CONTENTS: UK Biobank Re-contact Procedures

UK BIOBANK / RE-CONTACT PROCEDURES

A. INTRODUCTION

A.1 Background to UK Biobank

A.1.1 During 2006 -2010, UK Biobank conducted its recruitment phase in which 500,000 participants gave their consent, answered questions, had measurements and gave biological samples at the baseline assessment visit. Follow up of their health is now being conducted through medical and other health related records.

A.1.2 Access to the Resource commenced in April 2012. Researchers apply to access the Resource using the Access Procedures[1]. These applications are reviewed by the UK Biobank Co-ordinating Centre and the Access Sub-Committee in line with the criteria and process set out in the Access Procedures. The overriding objective of UK Biobank's Access Procedures is to encourage the extensive and appropriate use of the Resource.

A.2 Background to the Re-contact Procedures

A.2.1 The Access Procedures reflect the Access Policy outlined in UK Biobank's Ethics & Governance Framework[2] and undertakings given to the participants in the consent form[3] when they agreed to take part in UK Biobank. Both the Access Procedures (and the EGF from which they are derived) acknowledge that the re-contact of participants for research purposes raises particular issues over and above those involved in applications to access UK Biobank data and/or samples[4].

A.2.2 Participants were made aware in advance (through the information materials), when they attended the baseline visit and consented to participate, that they would be re-contacted by UK Biobank. However, it should be emphasised that a participant's decision to act upon any re-contact is entirely voluntary and also that UK Biobank recognises that it is akin to being a depletable resource[5] and needs to be managed as such.

A.2.3 The aim of these Re-contact Procedures is to outline the circumstances in which UK Biobank may re-contact its participants and the criteria that it uses (will use) to determine for each category of re-contact whether such re-contacts are appropriate. Specifically, there are three main categories of re-contact:

A.2.3.1 re-contact for the purpose of communication by UK Biobank;

A.2.3.2 re-contact for the purpose of additional phenotyping by UK Biobank; and

A.2.3.3 re-contact for the purpose of third party research, which may involve additional phenotyping by the researcher.

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1 The Access Procedures can be found at http://www.ukbiobank.ac.uk/resources

2 The EGF can be found at the same url as above.

3 The consent form can be found at the same url as above.

4 Application s for (depletable) samples do have discrete access issues.

5 Participant goodwill is not an unlimited resource and UK Biobank would never consider it as such.

A.2.4 For research applications that involve re-contact, the relevant provisions of these Re-contact Procedures should be read as an addendum to the Access Procedures as they set out the additional considerations that UK Biobank will consider in the review.

A.3 Relevant provisions of the EGF and the Access Procedures

A.3.1 The EGF contains a section on re-contact which is set out in full in Annex 1. In summary this section provides that participants should have an expectation of being re-contacted by UK Biobank for various reasons, including the following:

A.3.1.1 to inform participants about progress (including findings from research conducted using the resource but not results for individuals);

A.3.1.2 to collect new information for the Resource;

A.3.1.3 to seek consent for uses which are not covered by the participant consent; and

A.3.1.4 to ask participants whether they would be willing to be contacted by third party researchers for the purposes of an approved research project.

A.3.2 This section in the EGF also emphasised in relation to all third party research applications that:

A.3.2.1 participation would be entirely voluntary;

A.3.2.2 any initial re-contact would be undertaken by UK Biobank;

A.3.2.3 decisions on whether re-contact is appropriate would be made by UK Biobank with advice from the EGC[6] and subject to separate REC approval; and

A.3.2.4 when re-contacting participants (within specific sub-populations), care would need to be taken about selection criteria that might inadvertently reveal information to a participant of which they were not previously aware.

A.3.3 The Access Procedures also contain a section on re-contact which is set out in full in Annex 2. This section is based for the most part on the equivalent section in the EGF, whilst elaborating on the following matters:

A.3.3.1 re-contact will be carefully monitored by UK Biobank to ensure that participants are not overburdened;

A.3.3.2 researchers are obliged to make it clear when they apply to access the Resource whether re-contact will be involved; and

A.3.3.3 UK Biobank will generally seek independent scientific review of applications to use the Resource that involve re-contact.

[6] UK Biobank's independent Ethics and Governance Council.

B. THE RE-CONTACT PROCEDURES

B.1 Different types of re-contact

B.1.1 As set out above, there are essentially three categories of re-contact that UK Biobank makes or envisages making with its participants:

B.1.1.1 communication: UK Biobank re-contacting participants for information / communication / opinion purposes;

B.1.1.2 phenotyping: UK Biobank re-contacting participants for additional phenotyping to provide further information for the Resource; and

B.1.1.3 research*:* UK Biobank re-contacting participants to establish whether they are willing to take part in a third party research project (which may include additional phenotyping information that the researcher wishes to obtain).

B.1.2 These Re-contact Procedures will consider each of these categories in turn. There is an important distinction to bear in mind between non-selective re-contact and selective re-contact: the latter is more likely to reveal information to the participant about themselves of which they were previously unaware.

B.1.3 The EGF identifies a further type of re-contact, namely "to seek consent to proposed new uses that have passed scientific review but do not fall within the existing consent" but this option is not specifically addressed here, as these Re-contact Procedures govern proposed re-contact falling within the scope of the existing participant consent.

B.2 Re-contact by UK Biobank for the purpose of communication

B.2.1 Since the start of the recruitment phase (2006), UK Biobank has periodically re-contacted its own participants for the purpose of informing them about the progress of the Resource and communicating with them generally. This will continue: a key component of UK Biobank's original remit is to remain in touch with its participants, as part of UK Biobank's commitment to ongoing engagement with its participants, over the lifetime of the Resource.

B.2.2 This key features of this category of re-contact are that:

B.2.2.1 it is non-selective;

B.2.2.2 it does not require REC approval or input from the EGC[7];

B.2.2.3 the decision as whether to undertake the re-contact activity lies in the reasonable discretion of UK Biobank. It is not subject to any form of specific additional procedure or process within UK Biobank; and

B.2.2.4 UK Biobank monitors the frequency of this re-contact (of which more below).

B.2.3 A list of these re-contacts, and the dates of any that have already taken place, is provided in Annex 3.

[7] Although UK Biobank discusses re-contact with the EGC on a regular basis.

B.3 **Re-contact for the purpose of additional phenotyping by UK Biobank**

B.3.1 UK Biobank has re-contacted its participants for enhanced phenotyping (and will continue to do so). All such re-contact require ethics committee approval and review by the EGC This category of re-contact falls into the following sub-categories:

B.3.1.1 remote re-contact not requiring further consent: for example, invitations to (i) complete diet questionnaires, cognitive function tests and workplace surveys or (ii) wear accelerometers over a 7 day period;

B.3.1.2 direct re-contact not requiring further consent: for example, invitations to attend (and attendance at the) repeat assessment visits (i.e. completing the same assessment that was undertaken at baseline assessment visits). The first of such repeat assessments has already taken place with approximately 20,000 participants attending a bespoke assessment centre at the Co-ordinating Centre in Cheadle; and

B.3.1.3 direct re-contact requiring further consent: for example, this covers the proposed imaging assessment visit. The nature of imaging (and particularly the need to address the issue of related incidental findings) is such that it is considered necessary for UK Biobank to seek additional consent from participants who elect to participate. This additional consent will be consistent with the original consent whilst containing more detail about provisions for dealing with feedback of incidental findings arising from the imaging visit.

B.3.2 The key features of this category of re-contact are that:

B.3.2.1 it is generally non-selective, save that (to date) participants may have been more likely to have been re-contacted as a function of where they live. For example, the repeat assessment assessments have taken place at the Coordinating Centre in Cheadle and thus participants within a certain geographical reach have been re-contacted. However, it is likely that in the future UK Biobank will undertake selective re-contact in this category[8];

B.3.2.2 UK Biobank considers that this category of re-contact should be treated as a depletable resource as participants would expect quite reasonably that UK Biobank would not overburden them with requests involving re-contact and that such proposals would have been appropriately reviewed;

B.3.2.3 specific REC approval is required, which is obtained by UK Biobank along with input from the EGC;

B.3.2.4 the decision as to whether to undertake such re-contact lies in the reasonable discretion of UK Biobank (with such internal consents as necessary) and it is not subject to any specific additional process or procedure; and

B.3.2.5 UK Biobank will monitor the frequency of this re-contact (see below).

[8] for example, selecting participants on the basis of age.

B.3.3 A list of these phenotypical re-contacts, both past and planned, is set out at Annex 4.

B.4 **Re-contact for the purpose of further research**

B.4.1 The decision whether to approve research applications which involve re-contact will be taken by UK Biobank through the mechanisms outlined in the Access Procedures, using the criteria set out in both the Access Procedures *and* the relevant provisions of these Re-contact Procedures.

B.4.2 UK Biobank considers that this category of re-contact should be treated as a depletable resource as participants would expect quite reasonably that UK Biobank would not overburden them with requests involving re-contact and that such proposals would have been appropriately reviewed.

B.4.3 The key features of this category of re-contact are that:

B.4.3.1 it may well be selective[9], as re-contact research projects often involve participants who are selected because they have particular risk factors in the form of particular phenotypical or genetic characteristics and/or the occurrence (or not) of particular disease outcomes;

B.4.3.2 it will be treated as an application under the Access Procedures, although it will also be necessary for specific REC approval to be obtained by the researcher, and UK Biobank will seek input from the EGC;

B.4.3.3 UK Biobank will take the following factors (in addition to those set out in the Access Procedures) in account:

B.4.3.3.1 the scientific rationale of the project (with input, if UK Biobank considers this necessary, from independent scientific peer reviewers);

B.4.3.3.2 the track record of the research group (and in particular their track record handling participant data);

B.4.3.3.3 the level of duplication with other pre-existing or planned research projects involving re-contact;

B.4.3.3.4 whether there are (reasonable) alternative or better means for conducting the research;

B.4.3.3.5 the nature of the proposed re-contact, in terms of its frequency and intensity and the prior level of re-contact experienced by the relevant participants;

B.4.3.3.6 the propensity of the proposed re-contact to reveal information to the participants of which they might not be previously aware (for example a research project investigating the link between a known risk factor, the BRCA1 pathogenic mutation and the incidence of breast cancer) and how this will be addressed. This important factor is addressed in a Section [ ] below; and

B.4.3.3.7 any other relevant factors.

B.4.3.4 UK Biobank will monitor the frequency of this re-contact.

[9] This is probable but not inevitable.

C. PRACTICAL CONSIDERATIONS

C.1 Monitoring

C.1.1 The objective of monitoring is to ensure that participants are not overburdened with too many and/or too frequent:

C.1.1.1 informational updates;

C.1.1.2 requests to participate in phenotypical enhancements. This is to minimise instances of multiple requests to the same participant, where for example the same individual is asked to wear an accelerometer, participate in a re-assessment visit, complete a diet questionnaire and/or participate in the imaging visit; and

C.1.1.3 requests to participate in third party research projects, especially those where the re-contact is selective.

C.1.2 UK Biobank has established a detailed re-contact register[10], which lists all the re-contacts which UK Biobank has and will conduct, subdivided into the three categories of re-contact set out above**.** This register will include flags[11] within the UK Biobank database which indicate which participants:

C.1.2.1 have been invited to participate in phenotypical re-contact, and when, and whether they attended (or not);

C.1.2.2 have been invited to participate in approved research applications involving re-contact and whether they elected to participate (or not).

C.1.3 In light of its experience with re-contact generally, UK Biobank will review the frequency of re-contact to ensure that it does not become burdensome to participants and will seek to establish some identifiable parameters within which the frequency of re-contact should be maintained.

C.2 The mechanics of re-contact and additional consent

C.2.1 As part of the approval process for reviewing a third party research project involving re-contact (considered under the Access Procedures and the relevant provisions of these Re-contact Procedures):

C.2.1.1 UK Biobank would assess the number of participants that the researcher wishes to have re-contacted (and considered to be scientifically reasonable by UK Biobank);

C.2.1.2 UK Biobank would always make the first contact with participants to explain the nature of the re-contact proposal and to enquire whether they would be willing to participate in the project;

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10 The responsibility for maintaining the re-contact register will lie jointly with the UK BIobank scientific and communication teams.

11 Specifically, there will be re-contact study label tags (e.g. imaging visit, cognition questionnaire, diet questionnaire etc) which have a set of characteristics, including (1) gathering new research data or collecting / providing info; (2) web/postal questionnaire only vs in-person assessment; (3) UKB initiated versus third party request; (4) other characteristics of potential importance to participants such as distance to travel to assessment if in person; length of visit; and whether any 'invasive' procedure is involved (e.g. lumbar puncture proposed for small number of participants for dementia studies)

C.2.1.3 UK Biobank may elect (at its option) to conduct the re-contact itself, taking into account whether the extent of the further information sought and its propensity to directly enhance the Resource;

C.2.1.4 where the researcher seeks to invite the participant to a new visit then it is envisaged that the researcher (rather than UK Biobank) would conduct and manage these participant appointments;

C.2.1.5 certain re-contact research projects would be able to be conducted without revealing participant identity to the third party researchers. However, it is inevitable in certain cases (such as an invitation to a new visit) that UK Biobank would need to release identifiable information to a researcher with appropriate consent; and

C.2.1.6 UK Biobank would retain the same rights as it does in relation to other access applications, namely to audit the researcher and to require the return of results for inclusion in the Resource so that other researchers can use the data.

C.2.2 In terms of participant consent the following will apply:

C.2.2.1 in the event that information identifying the participant is passed on to a researcher then the express prior written consent of the participant will first be obtained; and

C.2.2.2 if the participant elects to participate in a third party research project, run by a researcher not through UK Biobank, then UK Biobank would require that the researcher seeks new and separate consent vis-à-vis participation in the third party research project from the participant.

C.3 **How to avoid revealing information to participants about which they are previously unaware**

C.3.1 The issue of revealing information to participants about themselves of which they are previously unaware may arise as a direct result of the hypothesis of the third party research project. For example, the participant is re-contacted (initially by UK Biobank) about taking part in a project with a hypothesis which provides that "… Research Group A are researching disease X and its connections with risk factor Y …" and the recipient of this communication has reason to believe that he/she either possesses risk factor y or will likely develop disease x.

C.3.2 In many re-contact research projects, participants are commonly already aware that they either have a particular risk factor or suffer from a particular disease. This is not the case in UK Biobank, as participants will not be aware of these matters *on the basis of information that UK Biobank has communicated to them*[12].

C.3.3 As such, UK Biobank needs to avoid creating a situation where the invitation to participate suggests to a participant that they may have a risk factor and/or have or may develop a disease outcome, either or both of which they are previously unaware.

C.3.4 In this context, there are some working assumptions / protocols that UK Biobank will adopt:

C.3.4.1 UK Biobank will assume that a participant is aware that they have exposure to a particular risk factor or a particular disease outcome if they have self-reported this

12 As UK Biobank does not feed back research results to participants.

fact to UK Biobank. UK Biobank may assume this if it is evident from their health records[13] (to which UK Biobank has secured linkage):

C.3.4.2 awareness of disease: taking into account that coded medical records are not 100% accurate, the invitation to participants can always be suitably phrased with an appropriate caveat[14];

C.3.4.3 awareness of a risk factor: consideration will be given to whether it is feasible to effectively blind participants as to whether they are (or are not) cases or controls.

C.3.5 These factors will all be taken into consideration and the default position will be that if there is a possibility that the existence of a risk factor or a disease outcome could be revealed to a participant (of which they are previously unaware) then the participant will not be re-contacted.

13 This more cautious assumption is based on the inevitable occurrence of miscoding or miscommunication errors.

14 For example: "from our linkage to the central health records that UK Biobank conducted in accordance with the consent that you provided at the baseline assessment visit it seems that you may have been diagnosed with X (but, since these coded records are not always precise, please accept our apologies if this is not correct)"

Annex 1 / The provisions on re-contact in the EGF

"Expectation of re-contact

It will be explained to participants that they may be re-contacted by UK Biobank for various reasons, including:

· To collect new information (such as questionnaire data, measures or samples) for the resource. It is anticipated that repeat assessment visits would be done every few years and would generally involve reasonably representative subsets of just a few tens of thousands of people, with different individuals selected for sequential repeat assessments. Invitations to provide additional information that do not require such visits (e.g. questionnaire data collected by mail or internet) might be sent to all participants at similar intervals during the study.

· To seek consent to proposed new uses that have passed scientific and ethics review but do not fall within the existing consent.

· To ask participants whether they would be willing for researchers to contact them to discuss possible involvement in a study that requires new information or samples.

It will be emphasised that participation in all such reassessments is entirely voluntary, and that any initial re-contact will be undertaken by UK Biobank.

Decisions on whether re-contact is appropriate for particular proposals will be made by UK Biobank with advice from the Ethics and Governance Council (see Section III.A.2), and will be subject to Research Ethics Committee approval.

When re-contacting special sub-populations, care will be taken over the use of selection criteria (such as genetic makeup) that might inadvertently reveal information to participants about themselves of which they may not be aware."

Annex 2 / the provisions on re-contact in the Access Procedures

"Research requiring re-contact of participants

Participants have consented to be re-contacted, but UK Biobank will monitor carefully the level of, and rationale for, re-contact to ensure that participants are not over-burdened. Initial re-contact for an approved study would always be undertaken by UK Biobank.

Re-contact may be for a variety of reasons, including to collect new information or samples; to seek additional consent for uses that fall outside the existing consent; and to ask participants whether they are willing to be contacted directly by approved researchers (e.g. to provide new information or take part in another study).

Researchers are required to make it clear in their Application if it is proposed that participants be re-contacted. Decisions on whether re-contact is appropriate will be made by UK Biobank, with advice from the EGC, and such re-contact requires separate approval from a Research Ethics Committee (and UK Biobank will generally also require independent scientific review to help ensure that re-contact is warranted).

Provision of new information, samples or consent by participants would be entirely voluntary. When re-contacting special sub-populations, UK Biobank will take appropriate care to ensure that the use of selection criteria (such as genetic make-up) does not inadvertently reveal information to participants about themselves of which they are not aware. "

Annex 3 / re-contact for communication purposes

Re-contact	Inclusion criteria	Dates
Participant newsletter	All email addresses and all postal addresses of participants without email (excluding death, withdrawals at relevant level, requests for no further contact). Roughly 500,000 participants.	February 2011 February – March 2012 March- April 2013 February- March 2014
Access Procedures consultation	All UK Biobank participants with email addresses – roughly 300,000	May- June 2011

Annex 4 / re-contact for phenotypical purposes

UK Biobank: Participant re-contacts up to March 2013

Re-contact	Inclusion criteria	Dates
Diet questionnaire	All email addresses – roughly 300,000, during each period (4 contacts in all)	Feb 2011 – April 2011 June 2011 – Aug 2011 Oct 2011 – Dec 2011 April 2012 – June 2012
Repeat assessment	By email: 84,000 By post: 15,000 Participants from Manchester, Bury, Leeds, Liverpool, Sheffield & Stoke	July 2012- June 2013
Activity monitor	Email survey: 470 participants selected randomly Invitation to wear monitor: All email addresses	June 2012 – August 2012 May 2013- May 2014
Imaging surveys	By email: 4,800 June 2011 By email: 3,200 January 2012 Randomly selected from across the country	June 2011 January 2012