METADAC finite samples guidelines
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The guidelines are subject to review and approval by the METADAC Committeee.

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

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. Successful formal peer review by a competent authority (*e.g.* MRC, Wellcome Trust, other major health charities) will be taken into consideration but may be supplemented by additional independent review.

The objective of the METADAC is to facilitate access to stored tissue samples so that they get the widest possible usage while ensuring 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

Applications to use samples should clearly demonstrate that the proposed study will make use of longitudinal data and cannot be carried out in samples obtained 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.

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. Scientific strength of the proposal, and potential impact

The proposed use of the sample must 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, 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).

3. Novelty of the scientific aims

The balance between a proposal's strength (in terms of potential impact) and its novelty (which studies have measured the biomarker and related measures to outcomes before) is a key factor.

4. Resource-appropriate biomarker characteristics

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. Projects that allow multiple tests to be run on the same sample will also maximize efficiency of sample use.

5. Assay test platform

Assays should, where possible, be carried out using gold standard automated methods. Accredited NHS laboratories, or those with external quality assurance schemes for the assay, are preferred. 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.

Any proposal should be able to demonstrate that the assay they propose is sensitive enough to detect a signal (<20% CV as absolute and more desirable <10%) 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.

7. Global Discovery Versus Specific Hypothesis

All the above refers to specific tests of hypotheses; an alternative approach would be a more global discovery approach; specifically, it would 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.

SUMMARY

Tissue samples in longitudinal studies are a valuable resource providing the assays is suitable for the samples' processing history. METADAC's considerations of biological samples are mindful of the following:

- Scientific strength of the proposal, and potential health or social impact, must justify use of samples.
- Evidence must be provided to show methodology is appropriate given the processing history of the samples.
- The assay test platform should have proven quality assurance measures in place and sampling strategy should be agreed to optimize the remaining resource.
- The methodology should include measures to ensure the quality of any remaining sample is not jeopardised and can be used in further assays which can be used on freeze-thawed samples.
- At least one aliquot of each sample type should be reserved for future global discovery projects.