



UK Biobank Re-contact Procedures for Third Party Researchers (version 2.0)

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INTRODUCTION

1. Background to UK Biobank

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 being conducted through medical and other health related records.

1.2 Access to the Resource commenced in April 2012. Researchers apply to access the Resource using the Access Procedures¹. These applications are reviewed by the UK Biobank Co-ordinating Centre and the Board's Access Sub-Committee in line with the criteria and process set out in the Access Procedures and related documents. The overriding objective of UK Biobank's Access Procedures is to encourage the extensive use of the Resource that is consistent with the original consent.

2. Background to the Re-contact Procedures for Third Party Researchers

2.1 The Access Procedures reflect the Access Policy outlined in UK Biobank's Ethics & Governance Framework² and undertakings given to the participants in the consent form³ 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 samples⁴.

2.2 Participants were made aware in advance (through the information materials), and when they attended the baseline visit and consented to participate, that they would be re-contacted by UK Biobank. However, it was emphasised that a participant's decision to act upon any re-contact is entirely voluntary, and UK Biobank recognises that it is akin to being a depletable resource⁵ and so needs to be managed as such.

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 to determine whether such re-contacts are appropriate.

2.4 There are essentially three categories of re-contact that UK Biobank makes, or envisages making, with its participants:

2.4.1 *re-contact for the purpose of communication by UK Biobank*: UK Biobank re-contacting participants for the purposes of providing information and opinion gathering;

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 Applications for samples do have discrete access issues, based upon their depletability, and the application process for samples is set out in more detail in the sample release strategy [url].

⁵ Participant goodwill is not an unlimited resource and UK Biobank does not consider it as such.

- 2.4.2 *re-contact for the purpose of additional phenotyping by UK Biobank:* UK Biobank re-contacting participants for the purposes of collecting further information about participants to include within the Resource; and
- 2.4.3 *re-contact for the purpose of third party research:* UK Biobank re-contacting participants to establish whether they are willing to take part in a third party research project.
- 2.5 ***These Re-contact procedures are aimed solely at this latter category in order to provide guidance to researchers about re-contact applications for third party research. UK Biobank has published separate information on how it manages its own re-contact activities [url].***
- 2.6 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 of an access application involving such re-contact.
3. **Relevant provisions of the EGF and the Access Procedures**
- 3.1 The EGF contains a section on re-contact which is set out in the attached [url]. In summary it indicates that participants should have an expectation of being re-contacted by UK Biobank for various reasons, including asking participants whether they would be willing to be contacted by third party researchers for the purposes of an approved research project.
- 3.2 It also emphasised in relation to all third party research applications that:
- 3.2.1 participation would be entirely voluntary;
- 3.2.2 any initial re-contact would be undertaken by UK Biobank;
- 3.2.3 decisions on whether re-contact is appropriate would be made by UK Biobank with advice from the EGC⁶ and subject to separate REC approval (which is a matter for the third party applicant to obtain); and
- 3.2.4 when re-contacting participants (within specific sub-populations), care would need to be taken about selection criteria that might inadvertently reveal diagnostic (or health-related) information to a participant of which they were not previously aware. ***The reason for this constraint is that UK Biobank's consent explicitly states there will be no feedback to participants about their individual results (e.g. diagnostic or other health-related information) that were not already known to them.***
- 3.3 The Access Procedures also contain a generic section on re-contact [url], that is based on the EGF. In summary, this states that:
- 3.3.1 all re-contact will be carefully monitored by UK Biobank to ensure that the participants are not overburdened;
- 3.3.2 researchers are obliged to make it clear when they apply to access the Resource whether re-contact will be involved; and
- 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.

RE-CONTACT PROCEDURES FOR THE PURPOSE OF THIRD PARTY RESEARCH

4. UK Biobank's assessment and review of third party proposals

- 4.1 The decision whether to approve research applications involving 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 these Re-contact Procedures.
- 4.2 In light of the exacting hurdle that is required for a re-contact application to be approved and the practical implications of conducting numerous re-contact applications, UK Biobank expects that it will only approve a very small number of recontact applications that are considered likely to be of greatest value for public health.
- 4.3 This category of re-contact will be treated as a depletable resource as participants would reasonably expect that UK Biobank would not overburden them with requests involving re-contact and that such proposals would have been appropriately reviewed by UK Biobank.
- 4.4 If the researcher is only seeking to acquire further information from participants (e.g., through a questionnaire), UK Biobank may elect to conduct the re-contact itself if it is considered (by UK Biobank) to be of sufficiently high scientific interest.
- 4.5 Other than in the circumstances set out in para 4.4 above, UK Biobank does not envisage carrying out the re-contact research itself. UK Biobank would note that if even if a third party researcher conducts the re-contact research, UK Biobank's participants⁷ may well perceive UK Biobank as having (at the least) implicitly endorsed the re-contact and the subsequent conduct of the re-contact research (over which UK Biobank may have very limited control), which has the potential for a significant adverse reputational impact on UK Biobank⁸.
- 4.6 UK Biobank would note the following practical factors of third party re-contact:
- 4.6.1 it will be treated as an application under the Access Procedures, although it will be necessary for specific REC approval to be obtained by the researcher (with advance input from UK Biobank on information, consent and withdrawal materials), and UK Biobank will also seek input from relevant (internal or external) ethical resources; and
- 4.6.2 the researcher will need to provide periodic updates on the progress of the re-contact research to UK Biobank which will review participant reaction (passive and active) as necessary and may set certain milestones for the researcher. In

⁷ UK Biobank has reviewed the reaction of UK Biobank participants after the first re-contact application was approved and conducted. UK Biobank's participants considered that the third party project was indeed endorsed (explicitly or implicitly) by UK Biobank.

⁸ This was also confirmed by our pilot analysis.

light of any adverse participant or public reaction, UK Biobank reserves the right, using its reasonable discretion and in consultation with the researcher, to consider whether or not to suspend the re-contact research.

- 4.7 It should be noted that, in reviewing a re-contact application, UK Biobank requires⁹:
- 4.7.1 a clearly formulated scientific case for the proposed re-contact (i.e. does it address important health-related problems) with evidence that any hypothesis is well founded and that the research project is capable of making a substantial additional contribution to existing knowledge. In this context, comments from grant reviewers should be included;
 - 4.7.2 a clear rationale as to why UK Biobank, as a prospective cohort, is the appropriate resource in which to conduct the proposed re-contact: the fact that UK Biobank offers a convenient means of identifying eligible individuals would not necessarily be sufficient to qualify as scientific justification;
 - 4.7.3 UK Biobank would retain the same rights as it does in relation to other access applications, namely to audit the research and to require the return of results for inclusion in the Resource so that other researchers can use the data; and
 - 4.7.4 If the re-contact is selective¹⁰ - as re-contact research projects often involve participants who are selected specifically because they have particular risk factors in the form of phenotypical or genetic characteristics and/or the occurrence (or not) of particular disease outcomes - then a suitable recruitment methodology needs to be agreed to address this matter (see sections 4.8.6, 6.2 and 7 below).
- 4.8 There are six principal criteria that UK Biobank's ASC will use when deciding on whether (or not) to approve the re-contact application are:
- 4.8.1 *Scientific merit of the research project*: UK Biobank will review whether the proposed re-contact has the potential to move science in the field forward;
 - 4.8.2 *Prospective resource*: UK Biobank will review whether the re-contact project requires the use of UK Biobank as a prospective resource;
 - 4.8.3 *The experience, quality and relevance of the track record of the research group*: UK Biobank will consider the track record of the research group as, given the potential impact on UK Biobank, it may be relevant from a reputational perspective;
 - 4.8.4 *Nature of the proposed re-contact (ethical)*: UK Biobank will review (UK Biobank has a distinct preference for being able to conduct such a review in advance of submission to the relevant REC) and, if necessary, require researchers to amend the re-contact materials (consent forms, informational materials, withdrawal options etc.) prior to the final approval from the REC;
 - 4.8.5 *Nature of the proposed re-contact (practical)*: UK Biobank will review the number, frequency, longevity and intensity of the proposed re-contact, taking into account the prior level of re-contact experienced by the relevant

¹⁰ This is probable but not inevitable.

participants. UK Biobank will also take into account the existence of other similar projects (which have already been) approved or applications which are in or about to begin the review process; and

- 4.8.6 *Revealing information to participants of which they are previously unaware:* UK Biobank will take into account the likelihood that the proposed re-contact research might reveal information about their own health 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 genetic mutation and the incidence of breast cancer) and how this will be addressed.

5. **The mechanics of re-contact and additional participant consent**

5.1 The practical matters that UK Biobank will take into account as part of the approval process for reviewing a third party re-contact research project include:

- 5.1.1 UK Biobank would assess the number of participants that the researcher wishes to have re-contacted¹¹ and the number of participants that the researcher needs to recruit for the project;
- 5.1.2 UK Biobank would always make the first contact with participants to explain the nature of the re-contact proposal. If they are interested in the project, they will be asked to contact the third-party researcher directly;
- 5.1.3 the third-party researcher is responsible for obtaining consent for that individual to join their approved study. This may include consent for UKB to release information to the researcher to determine whether the participant is eligible (e.g., eligibility based on genetic data or cognitive function tests). UKB's approach will be to release only data on whether an individual is eligible or not (based on the selection criteria proposed by the researcher) and not the underlying individual-level data itself;
- 5.1.4 the draft information and consent materials will be reviewed by UK Biobank as part of the application process. UK Biobank may either suggest or require changes to be made. The objective here is to ensure that a) information about UK Biobank is accurate and b) what is being proposed is compatible with UK Biobank's processes and procedures;
- 5.1.5 participants will be contacted and will be invited to contact the researcher directly; and
- 5.1.6 if the participant elects to participate in the particular third party research project, then UK Biobank would require that the researcher recruits the participant, using the consent forms and informational materials that have been approved by UK Biobank.

5.2 In relation to the conduct of the re-contact research:

- 5.2.1 UK Biobank may require a pilot phase to be conducted;

¹¹ It is unlikely that UK Biobank will consider any form of re-contact which does not involve email.

- 5.2.2 UK Biobank will require a periodic report on the conduct on the research, including numbers of participants joining the study (along with such information as will enable UK Biobank to flag the participants within the UK Biobank resource). It reserves the right to contact UK Biobank participants to establish their experience and assess their feedback. In the event that UK Biobank considers the research is generating a significant level of participant concern or confusion (as it relates to UK Biobank) then it reserves the right to suspend or terminate the research;
- 5.2.3 UK Biobank may require that specific data generated by the researchers from the participants (by the use of a monitor for example) – the scope of this data shall be pre-agreed as between the researcher and UK Biobank – shall be regularly returned and QCed¹²; and
- 5.2.4 UK Biobank will require the researcher to re-imburse the costs to UK Biobank of conducting the re-contact project.

6. Access to UK Biobank phenotypic and genetic data

- 6.1 UK Biobank is aware that researchers conducting re-contact studies may wish to access the phenotypic and genotypic data on UK Biobank participants within the UK Biobank resource. UK Biobank acknowledges that, generally speaking, it is in favour of the efficient use of participant data and thus the prospect of duplicating the generation of this data (whether by sample assay or the generation of a derived variable) might not represent a productive use of research funds.
- 6.2 However, UK Biobank would draw the attention of researchers to the fact that UK Biobank's policy is that it does not feedback personal health-related to participants. As such, should a researcher:
 - 6.2.1 require access to UK Biobank data on participants who are also taking part in the researcher's project; and
 - 6.2.2 intend to feedback certain data to these participants either for the purposes of selection or otherwise;

then UK Biobank would require the information materials and consent form to be very clear about this issue, in particular drawing attention to the fact that the feedback policies of UK Biobank and of the research project are distinct.

7. Further notes on selective re-contact

- 7.1 In many research projects, participants may already be aware that they have a particular risk factor or suffer from a particular disease. This is not necessarily the case with UK Biobank participants¹³.
- 7.2 As such, re-contact on the basis of selection of particular risk factor or condition (e.g. on the basis that they are "heterozygous for the APOE4 allele" or have "poor cognitive" scores or) is not something that UK Biobank can generally undertake, unless it is conducted in accordance with the criteria in sections 7.3 and 7.4 below (i.e. the participant is already

¹² This data will be considered in a similar way to assay data, in that the researcher can apply for a period of exclusivity.

¹³ As UK Biobank does not feedback individual subject research results to participants.

aware of the relevant factor/disease or the participant can be recruited into the re-contact research on the basis of a different consent).

7.3 In this context, there are some working assumptions on participant awareness that UK Biobank will adopt:

7.3.1 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 fact to UK Biobank;

7.3.2 UK Biobank may assume this if it is clearly evident from their health records¹⁴ (to which UK Biobank has secured linkage); however, taking into account that coded medical records are not 100% accurate, the invitation to participants can always be suitably phrased with an appropriate caveat¹⁵; and

7.3.3 consideration will be given to whether it is feasible to effectively blind participants as to whether they are (or are not) cases or controls, given what participants may reasonably infer from the research hypothesis (although UK Biobank's operating presumption is that such approaches will not prove to be workable¹⁶).

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 condition of which they are previously unaware could be revealed to a participant then such participant will not be re-contacted.

7.4 However, it is considered that it may be possible that a third party research project could, through UK Biobank, recruit on the basis of selective criteria in the following manner:

7.4.1 UK Biobank would contact (potentially) eligible participants on a non-selective basis and inform them about the third party study;

7.4.2 If the participant is interested in participating in the third-party study, then the participant will be invited to contact the researcher directly;

7.4.3 the researcher can then obtain the consent of the participant to participate in the third party study (along with their consent to the feedback of the relevant information); and

7.4.4 If the participant consents to this selective recruitment, then the researcher updates UK Biobank who informs the researcher whether the participant is or is not eligible to participate in the third party study.

¹⁴ This cautious assumption is based on the inevitable occurrence of miscoding or miscommunication errors.

¹⁵ 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)"

¹⁶ For example: "we are writing to 1,000 participants, 500 of whom possess the relevant risk factor and 500 of who do not". Although such communication would not of itself confirm to a participant whether or not they possessed the relevant risk factor, it would have the impact of substantively altering their belief about the probability of possessing such risk factor.