Health Research Authority

North West - Haydock Research Ethics Committee
3rd Floor - Barlow House
4 Minshull Street
Manchester
M1 3DZ

Telephone: 0207 104 8012

13 May 2016

Dr Tim Peakman
UK Biobank Limited
1-4 Spectrum Way
Adswood
Stockport
Cheshire
SK3 0SA

Dear Dr Peakman

Title of the Research Tissue Bank:	**UK Biobank: a large scale prospective epidemiological resource**
REC reference:	**16/NW/0274**
Designated Individual:	**Dr Tim Peakman**
IRAS project ID:	**200778**

The Research Ethics Committee reviewed the above application at the meeting held on 10 May 2016. Thank you for attending with Mr Jonathan Sellors and Ms Nicola Doherty to discuss the application.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this favourable opinion letter. The expectation is that this information will be published for all studies that receive an ethical opinion but should you wish to provide a substitute contact point, wish to make a request to defer, or require further information, please contact the REC Manager Ms Rachel Katzenellenbogen, nrescommittee.northwest-haydock@nhs.net.
Under very limited circumstances (e.g. for student research which has received an unfavourable opinion), it may be possible to grant an exemption to the publication of the study.

Favourable opinion

The members of the Committee present gave a favourable ethical opinion of the above research tissue bank on the basis described in the application form and supporting documentation, subject to the conditions specified below.

The Committee has also confirmed that the favourable ethical opinion applies to all research

projects conducted in the UK using tissue or data supplied by the tissue bank, provided that the release of the tissue or data complies with the attached conditions. It will not be necessary for these researchers to make project-based applications for ethical approval. They will be deemed to have ethical approval from this committee. You should provide the researcher with a copy of this letter as confirmation of this. The Committee should be notified of all projects receiving tissue and data from the tissue bank by means of an annual report.

This application was for the renewal of a Research Tissue Bank application. The previous REC Reference number for this application was 11/NW/0382.

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Research governance

Under the Research Governance Framework (RGF), there is no requirement for NHS research permission for the establishment of research tissue banks in the NHS. Applications to NHS R&D offices through IRAS are not required as all NHS organisations are expected to have included management review in the process of establishing the research tissue bank.

Research permission is also not required by collaborators at tissue collection centres (TCCs) who provide tissue or data under the terms of a supply agreement between the organisation and the research tissue bank. TCCs are not research sites for the purposes of the RGF.

Research tissue bank managers are advised to provide R&D offices at all TCCs with a copy of the REC application for information, together with a copy of the favourable opinion letter when available. All TCCs should be listed in Part C of the REC application.

NHS researchers undertaking specific research projects using tissue or data supplied by the research tissue bank must apply for permission to R&D offices at all organisations where the research is conducted, whether or not the research tissue bank has ethical approval.

Site-specific assessment (SSA) is not a requirement for ethical review of research tissue banks.

Summary of discussion at the meeting

Social or scientific value; scientific design and conduct of the study

The Committee were pleased to see that UK Biobank was constantly re-evaluating itself with regards to new technology and data collection. This meant that new tests were undertaken and new data and tissue collected allowing UK Biobank to grow and develop as a resource.

The Committee were very pleased that this resource was open access and also that researchers had to register to use it. The Committee noted that while UK Biobank owned the resource they had no preferential access. The Committee very happy to note that all research results had to be sent back to UK Biobank as part of a transparency agenda.

The Committee noted that the data was being used by a broad range of researchers and asked how use would be maximised in the future.

> You explained that originally UK Biobank had been designed to be used in case control studies. However, you had been able to demonstrate that centralised generation of large datasets had advantages of cost, standardisation and a lack of gaps. This meant that it was being used in more than just case control studies.
>
> You said that genotyping was being done on all participants and that they were currently measuring 34 biomarkers with the data available to all. You said that you were currently working up a proposal to measure 40 markers of infectious disease and were also looking at developing strategies to look at proteins and metabolites. You said it was important to maximise the tissue so that, for example, you wouldn't use tissue simply to measure glucose, but if you could run tests that delivered a lot of data, including glucose, then the data would be gathered in a good way.
>
> You said that the data was linked to various registers, including deaths, cancer and hospital visit. 30% of English participants had primary care information and this was a lot higher for Welsh and Scottish participants. This meant that you would be able to create a plausible calendar as to when the data would be mature for more common conditions and then you would put out a call for researchers.

The Committee noted that one of the criteria for accessing the biobank was that the research be "in the public interest". The Committee asked if any applications had been turned down because they had not been in the public interest.

> You said that no applications had been turned down because they were not in the public interest. In fact, only 2 or 3 requests for samples had been turned down and that was because they had either requested too much or actually did not need to turn to a biobank to do their research.

The Committee agreed that it had been an exemplary submission and had led to an interesting and informative discussion. The Committee looked forward to the publication regarding imaging and the reporting of findings and hoped the researchers would advise them of when it was published and how it could be accessed.

Care and protection of research participants; respect for potential and enrolled participants' welfare and dignity

The Committee agreed that the systems in place to avoid identifying participants were robust. Always growing and considering and developing.

The Committee noted that UK Biobank was regularly in touch with participants via newsletter and held an Annual General Meeting. The Committee agreed this was very important if participants were to stay motivated and interested as without this no new data or tissue could be added.

The Committee noted that the imaging Participant Information Sheet and consent form said that GPs would be contacted if anything clinically significant was discovered. The Committee noted that UK Biobank had had a policy of not feeding back findings and wondered if this policy had now changed. The Committee also agreed that they needed to know more about how significant

clinical findings were determined. For example, carotid arteries narrowed as people aged, so would all narrowing be reported or just ones with a certain percentage of narrowing.

The Committee asked what the current position was regarding feeding back clinically significant findings.

> You said that the position had not changed, although it was reconsidered on a regular basis. When participants came for their baseline visit in 2007-2010 if something was spotted during the visit, then it was fed back. However, assay or other research findings were not fed back.
>
> With regard to imaging, which could lead to acute findings such as cancer, you explained that you had spent 5-6 years working out the best protocol for that. The end result was that if the radiographer observed something that concerned them it was flagged and a radiologist would assess it. If the radiologist determined that it was significant then it was reported to the GP.
>
> You explained that during the imaging pilot you had run two protocols, the one that is in current use, and a second one that involved a radiologist screening all of the images. After follow up it became clear that this was hugely problematic, not because of cost or expediency, but because it had led to 200 false positives. At the extreme end there had been a lung section and a removal of ovaries for people with false positives. Scaling this up to 100,000 people meant there could be 20,000 false positives.
>
> You said that you had spoken to participants and to imaging projects and it had been agreed that while the radiographers might miss things, the best protocol was to have radiologists only look at images flagged by radiographers. You also said that you would be publishing the results of this research shortly.
>
> You said that, in short, the feedback policy was that anything of clinical significance discovered during data acquisition would be fedback but any other findings would not be.

The Committee agreed that this was acceptable, especially as it was all made very clear to participants in information sheets.

The Committee asked why radiologists were diagnosing so many false positives.

> You said that the images were research scans which, despite what many participants had thought, were not more detailed than ones taken for clinical purposes. Additionally, the radiologists did not have any of the other information they would have in normal diagnosis.

The Committee agreed that the level of commitment required from participants was high and the Committee agreed they would like to know how many participants had withdrawn and how many had simply been lost to contact. However, the Committee was impressed with the way UK Biobank kept participants informed of new developments and asked how many participants had been lost to contact or withdrawal.

> You said that just over 1,000 participants had withdrawn with about 600 of them having requested all tissue and data be removed from the resource. The Committee said that

while annual communications always sparked some withdrawals, the benefits of the communication far outweighed that problem.

You said that most communication was by email, including web based questionnaires. However, it was easier to keep in touch with people by post because if they moved you could usually find their new address. Also it was impossible to know how many emails were opened and read, so no one knew who actually read the newsletter.

You explained that response rates to questionnaires had actually gone up over time and that there had been a 50% response rate to the request for participants willing to wear an accelerometer. In fact, you had managed to recruit 100,000 participants to do that.

You said that you were now also starting to use mobile technology to contact participants.

Other ethical issues were raised and resolved in preliminary discussion before your attendance at the meeting.

Duration of ethical opinion

The favourable opinion is given for a period of five years from the date of this letter and provided that you comply with the standard conditions of ethical approval for Research Tissue Banks set out in the attached document. You are advised to study the conditions carefully. The opinion may be renewed for a further period of up to five years on receipt of a fresh application. It is suggested that the fresh application is made 3-6 months before the 5 years expires, to ensure continuous approval for the research tissue bank.

Research Tissue Bank Renewals

The Research Tissue Bank has been renewed for a further five years from the end of the previous five year period. The previous five year period ran from 17 June 2011 to 17 June 2016. This Research Tissue Bank may be renewed for further periods of five years at a time by following the process described in the above paragraph.

Approved documents

The documents reviewed and approved at the meeting were:

Document	*Version*	*Date*
Human Tissue Authority licence [HTA Licence 12002 & 12624]		26 July 2010
IRAS Checklist XML [Checklist_27042016]		27 April 2016
Other [Table 1: Comparison of the sample collection for the baseline assessment and imaging pilot]	1.0	02 March 2016
Other [Table 2: Progress with key cohort-wide linkages Q1-2 2016]	1.0	02 March 2016
Other [UK Biobank Ethics & Governance Framework]	3.0	01 October 2007
Other [Figure 1: Submitted Access Applications by areas of interest]	1.0	02 March 2016
Other [Table 3: Biochemistry assays being performed in all 500,000 participants]	1.0	02 March 2016
Other [Participant Withdrawal Form]	1.1	10 February 2012

Other [UK Biobank Newsletter June 2015]	1.0	22 June 2015
Other [Data Dictionary Showcase Sept15]	Sept 2015	24 March 2016
Other [Curriculum vitae - Timothy Peakman]	March 2016	24 March 2016
Other [RTB Report March 2016]	1.0	24 March 2016
Other [Appendix: Occupational Questionnaire]	1.0	27 August 2014
Other [Appendix: Occupational Questionnaire Invitation Text]	1.0	27 August 2014
Other [Appendix: Occupational Questionnaire Reminder Invitation Text]	1.0	27 August 2014
Other [Revised Imaging Invitation Email]	1.0	06 October 2014
Other [Imaging Reminder Text & SMS]	1.0	18 November 2014
Other [Feedback in the UK Biobank Imaging pilot study]	Jan 2014	29 January 2014
Other [Invitation letter for deliberative group interviews]	1.0	06 October 2014
Other [Imaging 2nd Invite email HTML]	0.1	01 January 2016
Other [Imaging 2nd Invite email PLAIN]	0.2	01 January 2016
Other [Imaging Participant pre-screening questionnaire]	1.3	27 October 2015
Other [Imaging Exit Survey]	0.1	01 January 2016
Other [Invite email reminder 6-month questionnaire HTML]	0.1	01 October 2015
Other [Invite email reminder 6-month questionnaire PLAIN]	0.1	01 October 2015
Other [Invite email reminder 6-week questionnaire HTML]	0.1	01 October 2015
Other [Invite email reminder 6-week questionnaire PLAIN]	0.1	01 October 2015
Other [Invite email reminder understanding consent questionnaire HTM]	0.1	01 October 2015
Other [Invite email reminder understanding consent questionnaire PLAIN]	0.1	01 October 2015
Other [Appendix 1: Mental Health Questionnaire]	1.2	23 March 2016
Other [Appendix 2: Rationale and tools used in Mental Health Questionnaire]	1.1	04 March 2016
Other [Appendix 3: Invitation email Mental Health Questionnaire]	1.2	11 March 2016
Other [Appendix 4: Reminder email Mental Health questionnaire]	1.2	11 March 2016
Other [Appendix 5: Reminder partial responder email Mental Health questionnaire]	1.1	11 March 2016
Other [Appendix 6: Last chance email Mental Health questionnaire]	1.0	11 March 2016
Other [Repeat Assessment email invitation]	1.0	09 August 2012
Other [Repeat Assessment invite letter]	1.0	26 March 2012
Other [Repeat Assessment confirmation letter]	1.0	11 July 2012
Other [Confirmation of imaging appointment letter]	1.0	08 April 2016
Other [Activity Monitor Information Letter]	26/03/2012	26 March 2012
Other [Activity Monitor Invitation Letter]	26/03/2012	26 March 2012
Other [Activity Monitor Return Reminder]	26/03/2012	26 March 2012
Other [UK Biobank Assessment form]	20061124	24 November 2006
Other [Diet Questionnaire]	1.0	11 April 2016
Other [UK Biobank Participant Invite letter]	1.0	11 April 2016
Other [Touch-screen questionnaire]	1.0	11 April 2016

Other [Touch-screen questionnaire addendum]	1.0	11 April 2016
Other [Cognitive Function tests]	1.0	26 March 2013
Other [Cognitive Function Web Questionnaire email invitation]	1.0	26 March 2013
Other [Cognitive Function Web Questionnaire email reminder]	1.0	26 March 2013
Other [Cognitive Function Web Questionnaire email reminder partial responder]	1.0	26 March 2013
Other [UK Biobank Protocol]	21/03/2007	21 March 2007
Other [UK Biobank Protocol addendum 1]	09/04/2009	09 April 2009
Other [UK Biobank Protocol addendum 2]	02/07/2009	02 July 2009
Other [Text Message to request email address]	1.0	20 April 2016
Other [UK Biobank TIME study invitation]	2.2	15 April 2016
Other [Imaging Questionnaire to assess participant understanding of consent]	January 2014	01 January 2014
Other [Imaging Participant Questionnaire sent at 6 weeks to assess IF]	January 2014	01 January 2014
Other [Imaging Participant Questionnaire sent at 6 months to assess impact of IF]	January 2014	01 January 2014
Other [Imaging Questionnaire sent to participants who did not receive IF feedback]	January 2014	01 January 2014
Other [Imaging Letters notifying participant and participant's GP of potentially serious incidental finding]	1.0	01 January 2014
Other [Imaging GP questionnaire sent at 6 months to assess the later impact of feedback of IF]	1.0	01 April 2015
Participant consent form [UK Biobank Consent form]	20061124	24 November 2006
Participant consent form [Consent Form for the imaging assessment: UK Biobank]	Jan 2014	29 January 2014
Participant information sheet (PIS) [Participant Information Leaflet]	21/04/2010	21 April 2010
Participant information sheet (PIS) [Biobank Imaging Information Leaflet]	Dec 2015	01 December 2015
Participant information sheet (PIS) [Repeat Assessment Participant Information Leaflet]	26/03/2012	26 March 2012
Participant information sheet (PIS) [Further Information Leaflet]	001	08 April 2016
Participant information sheet (PIS) [Biobank Imaging Information Leaflet including ECG monitoring]	2.0	26 November 2014
Protocol for management of the tissue bank [UK Biobank Access Procedures]	1.0	01 November 2011
REC Application Form [RTB_Form_24032016]		24 March 2016

Licence from the Human Tissue Authority

Thank you for providing a copy of the above licence.

Membership of the Committee

The members of the Ethics Committee who were present at the meeting are listed on the attached sheet. Dr Tim Sprosen helped set up UK Biobank and was a member of the Scientific Steering Committee. It was agreed that Dr Sprosen would leave the room during the discussion and take no part in the discussion or decision making. Dr Valerie Siddall, Alternate Vice-Chair, would chair

that portion of the meeting.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached standard conditions give detailed guidance on reporting requirements for research tissue banks with a favourable opinion, including:

- Notifying substantial amendments
- Submitting Annual Progress reports

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

User Feedback

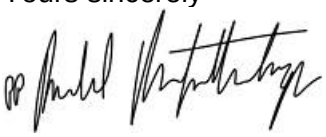
The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website:
http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/

HRA Training

We are pleased to welcome researchers and R&D staff at our training days – see details at http://www.hra.nhs.uk/hra-training/

16/NW/0274	**Please quote this number on all correspondence**

Yours sincerely



Dr Tim S Sprosen
Chair

E-mail: nrescommittee.northwest-haydock@nhs.net

Enclosures: List of names and professions of members who were present at the meeting and those who submitted written comments

Standard approval conditions

North West - Haydock Research Ethics Committee

Attendance at Committee meeting on 10 May 2016

Committee Members:

Name	*Profession*	*Present*	*Notes*
Mrs Moyra Ann Baldwin	Retired Senior Lecturer - Oncology	Yes	
Mr Stephen Edgar	Designer	Yes	
Dr Michael U Eshiett	Consultant Physician in Neurological Rehabilitation	No	
Mr Simon Hill	Pharmacist	No	
Dr Ben Johnson	Consultant Psychiatrist	No	
Dr Ezzat Kozman	Consultant Gynaecologist	Yes	
Mr Charles Otim	Research Support Officer	Yes	
Dr David Pilling	Consultant Radiologist	Yes	
Miss Anna Sekula	Nurse	No	
Dr Valerie E Siddall	Retired Senior Manager - Pharmaceutical Industry	Yes	Alternate Vice-Chair – Meeting Chair for this application
Dr Tim S Sprosen	Epidemiologist	Yes	Chair
Dr Zhe Wang	Medical Statistician	Yes	

Also in attendance:

Name	*Position (or reason for attending)*
Ms Rachel Katzenellenbogen	REC Manager

CONDITIONS OF ETHICAL APPROVAL

Research Ethics Committee:	North West - Haydock Research Ethics Committee
Research Tissue Bank:	UK Biobank: a large scale prospective epidemiological resource
REC reference number:	16/NW/0274
Name of applicant:	Dr Tim Peakman
Date of approval:	10 May 2016
IRAS project ID:	200778

Ethical approval is given to the Research Tissue Bank ("the Bank") by the Research Ethics Committee ("the Committee") subject to the following conditions.

1. Further communications with the Committee

1.1 Further communications with the Committee are the personal responsibility of the applicant.

2. Duration of approval

2.1 Approval is given for a period of 5 years, which may be renewed on consideration of a new application by the Committee, taking account of developments in legislation, policy and guidance in the interim. New applications should include relevant changes of policy or practice made by the Bank since the original approval together with any proposed new developments.

3. Licensing

3.1 A copy of the Licence from the Human Tissue Authority (HTA) should be provided when available (if not already submitted).

3.2 The Committee should be notified if the Authority renews the licence, varies the licensing conditions or revokes the Licence, or of any change of Designated Individual. If the Licence is revoked, ethical approval would be terminated.

4. Generic ethical approval for projects receiving tissue

4.1 Samples of human tissue or other biological material may be supplied and used in research projects to be conducted in accordance with the following conditions.

4.1.1 The research project should be within the fields of medical or biomedical research described in the approved application form.

4.1.2 The Bank should be satisfied that the research has been subject to scientific critique, is appropriately designed in relation to its objectives and (with the exception of student research below doctoral level) is likely to add something useful to existing knowledge.

4.1.3 Where tissue samples have been donated with informed consent for use in future research ("broad consent"), the Bank should be satisfied that the use of the samples complies with the terms of the donor consent.

4.1.4 All samples and any associated clinical information must be non-identifiable to the researcher at the point of release (i.e. anonymised or linked anonymised).

4.1.5 Samples will not be released to any project requiring further data or tissue from donors or involving any other research procedures. Any contact with donors must be confined to ethically approved arrangements for the feedback of clinically significant information.

4.1.6 A supply agreement must be in place with the researcher to ensure storage, use and disposal of the samples in accordance with the HTA Codes of Practice, the terms of the ethical approval and any other conditions required by the Bank.

4.2 A research project in the UK using tissue provided by a Bank in accordance with these conditions will be considered to have ethical approval from the Committee under the terms of this approval. In England, Wales and Northern Ireland this means that the researcher will not require a licence from the Human Tissue Authority for storage of the tissue for use in relation to this project.

4.3 The Bank may require any researcher to seek specific ethical approval for their project. Such applications should normally be made to the Committee and booked via the Central Booking System

4.4 A Notice of Substantial Amendment should be submitted to seek the Committee's agreement to change the conditions of generic approval.

5. Records

5.1 The Bank should maintain a record of all research projects to which tissue has been supplied. The record should contain at least the full title of the project, a summary of its purpose, the name of the Chief Investigator, the sponsor, the location of the research, the date on which the project was approved by the Bank, details of the tissue released and any relevant reference numbers.

5.2 The Committee may request access to these records at any time.

6. Annual reports

6.1 An annual report should be provided to the Committee listing all projects for which tissue has been released in the previous year. The list should give the full title of each project, the name of the Chief Investigator, the sponsor, the location of the research and the date of approval by the Bank. The report is due on the anniversary of the date on which ethical approval for the Bank was given.

6.2 The Committee may request additional reports on the management of the Bank at any time.

7. Substantial amendments

7.1 Substantial amendments should be notified to the Committee and ethical approval sought before implementing the amendment. A substantial amendment generally means any significant change to the arrangements for the management of the Bank as described in the application to the Committee and supporting documentation.

7.2 A Notice of Substantial Amendment should be generated by accessing the original application form on the Integrated Research Application System (IRAS).

7.3 The following changes should always be notified as substantial amendments:

7.3.1 Any significant change to the policy for use of the tissue in research, including changes to the types of research to be undertaken or supported by the Bank.

7.3.2 Any significant change to the types of biological material to be collected and stored, or the circumstances of collection.

7.3.3 Any significant change to informed consent arrangements, including new/modified information sheets and consent forms.

7.3.4 A change to the conditions of generic approval

7.3.5 Any other significant change to the governance of the RTB.

8. Serious Adverse Events

8.1 The Committee should be notified as soon as possible of any serious adverse event or reaction, any serious breach of security or confidentiality, or any other incident that could undermine public confidence in the ethical management of the tissue. The criteria for notifying the Committee will be the same as those for notifying the Human Tissue Authority in the case of research tissue banks in England, Wales and Northern Ireland.

9. Other information to be notified

9.1 The Committee should be notified of any change in the contact details for the applicant or where the applicant hands over responsibility for communication with the Committee

to another person at the establishment.

10. Closure of the Bank

10.1 Any plans to close the Bank should be notified to the Committee as early as possible and at least two months before closure. The Committee should be informed what arrangements are to be made for disposal of the tissue or transfer to another research tissue bank.

10.2 Where tissue is transferred to another research tissue bank, the ethical approval for the Bank is not transferable. Where the second bank is ethically approved, it should notify the responsible Research Ethics Committee. The terms of its own ethical approval would apply to any tissue it receives.

11. Breaches of approval conditions

11.1 The Committee should be notified as soon as possible of any breach of these approval conditions.

11.2 Where serious breaches occur, the Committee may review its ethical approval and may, exceptionally, suspend or terminate the approval.