Sample release policy and procedures

This UK Biobank document is in four sections:

i) UK Biobank's sample release policy;

ii) How UK Biobank will consider sample assay applications;

iii) UK Biobank's current approach to case-control research using the resource; and

iv) The QC process that UK Biobank will require for sample assays.

The guidance in this document may be updated from time-to-time.

1. **UK Biobank's sample release policy**

1.1 UK Biobank is a long-term prospective cohort and UK Biobank's policy for the assay of depletable biological samples is that the sample should be efficiently turned into non-depletable data. This approach:

1.1.1 maintains and preserves the UK Biobank resource; and ensures that

1.1.2 assay data is made readily available, in accordance with transparent and clear timelines, to all researchers equally.

1.2 As such, UK Biobank uses an equivalent approach to the one that it takes as regards assays that it conducts itself, namely to assess whether ***all*** the following criteria are satisfied in relation to the proposed assay:

1.2.1 *Complete coverage*: the assay should be conducted on all 500,000 participants or, at the very least, from a large sub-set of randomly-selected participants. This approach this ensures that any assay "batch effects" can be taken into account as and when the same assays are done subsequently on the remainder;

1.2.2 *Validated assay methodology:* the assay method should be a validated assay with a proven record of producing consistent, high quality and reproducible data;

1.2.3 *Minimal depletion*: the assay method should only use minimal amounts of sample. DNA sample can be considered somewhat differently in a differential manner as the white blood cells can be immortalised so that further DNA (de facto identical) can be produced (although there are cost implications of this);

1.2.4 *Maximal output*: the assay method should yield a significant number of different analyte measures (for example: genotyping or proteomic/metabolomics assay platforms); and

1.2.5 *Data usability:* confirmation that the data generated by the assay is commensurate with recognised data standards and does not use any proprietary format or require any form of third party licence / approval for use.

1.3 UK Biobank, through its Access Sub Committee, can determine whether an exception to this policy should apply, e.g. in the following circumstances:

1.3.1 Where the assay is so specialised/complex that the assay can only be done (or only needs to be done) on relatively small numbers of participant samples (taking into account, where possible, technology developments which have the capacity to render certain assays much more cost effective over time);

1.3.2 Where the assay is only ever likely to be relevant to a very small select group of participant samples (for example, the assay of a rare condition or where the genetic / phenotypic characteristics occur, in a generalizable way, among sufficiently large enough numbers of UK Biobank participants); or

1.3.3 A general exception for unforeseen events.

Applicants should note that where UK Biobank has proposals for cohort-wide assays under consideration - details of these are generally made available on the UK Biobank website - then applications that would potentially duplicate such proposed assays (or duplicate assays which have already been conducted) are highly unlikely to be approved.

2. UK Biobank's consideration of sample assay applications

2.1 UK Biobank's Access Sub-Committee will review any research application for sample assay to assess whether:

2.1.1 the application meets all the above criteria in section 1.2 or falls within one of the exceptions in section 1.3; and

2.1.2 Does not duplicate a prospective assay that UK Biobank has in mind or has previously conducted.

2.2 In addition to the above criteria, UK Biobank will also require all applications to meet the following scientific criteria in relation to the proposed research:

2.2.1 a clearly formulated scientific case for sample usage (e.g. does the application address an important medical and/or scientific problem) with solid evidence that any hypothesis is well founded and evidence that the research is capable of making an *additional* contribution to the prevailing medical / scientific knowledge;

2.2.2 a clear scientific rationale as to why UK Biobank, as a prospective cohort, is the appropriate resource in which to conduct the proposed research and undertake the relevant assay: the fact that UK Biobank offers a convenient means of conducting the research / undertaking the assay will not be sufficient to qualify as scientific justification.

Only those applications which satisfy the necessary criteria and do not duplicate a prospective or past assay are likely to be considered further under the sample release procedures.

3. **Case control work**

3.1 UK Biobank is aware that the number of cases in the resource for the more common diseases will soon reach the stage when "nested" case-control studies of sufficient statistical power can be conducted.

3.2 UK Biobank has considered and reviewed internally the question of case-control work using the UK Biobank resource and has sought advice from its International Scientific Advisory Board and from its Steering Committee. UK Biobank would make the following observations:

3.2.1 UK Biobank is not convinced that case-control work in UK Biobank, particularly in relation to the more common diseases, would *at this time* make a significant further contribution to the existing science: as large numbers of common disease cases have already been studied by researchers using prevailing assay technology;

3.2.2 UK Biobank is concerned that case-control work on two different (common) conditions - for example, coronary heart disease on one occasion and stroke on another - could involve conducting the same assay at different times: it would then be difficult to compare assay results across different case-control sets;

3.2.3 UK Biobank considers that it may be of greater scientific value *in the short to medium term* to undertake nested case-control work on rarer and less studied disease, particularly where it may be possible to undertake assays that have not been utilised before; and

3.2.4 If case-control work is to be undertaken, then UK Biobank considers that it may be preferable to adopt a case-control rather than a case-cohort approach: because of the potential biases in a case-cohort approach (owing to the assays for cases and controls being measured at different times).

3.3 Although UK Biobank had originally envisaged co-ordinating a series of case-control calls – starting with the most common diseases – over the next few years, in light of the above considerations, UK Biobank is not minded to commence such a process at this time. UK Biobank will keep this policy under review.

At this juncture, researchers should be aware that case-control applications for the more common diseases will be highly unlikely to succeed. Further, although UK Biobank does not seek to deter case-control applications for rarer disease (particularly where there is a substantive chance of adding in a material way to the existing science), it would note that any such application will need to a) satisfy the necessary criteria set out in this note and b) fall within one of the exceptions in clause 1.3 above.

4. UK Biobank's requirements for QC of sample assay

4.1 In the event that samples are released to researchers to conduct the assay, it will only be done using appropriate assessment and QC measures so that the quality of the assay can be tested and assured throughout the conduct of the assay. These measures include:

4.1.1 samples within a case-control set will be included in the same laboratory batch. Samples will be picked randomly and arrayed on plates using algorithms designed to avoid introduction of bias from the sequence in which participants were recruited, so that cases and controls will be positioned randomly across the plates and assay batches;

4.1.2 duplicate samples will be included in each batch (blinded to the researcher); and

4.1.3 quality control assessment may involve the use of samples from sources other than UK Biobank.

4.2 The QC of the assay will also likely involve:

4.2.1 a pilot stage (in order to verify adequate QC performance at the outset); and

4.2.2 periodic reviews against agreed QC metrics, such that if the assay data does not meet the agreed standard then the assay shall be suspended and the problem resolved before the assay can be continued.

Appropriate QC measures are a necessary requirement of any assay, particularly given the extensive usage that researchers will make of sample assay data.