reported to RINTAG, UKIC could decide and direct islets for research. No final decision was reached by the Group.

15 ELECTRONIC DATA CAPTURE

This item was covered elsewhere in the meeting.

16 RINTAG BTS ANNUAL MEETING

This is a two-day meeting on 17th & 18th January 2018. Members were asked to notify M McGee of suggestions for the agenda.

17 HORIZON SCANNING

- AI project: This is currently being developed. G Oniscu agreed to contact those involved with a view to inviting them to the next RINTAG. **GO**
- Innovation Observatory: This is an independent research team at Newcastle University which is incorporated as a research programme within NIHR and which explores trends in health innovation. A Fisher offered to liaise with MMG to arrange a meeting with the director, if of interest to RINTAG. **MMG**

18 ANY OTHER BUSINESS

18.1 V Gauden reported that in April 2017 the HTA issued new codes of practice on information for families. Following a review it was identified that there are inconsistencies in practice in dissemination of information to families. It is proportionate to provide a research information leaflet to explain what is research and hand it to the family asking them to read it and giving them the opportunity to ask questions. A form of wording and a DAT information sheet will be introduced for SNODs to follow in order to provide consistency and ensure that NHSBT is compliant with the code.

18.2 Clinical trials for medical devices taking place within the EU: It was agreed to seek wider views before the next RINTAG meeting on reporting of adverse events in the use of these machines as some of the trials have finished and the machines are used more extensively. There are currently two EU directives from 1993 relating to this which can be either device-related or non-device related. This would also be added to the agenda for the next RINTAG meeting. **C&SS**

18.3 Collection of perfusion data: It was noted that proposals agreed following the last meeting are not yet in place due to issues with manpower within NHSBT Statistics & Clinical Studies. The list of data to be collected has been agreed and work is progressing but is not the highest priority due to work on the ODT Hub. This will be an agenda item at the next meeting. It was suggested that basic information on the type of machine should be included in the data.

19 DATE OF NEXT MEETING

The next meeting is scheduled to take place on Friday, 11th May 2018 at the Medical Society London.