# METADAC finite samples guidelines

## Summary

METADAC's considerations of finite biological samples are mindful of the following:

- All applications to use samples should demonstrate a clear scientific rationale regarding why the study is appropriate to the proposed research, and for non-renewable samples, that the use of samples is justified by the expected contribution to the scientific body of knowledge. Applications that demonstrate a unique dependence on the study, for example use of longitudinal data not widely available, are preferred.
- Appropriate ethical approval must be in place and all applications must comply with relevant legislation, i.e. the Human Tissue Act 2004, which applies in England, Wales and Northern Ireland, and the Human Tissue (Scotland) Act 2006 [note: s 45 and Schedule 4 of the Human Tissue Act 2004 concerning non-consensual analysis of DNA apply also to Scotland].
- Scientific strength, novelty and potential health/social impact of the research proposal must sufficiently justify use of longitudinal study samples.
- Evidence must be provided to show methodology is appropriate to the processing history of the samples. e.g. published literature or pilot data.
- The assay test platform should have proven quality assurance measures in place, preferably in accredited facilities according to ISO standards.
- The assay strategy should aim for maximum research impact with minimal depletion of the resource.
- The methodology should include measures to ensure the quality of any remaining sample is not jeopardised and can be used in further assays.
- All data generated from samples must be returned to the study and made available to other users within an agreed timeframe
- Formal peer review is required.

## Objective of the scientific strategy guidelines

When a research proposal requires a finite resource, the application is seen as being in competition with other potential applicants (both current and future) and the quality of the science is reviewed formally. Independent review is required and reviews from major funders may be taken into consideration.

The objective of the METADAC is to facilitate access to stored tissue samples to maximise data generation and to ensure such data is readily available to researchers for further research. METADAC will ensure that scientific rigour is applied in selecting proposals that will yield data which are i) reliable ii) informative and iii) novel. As such, applications will be considered in light of the cohort design; successful proposals should maximise the epidemiological strengths of the cohort, whilst also recognising limitations of the biobank (in terms of sample protocols, processing, storage, and availability).

This document provides a framework for addressing and determining the scientific rationale for access issues for biomarker work, giving some relevant examples where appropriate. The framework will be reviewed as necessary to maintain current good practice

### 1. Use of the samples should be specifically relevant to the longitudinal study

All applications to use samples should demonstrate a clear scientific rationale regarding why the study is appropriate to the proposed research, and for non-renewable samples, that the use of samples is justified by the expected contribution to the scientific body of knowledge. Applications that demonstrate a unique dependence on the study, for example use of longitudinal data not widely available, are preferred. Evidence will be required to show that the assays could not reasonably be carried out using samples from another source. Global discovery proposals will be considered (see section 7) but are strengthened by including a specific area of research.

All data generated from samples must be returned to the study and made available to other users within an agreed timeframe.

Samples will be subject to the Material Transfer Agreement between the study and the researchers, which will define procedures for return or destruction of unused material.

Failure to return data or samples as required to the study will result in any further applications to METADAC being suspended until the issue is resolved.

## 2. Ethical Considerations

In addition to the ethical criteria that apply to all applications, use of biological samples requires that:-

i) The project must be in line with participant information and consents for the use of samples

ii) Appropriate ethical approval must be in place for the analysis. If the work is not covered by an existing approval held by the study, this may require submission of an ethical proposal to an NHS recognised Research Ethics Committee (REC).

iii) Applications must comply with the relevant legislation, being the Human Tissue Act 2004 and/or the Human Tissue (Scotland) Act 2006

iv) No samples will be issued unless the receiving institution signs the Study's Material Transfer Agreement (MTA). Please have the MTA checked before applying to METADAC.

In some situations applications may be approved "subject to ethical approval" or "subject to funding" in which cases samples will be reserved for a reasonable period to enable the appropriate approval or funding to be obtained.

## 3. Scientific strength of the proposal, and potential impact

The proposal must justify the use of the particular study's sample and be to answer a relevant and meaningful question, with a reasonable likelihood of impactful results. Use of longitudinal data to investigate associations (hazard ratios, or risk ratios) must be justified on the grounds of potential clinical (or social) relevance, and/or the particular characteristics of the samples/study, e.g .

i) disease diagnosis

ii) evidence for public health messages, or clinical guidelines

iii) clinical or social evidence risk-stratify patients – e.g. novel predictors of clinical or social outcomes.

iv) evidence for therapy selection – e.g. a biomarker that may predict a better (or worse) response to therapy options.

v) disease pathogenesis. Wherever possible, a robust approach to causal identification must be applied, for example whether the DNA resource can be

combined with a biomarker proposal to use a Mendelian randomisation approach (assuming valid genetic instrumental variables are known and measured).

## 4. Contribution to Scientific Knowledge

The proposed research should aim to make an additional contribution scientific knowledge and to the study resource (by generation of new data). Samples will not generally be released to repeat analysis which already exists but may be considered on a case by case basis if the work could be justified on the grounds they would make an additional contribution to scientific knowledge.

## 5. Suitability of samples for assay in question

Given the scarce nature of the bioresource, all proposals must clearly demonstrate that the biomarkers can be measured reliably using the available samples. Robust evidence, taking into account processing time, methods, and storage history, should be provided – whether from with a pilot study, or published data. Sampling strategies should be optimized as appropriate to maintain the value of the resource. For example, not depleting the smallest samples (or sample types), and safeguarding un-thawed samples when freeze-thaw history is not an issue for the current research.

Studies reserve the right to specify where an assay is carried out to minimise batch effects and for quality assurance purposes.

## 6. Assay test platform

Where possible, all sample and assay handling should be performed in accredited facilities according to ISO standards. Where this is not possible, applicants should seek to achieve standards equivalent to those of accredited units. Assays should, where possible, be carried out using gold standard automated methods. Manufacturers' recommended quality assurance protocols and internal ones will be considered. Evidence of the assay standard should be provided with a statement on why it is the appropriate choice. The assay strategy should aim for maximum research impact with minimal depletion of the resource. For example, where 10 markers can be assayed in parallel this is better use of the sample than only checking one biomarker.

Any proposal should be able to demonstrate that the assay they propose is sensitive enough to detect a signal (*e.g. as assessed by coefficient of variation*) in a majority of the samples (commensurate with the aims). Ideally the platform/manufacturer used should be established in the literature, to maximise the potential impact of the results, and minimise potential referee criticisms.

The volume of sample required for each assay must also be documented and will be taken into account in assessing the potential impact of the study. The assay method should ensure the quality of the remainder of the sample is not jeopardised.

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

## 7. Global Discovery Versus Specific Hypothesis

Studies reserve the right to retain samples for as yet undefined global discovery projects. While the discussion above refers to specific tests of hypotheses an alternative would be a global discovery approach. For example, it may be of interest across a wide range of disease states and phenotypes to acquire as much data as possible on the lipidome, proteome and metabolome from high dimensional methods. Mass spectroscopy and Nuclear magnetic resonance (NMR) based methods, antibody-based arrays, or proximal ligation assays for proteins, or serum micro RNAs are all potential global discovery assays. Careful attention should be paid by applicants to demonstrating the replicability of any proposed high dimensional assay and the strength of the statistical method for analysis. The linkage of any global measurements to pre-defined outcomes or to answer specific questions on disease pathology will help focus analyses.

Studies also reserve the right to retain some samples to take advantage of study enhancements planned for the future. Analysis based on longitudinal samples approximately 15-20 years apart will be of potential utility to bioscience internationally.

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The guidelines are subject to review and approval by the METADAC Committee.
These guidelines were adapted for use in multiple studies from the 1958 Birth Cohort Biosample Strategy Guidelines (2013) authored by Naveed Sattar and Paul Welsh, University of Glasgow; Helen Colhoun, University of Dundee and Susan Ring, University of Bristol.