



Health Research Authority

North West - Haydock Research Ethics Committee

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Manchester
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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 feedback 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:

<i>Document</i>	<i>Version</i>	<i>Date</i>
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:

<i>Name</i>	<i>Profession</i>	<i>Present</i>	<i>Notes</i>
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:

<i>Name</i>	<i>Position (or reason for attending)</i>
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.

Welcome to the Integrated Research Application System

IRAS Project Filter

The integrated dataset required for your project will be created from the answers you give to the following questions. The system will generate only those questions and sections which (a) apply to your study type and (b) are required by the bodies reviewing your study. Please ensure you answer all the questions before proceeding with your applications.

Please complete the questions in order. If you change the response to a question, please select 'Save' and review all the questions as your change may have affected subsequent questions.

Please enter a short title for this project (maximum 70 characters)

UK Biobank: a large scale prospective epidemiological resource

1. Is your project research?

☒ Yes ☐ No

2. Select one category from the list below:

- ☐ Clinical trial of an investigational medicinal product
- ☐ Clinical investigation or other study of a medical device
- ☐ Combined trial of an investigational medicinal product and an investigational medical device
- ☐ Other clinical trial to study a novel intervention or randomised clinical trial to compare interventions in clinical practice
- ☐ Basic science study involving procedures with human participants
- ☐ Study administering questionnaires/interviews for quantitative analysis, or using mixed quantitative/qualitative methodology
- ☐ Study involving qualitative methods only
- ☐ Study limited to working with human tissue samples (or other human biological samples) and data (specific project only)
- ☐ Study limited to working with data (specific project only)
- ☒ Research tissue bank
- ☐ Research database

If your work does not fit any of these categories, select the option below:

☐ Other study

2a. Will the bank be established within a NHS / HSC diagnostic archive?

☐ Yes ☒ No

2b. As well as biological samples and data, will the bank also collect and store radiological images from sample donors?

☒ Yes ☐ No

Will donors be invited to undertake any ionising radiation exposures (e.g. X-Rays, CT scans) additional to those authorised as part of normal clinical management?

☒ Yes ☐ No

3. In which country of the United Kingdom is the bank established?

- ☒ England
☐ Scotland
☐ Wales
☐ Northern Ireland

3a. In which countries of the United Kingdom will centres collecting and/or supplying tissue and data to the bank be located? (tick all that apply)

- ☒ England
☒ Wales
☒ Scotland
☐ Northern Ireland

4. Which applications do you require?

- ☐ IRAS Form
☒ Research Ethics Committee
☐ Confidentiality Advisory Group (CAG)

For NHS/HSC R&D Offices in Northern Ireland, Scotland and Wales the CI must create NHS/HSC Site Specific Information forms, for each site, in addition to the study wide forms, and transfer them to the PIs or local collaborators.

For participating NHS organisations in England different arrangements apply for the provision of site specific information. Refer to IRAS Help for more information.

6. Do you plan to include any participants who are children?

- ☐ Yes ☒ No

7. Do you plan at any stage of the project to undertake intrusive research involving adults lacking capacity to consent for themselves?

- ☐ Yes ☒ No

Answer Yes if you plan to recruit living participants aged 16 or over who lack capacity, or to retain them in the study following loss of capacity. Intrusive research means any research with the living requiring consent in law. This includes use of identifiable tissue samples or personal information, except where application is being made to the Confidentiality Advisory Group to set aside the common law duty of confidentiality in England and Wales. Please consult the guidance notes for further information on the legal frameworks for research involving adults lacking capacity in the UK.

8. Do you plan to include any participants who are prisoners or young offenders in the custody of HM Prison Service or who are offenders supervised by the probation service in England or Wales?

- ☐ Yes ☒ No

10. Will this research be financially supported by the United States Department of Health and Human Services or any of its divisions, agencies or programs?

- ☐ Yes ☒ No

11. Will identifiable patient data be accessed outside the care team without prior consent at any stage of the project (including identification of potential participants)?

☐ Yes ☒ No

RESEARCH TISSUE BANK / BIOBANK



Application to NHS / HSC Research Ethics Committee

Short title and version number: (maximum 70 characters - this will be inserted as header on all forms)
UK Biobank: a large scale prospective epidemiological resource

Please complete these details after you have booked the REC application for review.

REC Name:

NRES Committee North West - Haydock

REC Reference Number:

16/NW/0274

Submission date:

24/03/2016

Preliminary checklist:

Please tick all activities to be undertaken by or within the establishment (i.e. the legal entity with control of the tissue/data):

- ☒ Existing holding of stored tissue (any "relevant material" as defined by the Human Tissue Act and held prior to 1 September 2006)
- ☒ Removal, collection and storage of new tissue from the living for research
- ☒ Collection and storage of existing/residual tissue from the living (includes samples held in diagnostic archives)
- ☐ Removal of organs or tissue from the deceased
- ☐ Collection and storage of organs or tissue from the deceased
- ☒ Collection and storage of DNA
- ☒ Collection and storage of other biological material
- ☒ Arranging the collection of new tissue samples or other biological material by collaborator(s)
- ☒ Collection of new data from the living
- ☒ Collection of clinical data from patient records
- ☒ Other research procedures involving contact with participants (e.g. questionnaires, imaging)
- ☒ Conducting research projects using the samples or data
- ☒ Releasing samples or data to other researchers with no involvement of the establishment in conducting the research
- ☒ Releasing samples or data to commercial suppliers
- ☒ Export of samples or data outside the UK
- ☐ Collection and storage of identifiable samples or data relating to adults unable to consent for themselves due to physical or mental incapacity

Part A: Core Information

Administrative information

1. Title of the bank.

UK Biobank: a large scale prospective epidemiological resource of 500,000 people aged 40-69 from around the UK.

2. Name and address of the establishment responsible for management of the bank.

Organisation UK Biobank Limited
Address 1-4 Spectrum Way
Adswood
Stockport
PostCode SK3 0SA
Telephone 01614755360
Fax 01614755361

Please give details of the locations at which tissue will be stored:

UK Biobank, 1-4 Spectrum Way, Adswood, Stockport SK3 0SA;
NIHR National Biosample Centre, Units 2-3 Java Park, Bradbourne Drive, Tilbrook, Milton Keynes MK7 8AT; and
NIHR National Biosample Centre, Ferry Hinksey Road, Osney Mead Industrial Estate, Oxfordshire OX2 0AP

3. Name of the tissue bank manager within this organisation.

This person will be the main contact point with the REC for purposes of the application.

	Title Forename/Initials Surname
	Dr Tim Peakman
Address	1-4 Spectrum Way Adswood Stockport
PostCode	SK3 0SA
E-mail	tim.peakman@ukbiobank.ac.uk
Telephone	01614755360
Mobile	07786682081
Fax	01614755361

A copy of a current CV (maximum two pages of A4) must be submitted with the application.

Questions 4-6 should be answered in relation to each establishment. Please open a separate set of the questions for each establishment.

Storage establishment 1

4. Name and address of the establishment responsible for storage of any relevant material under the Human Tissue

Act. *Where relevant material will be held in more than one establishment, please give details of each establishment.*

Organisation UK Biobank Limited
Address 1-4 Spectrum Way
Adswood
Stockport
PostCode SK3 0SA
Telephone 01614755360
Fax 01614755361

5. Does this establishment hold a licence from the Human Tissue Authority to store tissue for use for a scheduled purpose? *Please enclose copy of licence if available.*

☒ Yes ☐ No ☐ Licence application pending

Licence No.: 12002

6. Please give the name of the “designated individual” for purposes of licensing by the Human Tissue Authority:

	Title Forename/Initials Surname
	Dr Tim Peakman
Address	1-4 Spectrum Way Adswood Stockport
PostCode	SK3 0SA
E-mail	tim.peakman@ukbiobank.ac.uk
Telephone	01614755360
Mobile	07786682081
Fax	

Storage establishment 2

4. Name and address of the establishment responsible for storage of any relevant material under the Human Tissue Act. *Where relevant material will be held in more than one establishment, please give details of each establishment.*

Organisation	NIHR National Biosample Centre
Address	Units 2-3 Java Park Bradbourne Drive Tilbrook, Milton Keynes
PostCode	MK7 8AT
Telephone	01908870800
Fax	01908870801

5. Does this establishment hold a licence from the Human Tissue Authority to store tissue for use for a scheduled purpose? *Please enclose copy of licence if available.*

☒ Yes ☐ No ☐ Licence application pending

Licence No.: 12624

6. Please give the name of the “designated individual” for purposes of licensing by the Human Tissue Authority:

	Title Forename/Initials Surname
	Dr Tim Peakman
Address	1-4 Spectrum Way Adswood Stockport
PostCode	SK3 0SA
E-mail	tim.peakman@ukbiobank.ac.uk
Telephone	01614755360

Mobile 07786682081
Fax 01614755361

Storage establishment 3

4. Name and address of the establishment responsible for storage of any relevant material under the Human Tissue Act. *Where relevant material will be held in more than one establishment, please give details of each establishment.*

Organisation NIHR National Biosample Centre
Address Ferry Hinksey Road
Osney Mead Industrial Estate
Oxfordshire
PostCode OX2 0AP
Telephone
Fax

5. Does this establishment hold a licence from the Human Tissue Authority to store tissue for use for a scheduled purpose? *Please enclose copy of licence if available.*

☒ Yes ☐ No ☐ Licence application pending

Licence No.: 12624

6. Please give the name of the "designated individual" for purposes of licensing by the Human Tissue Authority:

Title Forename/Initials Surname
Dr Tim Peakman
Address 1-4 Spectrum Way
Adswood
Stockport
PostCode SK3 0SA
E-mail tim.peakman@ukbiobank.ac.uk
Telephone 01614755360
Mobile 07786682081
Fax 01614755361

7. Has this bank (or any part of the bank) previously been the subject of an application for ethical review?

☒ Yes ☐ No

If Yes, was the application approved?

☒ Yes ☐ No

Name of Research Ethics Committee: NRES Committee North West - Haydock
Date of decision: 17/06/2011
REC reference number: 11/NW/0382

Purpose of the Bank

8. Please summarise the types of tissue sample or other biological material to be collected/stored from the living.
Please state the selection criteria for inclusion of samples in the bank. Indicate what samples are already held and summarise plans for further collection.

During 2006-2010, UK Biobank conducted its recruitment phase and recruited 500,000 men and women from the UK population, who were aged 40-69 at the date of their baseline assessment visit.

There was extensive consultation and discussion on which biological samples to collect at the baseline assessment centre visit. The inclusion criteria for samples were based on the likely value of the additional information that would be made available by collecting some particular sample type (i.e. the range of assays that could be made and the physiological coverage of the material), and the feasibility and cost of collecting and processing such samples from the 500,000 participants. On this basis, it was decided to collect about 50 ml of blood and a random urine sample. It was subsequently decided to also collect 2-4 ml of saliva due to the potential for this sample to provide a wide range of additional useful information that would not be provided by the blood and urine samples collected.

Blood, urine and saliva samples were collected at:

- the baseline assessment visit of 500,000 participants during 2007-2010;
- the repeat assessment visit of 20,000-25,000 participants during 2012-2013; and
- the multi-modal imaging assessment pilot visit which commenced recruitment in May 2014 and, to date, has recruited ~7,500 participants.

See table 1 "Comparison of the sample collection for baseline assessment and imaging pilot" for further detail of the samples collected and the aliquots taken.

Since 2003-2004, when UK Biobank's sample collection protocol for the baseline visit was developed, analytical technology and supporting informatics have advanced very substantially. Consequently, the sample collection protocol for the main phase of imaging assessments on 100,000 participants was reviewed by UK Biobank's Enhancement Working Group (chair Prof Paul Elliott, Imperial College London) with additional input from relevant experts.

The Working Group considered which sample types from the baseline visit to collect and how many aliquots of the various fractions should be stored. They also considered whether collection of new sample types would add substantial scientific value while still being feasible and affordable on this scale. Table 1 "Comparison of the sample collection for the baseline assessment and imaging pilot" sets out the samples to be collected during the main phase of imaging (commencing 2016 until 2022). The acid citrate dextrose tube, which was collected at the baseline visit to provide a long-term source of genomic DNA from EBV-transformed B-cells, has been omitted because technologic advances mean that much less DNA is required for genomic analysis (so the DNA already extracted from buffy coat fractions will be sufficient for whole genome sequence and other analyses, such as methylation profiling). The tubes collected at baseline for immediate haematology assays and RNA extraction have been excluded here because of the relatively high cost of their collection in the main phase of imaging. There was not considered to be sufficient added value from repeat collection of saliva.

Faeces (stool sample) is a new sample type proposed by UK Biobank's Enhancement working (chair; Prof Paul Elliott, Imperial College) primarily to enable research in to the gut microbiome. It will be collected only if additional funding is obtained.

9. Please summarise the types of organ, tissue sample or other biological material to be collected from the deceased.
Please state the selection criteria for inclusion of samples. Indicate what samples are already held and summarise plans for further collection. If the establishment will be removing organs or tissues from the deceased in England, Wales or Northern Ireland, please provide a copy of the pathology licence.

None

10. Please summarise the types of data to be collected and linked with the samples.
Indicate whether any personal identifiers will be held and explain why this is necessary. Say whether any particularly sensitive data will be held.

During 2006-2010, UK Biobank conducted its recruitment phase and recruited 500,000 men and women from the UK population, who were aged 40-69 at the date of their baseline assessment visit.

Personal identifiers are held as they were required to enable UK Biobank to recruit the cohort and are necessary to enable re-contact of participants on an on-going basis. Direct identifiers (i.e. NHS/CHI numbers, sex, DoB, address, name) are also held as they are required for record linkage to a wide range of electronic medical records across

different service providers (each of which may use different identifiers) - further detail of linkage to health-related records is provided below. Address data are also required to re-contact participants via post, and to provide suitable geographical units for spatial analyses (e.g., grid co-ordinates, super lower output area).

Extensive data was collected at baseline from all participants on their lifestyle, environment, personal and family medical history. Participants also underwent a wide range of physical measures, and provided samples of blood, urine and saliva.

Baseline data

- Touch-screen questionnaire data included lifestyle, environment, personal and family medical history.
- Physical measurement data included blood pressure and heart rate; hand grip; standing and sitting height; weight and bio-impedance; hip and waist circumference; spirometry; bone density; arterial stiffness; eye examination (refractive index, intraocular pressure, acuity, retinal photograph and optical coherence tomography) and fitness test.
- Biological sample data included numbers and types of aliquots and haematological assays results.

With regards to sensitive data, UK Biobank collected self-reported data on number of sexual partners (including same-sex partners). We also intend to collect self-reported data from a web-based questionnaire (in Q2-2016) on mental health issues, including questions on substance and childhood abuse.

Additional assessments to enhance phenotyping

In July 2006, the UK Biobank protocol was endorsed by an International Peer Review Panel (IPRP), which also strongly recommended that UK Biobank consider adding more intensive phenotyping among large subsets of the cohort. The IPRP also recommended consideration of the feasibility of including some more ambitious phenotypic enhancements that would significantly improve the existing data or provide entirely new types of data. The following data has so far been collected:

- Repeat assessment data – the baseline visit was repeated in a sub-set of 20,000 participants in 2012-2013 and will be repeated as part of the imaging assessment visit.
- Biochemical assays on stored blood and urine samples for all 500,000 participants – a panel of 36 biomarkers were selected to be measured. All assays will be completed by the end of 2016.
- Genome-wide genotyping data – Genome-wide genotyping of all 500,000 participants, using a custom-designed UK Biobank Axiom array, was completed in 2015 and all of the data will be available by the end of 2016.

Enhanced phenotyping in large subsets

- Data collected by web-based questionnaires – a 24-hour dietary recall questionnaire was completed by 211,000 participants between Feb 2011-June 2012; a web-based questionnaire on cognitive function was introduced between Nov-Dec 2014 and 143,000 participants completed the first test and 120,000 participants completed the full test; and a web-based questionnaire on occupational history was introduced July-August 2015 and 122,000 participants partially completed it and 100,000 participants fully completed it. A web-based questionnaire to assess mental health is currently being developed and is planned to be introduced in Q2-2016.
- Accelerometry data – 7-day physical activity data was collected on 100,000 participants using a wrist-worn triaxial accelerometer.
- Multi-modal imaging data – this enhancement will be completed on 100,000 participants over the next 6 years and will include magnetic resonance (MR) scans of the brain, heart and body, dual-energy x-ray absorptiometry (DXA) scan of bones, joints and body composition, ultrasound scan of the carotid arteries, plus a repeat of the baseline visit.

Linked Health data

As part of the consent process, all UK Biobank participants gave permission for access to their medical and other health-related records (see Table 2 "Progress with key cohort-wide linkages Q1-2 2016" for data received).

- Death and cancer registry data – cohort-wide linkages have been established in England, Scotland and Wales. In addition to death and cancer, we also receive data on address changes from the same provider.
- Hospital episode datasets (inpatients, outpatients, critical care, A&E, minimum mental health dataset, diagnostic imaging dataset) – cohort-wide linkages have been established in England, Scotland and Wales.
- Primary care data – linkages have been established in Scotland and Wales and are being established with data providers in England.

Linked data have also been obtained, or are being sought, from several national disease-specific registries or audits (e.g., national myocardial infarction, diabetes and stroke audits, national renal registries). Linkages to a wide range of

other databases are being actively explored and piloted, including those with information on: laboratory reports; electronic histopathology reports and tumour specimens; imaging; drug dispensing; dental records; and the national infectious disease surveillance database.

Please enclose a list of all data items to be stored.

11. How is it intended to make beneficial use of the samples or data in research?

Please summarise the overall policy of the bank/establishment for use of the samples or data, including release to other researchers or research organisations

UK Biobank's overriding objective is to ensure that the UK Biobank Resource is used extensively and appropriately for health-related research that is in the public interest by academic or commercial researchers (with no exclusive or preferential access), while at the same time maintaining the underlying agreement made with the participants regarding the confidentiality and use of their data and samples.

When UK Biobank was established a detailed Ethics and Governance Framework (EGF) was drafted (see attached UK Biobank Ethics & Governance Framework). The EGF sets out the governance structure for UK Biobank and describes UK Biobank's purpose as to: "build a major resource that can support a diverse range of research intended to improve the prevention, diagnosis and treatment of illness and the promotion of health throughout society". The EGF also outlines UK Biobank's Access Policy.

Following a public consultation UK Biobank finalised its access procedures and systems to facilitate access by approved researchers to the resource of baseline information and samples in March 2012. The final Access Procedures were approved by UK Biobank's Board and published in November 2011 (see attached document: Access Procedures).

Access to the UK Biobank Resource continues to be governed by the Access Procedures.

Access key points:

- The Resource is open access, although researchers have to register to use it. Approved academic or commercial researchers from around the world are able to apply to use it for health-related research that is in the public good.
- UK Biobank has built and owns the Resource, but there is no preferential access and no requirement for researchers to collaborate with the scientific team that has developed it.
- Stringent measures are in place to ensure that UK Biobank participants are not identified.
- When approved researchers are ready to publish results based on the Resource, they are obliged to share their results with UK Biobank so that advances can be built on by others.

There are 4 stages to the application process:

- Registration: To confirm the identity of each person seeking to use the Resource and to check their bona fides before registering them as an approved researcher;
- Preliminary application: To allow approved researchers to determine: (i) whether their proposed research use is likely to be approved; (ii) whether the resource contains the data and/or samples required for their proposed research; and (iii) the indicative cost of obtaining such data and/or samples (e.g. in preparation for a funding application);
- Main application: To allow UK Biobank to assess: (i) whether the proposed research use meets the required criteria for access (including having relevant scientific and ethics approval); (ii) whether the amount of depletable sample required is scientifically justified; and (iii) the cost of providing such data and/or samples;
- Material Transfer Agreement: For approved applications, the Material Transfer Agreement must be executed and access charges paid before release of data and/or samples to the approved researcher.

The application process currently requires researchers to submit a preliminary and a main application, although we are currently developing a more streamlined system so that only a single application is required, in order that we can assess whether the resource contains the data and/or samples required for their proposed research and, for sample and re-contact requests, to determine whether there is sufficient scientific justification for using such limited resources.

All applications are subject to final approval by UK Biobank's Access Sub-Committee.

12-1. How have you actively involved, or will you involve, patients, service users, or members of the public in establishing the bank and its policies?

There has been extensive consultation with stakeholders, members of the public and the scientific community throughout the life of UK Biobank, with rigorous review of its procedures.

An independent Ethics and Governance Council (EGC) was formed in 2004. This expert group is currently chaired by Baroness Helene Hayman. Further details can be found at www.egcukbiobank.ac.uk

Following successful recruitment of the planned 500,000 participants to UK Biobank during 2006-2010, the plans for subsequent phases of the project have been subject to peer review and continued funders approval.

An International Scientific Advisory Board meets annually. The Board is chaired by Prof Bernard Keavney, BHF Professor of Cardiovascular Medicine and Director of the Institute of Cardiovascular Sciences at the University of Manchester.

From 1 June 2011 to the 6 July 2011, UK Biobank completed a public consultation on its Access procedures. Its purpose was to obtain the views of participants, scientists, members of the public and other interested parties on the draft procedures for allowing access to the UK Biobank Resource. Input from the consultation was used to refine and finalise the Access Procedures in November 2011.

UK Biobank makes contact with all of its participants at least once a year by newsletter to ensure they are kept up-to-date on current activity and future plans. The 2015 newsletter was mailed to participants during June and July and a copy is enclosed. Additionally, UK Biobank has commenced a series of participants' meetings which it intends to hold in towns and cities across the UK where participants were recruited. These meetings provide UK Biobank with an opportunity to thank participants for their participation and to tell them more about how the resource is being used, with guest scientists speaking about research they have undertaken using UK Biobank data. They also importantly provide participants with the opportunity to ask questions and provide feedback on the study. The next meeting is scheduled to take place in Leeds in March.

UK Biobank's annual meeting will be held on the 13 June 2016, and participants and scientists who have used the resource will be invited to present updates to the research community. The possibility of web-casting the meeting so that participants can join remotely is being investigated.

13. How will you inform donors and other patients, service users and members of the public of the results of research?

Details of who is using the resource and summaries of their research projects is published on the UK Biobank website (www.ukbiobank.ac.uk) and UK Biobank reminds its participants in communications to visit the website to receive regular updates. A research update is also included in the Participant Newsletter, which is sent annually to all participants.

14. How will the bank be managed and financed?

It is managed by an executive team of experienced scientists and managers. They are supported by operational, administrative, IT, finance and legal staff. The CEO/PI and deputy CEO report to a quarterly board meeting with associated audit and risk committees.

It is funded through core funding from its major funders (MRC and Wellcome Trust) with additional funders contributing for specific projects (e.g. NIHR, BHF).

Information governance

15. What personal identifiers will be held with the data records? Please tick all that apply.

- ☒ Initials
- ☒ Full name
- ☒ Address
- ☒ NHS or CHI number
- ☒ Hospital ID no.
- ☒ GP registration
- ☒ Date of birth
- ☒ Year of birth

☒ Date of death

☒ Postcode

☐ District level

☐ Sector level

☐ Sub-sector level

☒ Unit level

☒ Other geographical identifiers

please specify

Address data has been converted to grid co-ordinates (Northing and Easting), which have been rounded up to a 1km distance, and are available for research use. More detailed data (up to 100m granularity) is also available but only upon special request.

Postcode data is held, but is converted into grid co-ordinates for data release.

We also intend to release lower super output area.

Purpose for which postcode/geographical identifiers required:

☒ Deprivation scoring

☒ Lifestyle analysis

☒ Geographical analysis

☒ Gender

☒ Occupation

☒ Ethnicity

☐ Other identifiers

16-1. What systems will be in place to ensure the confidentiality of personal data? What will be your policy for limiting access to identifiable data within the establishment. Say who will have access and for what purposes, what training they will have and how the confidentiality policy will be monitored and enforced.

UK Biobank is accredited for, and operates to ISO 27001:2013, the international standard for information management and security. Data are held in secure databases either at the coordinating centre in Cheadle, Stockport or at the Clinical Trial Service Unit and Epidemiological Studies Unit (CTSU) in the University of Oxford. Security is regularly monitored through internal processes and audit and periodic penetrance testing by independent auditors. Information and cybersecurity is now reported as a regular UK Biobank Board item and all database access is monitored to ensure no unauthorised access.

For identifiable information, only a small number of the scientific team can view these data and they are trained to the ISO 27001 standard (which includes audit of confidentiality – any non-conformance is tracked and corrective or preventative actions are put in place). Data provided to researchers are pseudonymised and they sign an MTA stating they will not attempt to re-identify the participants. If potentially identifiable data are ever released to researchers due to the specific needs of the research, the steps required to secure the data are specified as part of the Material Transfer Agreement ("MTA") and can be audited.

17. What security and audit measures will be in place to secure access to identifiable data held by the bank?

Please refer to the response given to Question 16-1.

Use of samples or data in future research

Questions 18 - 27 apply where the bank/establishment will be conducting its own research using the samples or data. Answer in relation to this research programme.

Questions 28 - 39 apply where the bank will be releasing its own samples and data to other researchers.)

18. Do you wish to seek generic ethical approval for research projects conducted by the bank/establishment using the stored samples/data, under conditions agreed with the REC, without requirement for the researchers to apply

individually to the REC for approval?

☐ Yes ☒ No

If Yes, questions 19 - 27 will be enabled.

If No, questions 19 - 27 will be disabled. Researchers will be required to apply individually to obtain ethical approval using the project-based application form.

Questions 28 - 39 apply where the bank will be releasing samples and data to other researchers.

28. Do you wish to seek generic ethical approval on behalf of external researchers who will be using samples or data supplied by the bank, under conditions agreed with the REC, without requirement for researchers to apply individually to the REC for approval?

☒ Yes ☐ No

If Yes, questions 29 - 39 will be enabled

If No, questions 29 - 39 will be disabled. Researchers receiving tissue or data will be required to apply individually to the REC to obtain ethical approval using the REC project-based application form.

29. What types of research will be undertaken by other individuals/organisations using the samples or data and in what field(s) of biomedicine? Name any research organisations or units you plan to collaborate with at this stage.

The main purpose of the UK Biobank Resource is to assess the relevance of different exposures assessed at the baseline visit to health outcomes that occur during long-term follow-up. UK Biobank is an open access resource with a no-preferential access policy. On this basis, any bona fide researcher from an international or national laboratory in an academic, charity-funded or commercial organisation can apply for access to the resource.

UK Biobank aims to encourage the widest possible use of the Resource to help develop improvements in the treatment and prevention of many different diseases. Bona fide researches working in countries around the world are able to apply to use the Resource for all types of health-related research that is in the public interest.

Since March 2012, when Access to the UK Biobank Resource was launched, a total of 509 applications have been submitted (see attached Figure 1 "Submitted Access Applications by areas of interest"). During 2014 and 2015, UK Biobank actively promoted the Resource widely to encourage greater usage. UK Biobank's Data Showcase (<http://biobank.ctsu.ox.ac.uk/crystal/>) allows scientists and members of the public to view the valuable information that has been collected to help improve the health of future generations and includes timelines for future planned releases of data.

Due to UK Biobank being a prospective study and available to any bona fide researcher worldwide, the types of research use are wide-ranging and hard to predict. To date, interest has ranged from investigating the cross-sectional determinants of factors assessed at baseline, through to genome-wide association scans of particular phenotypes, through to machine-learning approaches to identify novel patterns between a wide range of genetic and environmental exposures and a wide range of health outcomes.

In due course, UK Biobank will put out calls for particular disease-based studies, as the numbers of incident cases of diseases accrue, to enable a co-ordinated approach to assaying biological samples within nested case-control subsets.

As the biological samples collected are a finite resource, UK Biobank has adopted an approach, where possible, to undertake analyses itself and make the results of these analyses available for research. This approach has a number of advantages. It preserves as much of the sample as possible because it allows multiple tests to be done simultaneously. Doing the same analyses on all the samples at the same time also helps with quality control and keeps down costs. Coordination of the assays also reduces the need to thaw and re-freeze samples many times, which may affect their quality. The following analyses have been completed, or are in progress or are planned by UK Biobank:

Measurement of 36 biochemical markers in samples collected at baseline from all 500,000 participants. These included biomarkers that are established risk factors for disease (e.g., lipids for vascular disease, sex hormones for cancer), diagnostic measures (e.g., HbA1c for diabetes) and markers that characterize phenotypes not otherwise well assessed (e.g., biomarkers for renal and liver function). The full list of biomarkers is shown in attached Table 3. UK Biobank obtained funding from the Wellcome Trust, British Heart Foundation and Diabetes UK to undertake these assays and they are due to be completed at the end of 2016.

A second panel of biomarker assays for infectious disease markers is currently being developed by UK Biobank and a funding bid for this panel to be measured in samples from all 500,000 participants, will be submitted in 2016, with the intention for the project to commence Q2-2017.

Whole cohort SNP genotyping, involving the analysis of around 800,000 SNPs in the DNA of all UK Biobank participants. This project commenced in March 2013. Extraction of DNA from buffy coat samples for all 500,000 participants was completed at the UK Biobank coordinating centre in April 2015 and genotyping was completed by Affymetrix in California in June 2015. Genotype data were sent to the Wellcome Trust Centre for Human Genetics in Oxford for quality control checks and imputation. Measured and imputed data (covering an additional 73 million variants with high informativeness) for 150,000 of the participants was made available to researchers in May 2015 and are expected to be available for all 500,000 participants during Q3-2016.

Telomere assays will be conducted during 2015-18 using residual DNA from UK Biobank's genotyping project, and these data will also become available to researchers in due course.

UK Biobank anticipates the following assays will also be used on the samples: analyses of the proteome and metabolome (Mass Spectrometry or NMR).

30. Will any types of research or research organisation be excluded from receiving samples or data?

☒ Yes ☐ No

If Yes, please give details:

Only health-related research that is in the public interest will be approved by UK Biobank.

31. Will samples be released for use in animal research?

☐ Yes ☒ No

32. Will the samples be used in research into termination of pregnancy or reproductive cloning?

☐ Yes ☒ No

33. What arrangements will be made to consider applications from researchers for use of the samples or data? How will decisions on access be made and who will be involved?

Please refer to the response given to Question 11 and consult UK Biobank's Access Procedures version 1.0 (November 2011) for further detail.

34. What conditions will apply to the sharing of data with researchers? Please say how this will be monitored and enforced.

UK Biobank's Material Transfer Agreement (see MTA) sets out the conditions and obligations which will apply on the Applicant PI, researchers and Institution of any approved research application. The content of UK Biobank's standard MTA, and the conditions contained within it, are non-negotiable.

The MTA includes a provision for UK Biobank to complete an audit of the approved applicant to monitor compliance with the terms of the MTA.

35. Please give details of how data will be effectively anonymised or pseudonymised to protect the confidentiality of subjects. What measures will you take to prevent possible re-identification by linking to other databases?

UK Biobank irreversibly pseudonymises all data supplied to researchers uniquely on a per project basis. For each project, all participants within a dataset are allocated identifiers from a long-period random number generator and these identifiers are then replaced by a ranking score according to their magnitude, effectively removing any residual information from the random number generator.

Within the UK Biobank core systems, personally-identifying data (name, address) are held on a different system, run by a different IT team, to the clinical data. The UK Biobank laboratory team do not have access to personally-identifying data or to the servers upon which it is stored.

Researchers are legally obliged by a custom contract ("MTA") signed before supply of data not to attempt reverse identification of UK Biobank participants by linking to external datasets. The data items which might facilitate such linkage (e.g. date of birth, home region) are only supplied for research projects that can demonstrate that such precise details are essential to their task, otherwise degraded information is substituted (for instance year of birth rather than exact day).

UK Biobank's summary de-identification protocol can be found at:
<http://www.ukbiobank.ac.uk/wp-content/uploads/2013/10/ukbiobank-summary-de-identification-protocol.pdf>

Projects receiving identifiable samples or data should apply separately for ethical review using the project-based application form and give details of the consent arrangements.

36. Will samples or data be released to individuals/organisations conducting research outside the UK?

☒ Yes ☐ No

If Yes, please give details and describe any additional safeguards you will put in place:

We will apply the same standards to security and feedback of data as we do to applicants conducting research within the UK.

37. What will your policy be for requiring feedback of research findings specific to the donor to be linked with the stored samples/data?

It is a requirement of the Material Transfer Agreement ("MTA") that research findings from users of the resource are returned – these can be linked with the original donor through the unique identifying code and incorporated back into the central data repository so that they can be used by other researchers.

38. Where research findings are clinically significant for individuals, will arrangements be made to notify the individuals concerned? If Yes, please say what arrangements will be made and give details of the support or counselling service. If No, please explain the reasons why the findings will not be notified to subjects or other healthcare professionals.

☐ Yes ☒ No

There will be no routine reporting or feedback of findings from subsequent research (i.e. either findings from sample assays, scans or from data analysis) due to the value of such feedback being questionable. Please refer to UK Biobank's Ethics and Governance Framework (EGF) for further justification. In conjunction with the consent form (see attached) and the information materials, the EGF formed the basis on which the 500,000 participants were enrolled in the study.

39. What arrangements will be made with researchers for return, disposal or further storage of samples and data when studies are completed? What mechanisms will be in place for approving further studies?

Because the biological samples are a finite resource, UK Biobank will agree the minimum amount of sample required for their research with approved research applicants.

Approved research applicants are required to sign a Material Transfer Agreement (MTA) which includes the provision that, on the completion of the Research Project, the applicant will destroy or return any residual samples and confirm to UK Biobank (in writing) that this has taken place.

Sample collection and informed consent arrangements

Questions 40 - 41 apply only to the bank's existing collections of stored samples/data:

40. Has informed consent already been given for use of samples/data in research?

☒ Yes ☐ No ☐ Not applicable

If Yes, for what purposes has consent been given?

Each participant has given permission for long-term storage and use of biological samples for health-related research purposes (even after incapacity or death), and relinquishes all rights to these samples which are donated to UK Biobank.

Please enclose a copy of the information sheet and consent form used (if available).

41. If informed consent has not been given, is it proposed to seek consent for future use of samples/data in research?

☐ Yes ☐ No ☒ Not applicable

Application should be made to the Confidentiality Advisory Group' (CAG) to process the identifiable data of living donors without consent in England and Wales – see guidance notes.

Question 42 applies to collections from the deceased only:

42. What arrangements will be made to seek appropriate consent (or authorisation in Scotland)? Please describe the involvement of collaborators.

Not applicable

Please enclose copy of information sheet(s) and consent form(s).

Questions 43 - 46 apply to prospective collection of samples or data from the living:

43-1. How and by whom will donors be identified? Who will carry this out and what resources will be used? For example, identification may involve a disease register, computerised search of GP records, or review of medical records. Indicate whether this will be done by the direct healthcare team or by researchers acting under arrangements with the responsible care organisation(s).

No new participants will be recruited to the study.

43-2. Will the identification of potential participants involve reviewing or screening the identifiable personal information of patients, service users or any other person?

☐ Yes ☒ No

44. How and by whom will donors first be approached? Indicate whether this will be in the course of healthcare provision or whether additional procedures will be involved?

In the case of additional procedures, what burdens could arise for participants?

No new participants will be recruited to the study.

Please enclose a copy of any questionnaire to collect data from donors which is additional to data collected in the course of normal healthcare provision.

45. Will there be any further contact with donors to collect additional samples or data following the initial donation?

☒ Yes ☐ No

If Yes, please give details:

Participants gave permission, in their original consent, for UK Biobank to re-contact them. This has been done for a number of enhancements to the study such as collection of seven-day physical activity data, data provided through web-based questionnaires, and enrolment in the first round of repeat assessment and the current imaging enhancement.

46. Will you obtain informed consent to use samples and data in research?

☒ Yes ☐ No

If you will be obtaining consent from adult donors, please give details of who will take consent and how it will be done, with details of any steps to provide information (a written information sheet, videos or interactive material). Arrangements for adults unable to consent for themselves should be described separately in Part B Section 1, and for children in Part B Section 2. If you plan to seek informed consent from other vulnerable groups, say how you will ensure that consent is voluntary and fully informed.

If you will not be obtaining informed consent, please complete question 47. Participants who agree to take part in the imaging enhancement will be asked to provide their written consent - see attached "Consent Form for the imaging assessment". The consent process takes place at the UK Biobank imaging assessment centre.

Please enclose a copy of the information sheet(s) and consent form(s).

Questions 48-49 apply in all cases where consent to research is to be sought:

48. Will you record informed consent in writing?

☒ Yes ☐ No ☐ N/A

49-1. What arrangements have been made for persons who might not adequately understand verbal explanations or written information in English, or who have special communication needs? (e.g. translations, use of interpreters)

UK Biobank provided interpreting and assistance services for participants with disabilities. For non-English speakers, UK Biobank encouraged participants to be accompanied by a relative or friend to interpret on their behalf.

49-2. What arrangements will you make to comply with the principles of the Welsh Language Act in the provision of information to data subjects in Wales?

Participant invitation literature, including instructions regarding the consent process, were available in Welsh.

Questions 50 - 51 apply to all applications

50. Will any financial or other incentives be offered to donors?

☐ Yes ☒ No

51. What steps will be taken where donors or relatives subsequently withdraw consent to the use of samples/data for research? What information will participants be given about this?

As part of the recruitment process, persons invited to take part in the study were provided with detailed information about UK Biobank, so that they could make an informed decision as to whether or not to take part. However, an equally important part of the information provided was the detail on how a participant might withdraw from the study, should they change their mind at a later date.

UK Biobank defined 3 levels of withdrawal:

No Further Contact ("NFC"): This means that UK Biobank would no longer contact the participant directly, but would still have permission to use information and samples provided previously and to obtain further information from their health-relevant records.

No Further Access ("NFA"): This means that UK Biobank would no longer contact the participant or obtain information from their health-relevant records, but would still have permission to use the information and samples provided previously.

No Further Use ("NFU"): This means that, in addition to no longer contacting the participant or obtaining further information about them, any information and samples collected previously would no longer be available to researchers. UK Biobank would destroy the samples (although it may not be possible to trace all distributed sample

remnants) and would only hold information for archival audit purposes. The participant's signed consent and withdrawal would be kept as a record of their wishes. Such a withdrawal would prevent information about the participant from contributing to further analyses, but it would not be possible to remove their data from analyses that had already been done.

Whilst accepting that withdrawals would inevitably occur, UK Biobank sought to minimise the number of withdrawals by providing participants with detailed information at the outset. A dedicated Participant Resource Centre was established and remains in place to handle individual queries and concerns received by telephone or email. Participants who wish to withdraw are required to provide written confirmation of this by completing a withdrawal form (see attached Participant Withdrawal Form).

Sample collection and informed consent arrangements

Summary of the application

56. Please provide a brief summary of the application in a form suitable for publication, using language easily understood by patients and public. The summary will be published on the website of the National Research Ethics Service following the ethical review. You may cut and paste from answers to other questions.

Title of the bank: UK Biobank: a large scale prospective epidemiological resource of 500,000 people aged 40-69 from around the UK.

Human Tissue Authority storage licence no:
12002

Establishment responsible for management of the bank:

Organisation	UK Biobank Limited
Address	1-4 Spectrum Way Adswood Stockport
PostCode	SK3 0SA
Telephone	01614755360
Fax	01614755361

Please give details of the locations at which tissue will be stored:

Samples/data to be stored and collection/consent arrangements (maximum 200 words):

During 2006-2010, UK Biobank recruited 500,000 men and women from the UK population, aged 40-69 at the date of their baseline assessment visit. Participation in the study was entirely voluntary.

Each participant provided their written consent to confirm their willingness to take part and agreed to the following:

- That they may be re-contacted by UK Biobank (e.g. to answer some more questions and/or attend another assessment visit), but this would be optional.
- To give permission for access to their medical and other health-related records, and for long-term storage and use of this and other information about them, for health-related research purposes (even after incapacity or death).
- To give permission for long-term storage and use of biological samples for health-related research purposes (even after incapacity or death).
- That they understood that none of their results would be given to them (except for some measurements during the visit) and that they would not benefit financially from taking part.

Extensive data was collected at baseline from all participants on their lifestyle, environment, personal and family medical history. Participants also underwent a wide range of physical measures, and provided samples of blood, urine and saliva.

In addition to information collected at baseline (which has also been repeated) participants have been invited to wear a wrist-worn activity monitor (to record 7-day physical activity); and complete detailed web-based questionnaires on their diet, cognitive function and work history.

Participants are currently being invited to attend an imaging assessment centre and undergo magnetic resonance (MR) scans of the brain, heart and body, DXA scan of the bones, joints and body composition, and ultrasound scan of

the carotid arteries.

Samples are stored at UK Biobank (in Stockport) and the NIHR National Biosample Centres (in Milton Keynes and Oxfordshire).

Research programme/community supported by the bank (maximum 200 words):

UK Biobank is a major national health resource, with the aim of improving the prevention, diagnosis and treatment of a wide range of serious and life-threatening illnesses – including cancer, heart diseases, stroke, diabetes, arthritis, osteoporosis, eye disorders, depression and forms of dementia

UK Biobank is open to bona fide researchers anywhere in the world, whether funded by academia or industry, for health-related research that is in the public good.

Part C: Tissue Collection Centres

Please enter details of the organisations (NHS or other) in the UK that will act as tissue collection centres for this research tissue bank.

Tissue collection centre

Local collaborator

Part D: Declarations

D1. Declaration by the applicant:

1. The information in this form is accurate to the best of my knowledge and belief and I take full responsibility for it.
2. If the application is approved I undertake to adhere to the terms of the application of which the REC has given a favourable opinion and any conditions set out by the REC in giving its opinion.
3. I undertake to seek an ethical opinion before implementing substantial amendments to the terms of the application of which the REC has given a favourable opinion.
4. I undertake to submit annual progress reports to the REC.
5. I understand that the information contained in this application, any supporting documentation and all correspondence with NHS Research Ethics Committees or their operational managers relating to the application:
 - Will be held by the main REC indefinitely (or until 3 years after the closure of the tissue bank).
 - May be disclosed to the operational managers or the appointing body for the REC in order to check that the application has been processed correctly or to investigate any complaint.
 - May be seen by auditors appointed by the National Research Ethics Service to undertake accreditation of the REC.
 - Will be subject to the provisions of the Freedom of Information Acts and may be disclosed in response to requests made under the Acts except where statutory exemptions apply.
 - May be sent by email to REC members.
6. I understand that a summary of this application will be published on the website of the National Research Ethics Service (NRES), together with the contact point for enquiries named below. Publication will take place no earlier than 3 months after issue of the ethics committee's final opinion or the withdrawal of the application.

Contact point for publication

NRES would like to include a contact point with the published summary of the application for those wishing to seek further information. We would be grateful if you would indicate one of the contact points below.

- ☐ Applicant named at A3
- ☐ Designated Individual
- ☒ Other – please give details
- ☐ None

	Title Forename/Initials Surname
	Ms Nicola Doherty
Post	Senior Clinical Study Administrator, UK Biobank
Work address	1-4 Spectrum Way Adswood, Stockport SK3 0SA
Work email	nicola.doherty@ukbiobank.ac.uk
Work telephone	01614755360

Access to application for training purposes

Optional – please tick as appropriate:

☐ I would be content for members of other RECs to have access to the information in the application in confidence for training purposes. All personal identifiers and references to the establishment and other research units and collaborators would be removed.

This section was signed electronically by Dr Tim Peakman on 12/04/2016 16:53.

Job Title/Post:	Deputy CEO
Organisation:	UK Biobank
Email:	secretary@ukbiobank.ac.uk

D2. Declaration by the Designated Individual

I confirm that the information in this form is true and accurate to the best of my knowledge and I support the application.

This section was signed electronically by Dr Tim Peakman on 24/03/2016 17:45.

Job Title/Post:	Deputy CEO
Organisation:	UK Biobank
Email:	secretary@ukbiobank.ac.uk