



Financing UK biobanks: rationale for a National Biobanking Research Infrastructure



Work Package 7: Cost Model

Final Report

Sally Gee*, Luke Georgiou*, Rob Oliver** & Martin Yuille***

*Manchester Business School * & Faculty of Medical and Human Sciences** University of Manchester*

⁺ contact Martin.Yuille@manchester.ac.uk

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Acknowledgements: Funding was provided through a public-private partnership supported by the Technology Strategy Board (TSB). The authors would like to acknowledge the contributions of Julie Corfield (Areteva), Margaret Clotworthy (Human Focused Testing), Chris Womack, Rachel Mager and Mark Roberston (AstraZeneca), Balwir Matharoo-Ball and Brian Thomson (NHSB), James Ironside and Chris Tindal (UKBBN), Lesley Stubbins (GSK), Caroline Magee (NCRI), Aino Telaranta-Keerie (Lab21), Louise Jones (CRUK), Catherine Elliot and Joanna Jenkinson (MRC), Ariane Herrick (Salford Royal NHS Foundation Trust), Paul Downey and Pamela Moore (UK Biobank), David Walsh (ARUK Pain Centre), Gisli Jenkins (University of Nottingham), Finbarr Cotter (Royal College of Pathologists), Julie Barnes and Ian Jacobs (Abcodia), Kate Dixon, Bill Ollier, Melanie Lythgo and Craig Sykes (The University of Manchester). The analysis, opinions and any errors are the authors own.

EXECUTIVE SUMMARY

The provision of human biological samples (HBS) with associated data is critical for the identification and validation of biomarkers, and the adoption of stratified medicines¹. Although crucial for academic and industrial research and development (R&D) the way biobanking is currently financed and organised in the UK no longer meets the needs of the scientific community. Despite several examples of good practice, and of coordinated efforts promoted by funders, these are not representative of the system as a whole. An inadequate supply of high quality HBS, resulting from a lack of coordination and excessive complexity in biobanking, is hampering biomedical R&D, and the potential value of HBS and the associated data is not being realised.

The STRATUM project addresses this increasingly serious bottleneck by defining policy for a biobanking network and by providing building blocks and recommendations to facilitate effective operations for collection of HBS, with the aim of making these widely accessible to a diverse range of users. The research reported here contributes to the overall aim of the STRATUM project by focusing on the financial arrangements for biobanking. A qualitative case-study approach was designed to capture the diversity of biobanks in the UK and enable a detailed examination of institutional arrangements, with a particular focus on costings. During the course of this research it became clear that most biobanks are not fully aware of their costs and many costs are 'hidden', often as a result of complex inter-institutional arrangements and mixed funding streams. Those biobanks that have invested in calculating their costs have found that the costs associated with HBS vary according to sample type, accrual and access arrangements, as well as institutional context. All the biobank case studies who charged access fees for HBS set the access price according to the ability or willingness of users to pay. Overall, price charged for HBS does not recover the full cost. The empirical data aligns with established principles for the public funding of science and strongly suggests that a full cost-recovery model is not viable.

The accessibility of sufficient numbers of high quality HBS to support R&D therefore requires support from funders. Public funding of research is important to establish a science base and underpin economic activities. Firms alone do not invest sufficiently in research activities (e.g. because of uncertainty, long time to market) and the social rate of return is greater than the private rate of return (i.e. society as a whole benefits more from research than individual firms). Biobanking supports biomedical R&D and should be examined not only as a research activity in its own right but as a Research Infrastructure (RI). Research Infrastructures are the facilities, resources and related services that are used by the scientific community to support knowledge creation and distribution. A key characteristic of RI is that it serves both internal and external users. As opposed to large single-site facilities, biobanking is best understood as a 'distributed' RI involving coordination across multiple sites.

In this report a biobanking research infrastructure (RI) refers to a national network of biobanks, including disease or tissue-specific networks.

The creation of a national biobanking RI has the potential to increase the medical, social and economic returns of biobanking by achieving critical mass, optimising resources and enabling access. It may also reduce the costs associated with biobanking and the use of HBS through standardisation of operating and quality procedures, and by reducing unnecessary duplication of HBS collection, as well as the transaction costs associated with accessing multiple sites individually. The benefits of coordinated networking have already been demonstrated by smaller scale initiatives, for example, the UK Brain Bank Network. These

¹ The STRATUM project focuses primarily on the delivery of stratified medicines. Human Biological Samples (HBS) also make an important contribution to other areas of science.

existing disease/tissue networks are partial solutions, and can be perceived as elements of an emerging biobanking RI. This report draws on new and existing research to argue that a new financial approach is required to promote national coordination across biobanks and existing networks. It is beyond the scope and evidence base of this report to make proscriptive recommendations or specify a governance structure. Some key insights and general recommendations for financing a biobank RI include;

- 1) The population of biobanks in the UK is extremely diverse, reflecting differences in purpose, location and ownership; size, scale and scope; as well as financing and access arrangements. The cases presented in this report illustrate that it is not possible (or desirable) to apply a standard cost model across such a diverse population.
- 2) Coordination across this diverse population requires dedicated resources. This could take a variety of forms. A coordination centre may be required and this should be financed centrally by public funds, possibly supplemented by industrial funding. Such a scheme requires careful consideration to allow fair access by all users. Central funding is necessary to support the development and maintenance of a national searchable portal for HBS and drive quality standards across the biobank population.
- 3) The majority of the existing financial arrangements do not support the long-term maintenance and provision of high quality HBS. This report recommends that; a) HBS acquisition should continue to be costed into projects and project proposals to ensure biobanking is driven by research needs; b) core biobanking activities and facilities should be supported by central public funds to overcome discontinuity of funding problems and enable investment in best practice. These core costs could be distributed directly to the host public institutions; and c) the marginal costs associated with accessing samples could be paid for by the user.

These financial arrangements, incorporating the adoption of standards and the enrichment of the annotated data associated with HBS by users, will support the creation of a sustainable distributed biobanking RI necessary for the delivery of stratified medicines, and the realisation of the associated societal and economic benefits. The opportunity costs to the UK of *not* investing in a comprehensive biobanking RI could be significant.

The term ‘biobank’ commonly refers to a ‘collection of human HBS (tissues, blood and bodily fluids and their derivatives) and associated data that are utilised for research purposes’ (Watson and Barnes, 2011).

INTRODUCTION

Strategic Tissue Repository Alliances Through Unified Methods (STRATUM) is an 18-month project to define the scope and provide the building blocks for a national biobanking solution that facilitates biomedical R&D. The project is funded by the private and public sectors, with public funds being awarded after a competitive bid made to the Technology Strategy Board. There are six partners: the UK’s two largest pharmaceutical companies (AstraZeneca, as Sponsor, and GlaxoSmithKline), a clinical diagnostic small-medium enterprise (SME) (Lab21) and the universities of Manchester, Nottingham and Leicester.

STRATUM was funded under the TSB Stratified Medicines Programme: Developing Business Models and Value Systems. The aim of the programme was to increase understanding of the stratified medicines value system and develop business models for capturing this value. The Stratified Medicines Programme evolved into the Stratified Medicine Innovation Platform (SMIP); one of 6 innovation platforms focusing on societal challenges. Both iterations of the programme have been supported by the Department of Health, the Scottish Government Health Directorates, the Medical Research Council (MRC), Cancer Research UK and the National Institute for Health and Clinical Excellence (NICE). The aim of the Innovation Platforms is to improve co-ordination between key players in industry, academia and government in order to develop innovative solutions to these societal challenges. Ultimately, the TSB aims to support innovation, economic performance and public service provision.

The specific aim of the Stratified Medicines Innovation Platform (SMIP) is: *‘to place the UK at the centre of a new era of molecular-based healthcare by catalysing the commercial application of new technologies for diagnosing and treating disease. This will provide business, health and economic benefits to the UK in a competitive global market. It will also help the pharma industry to develop an increased number of more effective drugs targeted at smaller patient groups, the diagnostics industry to develop further the companion diagnostic tests that underpin this, and the healthcare providers to improve their cost effectiveness.’* (TSB, 2010)

The provision of human biological samples (HBS) with associated data is critical for the identification and validation of biomarkers, in understanding disease processes, and for the development and the adoption of stratified medicines. A biomarker is a characteristic or molecule that can be measured as an indicator of normal biological processes, pathogenic processes, or pharmacological responses. The identification of biomarkers enables patients to be ‘stratified’ into sub-groups to allow treatment for their condition(s) to be ‘personalised’². Discovering associations between biomarkers, people’s health status and responses to treatment requires a co-ordinated ‘big science’ approach (Poste, 2011). Researchers³ in pharmaceutical, biotechnology and diagnostic companies, hospitals and public research institutes, all require large numbers⁴ of well characterised high quality HBS to develop the knowledge, technologies and tools necessary for stratified medicine. Maintaining access to cutting edge experimental facilities and services is an essential part of ensuring UK R&D remains competitive (BIS, 2011).

2 Biomarkers developed as companion diagnostics (tests to identify patients’ likely responses to drugs) can improve R&D productivity by decreasing trial size, reducing attrition rates and/or increasing speed to market, and can improve commercial performance by improving market share and/or supporting higher drug prices (Davis et al, 2009).

3 The term researchers includes doctors, scientists and other healthcare researchers, managers and technical staff in academia and industry, as well as individual investigators with collections at Universities or research institutions.

4 Hundreds to tens of thousands of HBS are required to generate the statistical power necessary to demonstrate a robust association between multiple biomarkers and a particular disease, condition or response to a drug.

‘A recent CBI study found that the quality of our scientific research base is one of the most significant factors encouraging international companies to bring high-value investment here.’

(George Osborne, 2012)

Biobanking performs an important function in academic and industrial biomedical R&D and has been identified as an activity of national strategic importance (e.g. by BIS, ESRC, RCUK and SMIP). However, the way biobanking is currently financed and organised in the UK no longer meets the needs of the scientific community, and the high potential value of HBS and associated data are not being realised⁵. Indeed, an inadequate supply of quality HBS⁶, lack of coordination and excessive complexity in biobanking is hampering biomedical R&D. The STRATUM project addresses this increasingly serious bottleneck. The aim of STRATUM is to define and recommend the most effective options for the collection of future HBS (and, where appropriate, incorporation of existing collections), while making these widely accessible to a diverse range of users in the scientific community. STRATUM's intentions are endorsed by the Royal College of Pathologists (RCPATH) and the Experimental Medicine Funders Group⁷, which includes the MRC, the Wellcome Trust, Cancer Research UK, British In Vitro Diagnostics Association (BIVDA) and the Association of British Pharmaceutical Industry (ABPI).

Research Infrastructures (RI)

Biobanking supports scientific R&D activities and can be usefully understood as a type of research infrastructure⁸. Typically, we refer to infrastructure as technical structures, physical components or interrelated systems (for example, roads, electrical grids and the internet) underpinning a wide range of economic and social activities. Infrastructures confer benefits to a wide range of organisations and act as a shared or public resource. Research Infrastructures⁹ (RI) are the facilities, resources and related services that are used by the scientific community to support knowledge creation and distribution. A key characteristic of RI is that it serves both internal and external users, and is of high quality. As opposed to large single-site facilities, biobanking is best understood as a ‘distributed’ RI (ESFRI¹⁰) involving coordination across multiple sites. A centralised approach to biobanking (involving centralised funding, facilities and shared informatics) is neither viable nor would it support research and innovation.

In this report a biobanking research infrastructure (RI) refers to a national network of biobanks, including disease or tissue-specific networks.

Creating a national biobanking RI involves coordination of distributed individual biobanks (as well as any existing biobank networks) to enable coordinated acquisition and storage of HBS and associated data to ensure that they are visible and accessible to a wide variety of appropriate users. The creation of a national biobanking RI builds on efforts to create disease and tissue specific biobank networks. As new data becomes associated with remaining portions of HBS, coordination can then also support the creation of wider (‘spillover’) benefits, including access to knowledge, that extend beyond a single organisation. New knowledge is diffused quickly and innovation is supported for a variety of organisations (e.g. Marshall, 1920; Bresnahan, 1986; Jaffee, 1986). This is one mechanism through which RI's plays an

⁵ Market and system failures are resulting in under exploited opportunities for the country (discussed further on page 32).

⁶ In a 2009, NIH survey, researchers from 80% of 700 laboratories reported that they struggled to obtain standardised HBS for biomarker research (Poste, 2011).

⁷ The UKCRC Experimental Medicine (EM) Funders Group was established to bring together the major stakeholders that influence experimental medicine research in the UK, including governmental, public sector, charitable and commercial funding bodies.

⁸ See for example, BBMRI (http://cordis.europa.eu/search/index.cfm?fuseaction=proj.document&PJ_RCN=10239673); Meijer et al, 2012 (<http://spp.oxfordjournals.org/content/early/2012/05/02/scipol.scs033>).

⁹ Although RIs are well established in the physical sciences it was not until 2006 (ESFRI, 2006) that a major need was recognised for RI in the biological sciences.

¹⁰ European Strategy Forum on Research Infrastructures: http://ec.europa.eu/research/infrastructures/index_en.cfm?pg=esfri

increasingly important role in knowledge creation and innovation and have a positive effect on economic and social¹¹ welfare (e.g. Tassey, 2008; Lester, 2005; OECD, 2012).

This report focuses on the financial arrangements of biobanking in the UK. The structure, governance arrangements and level of coordination of such networks vary and are beyond the scope of this research.

Although the impact of individual biobanks on science (for e.g. measured through publication) has been well documented (e.g. Technopolis, 2010); it is difficult to isolate the effects of a national biobanking RI before it has actually been created (Fraunhofer, 2009; BETA et al, 2010), and quantifying all of the returns is difficult as they are wide-ranging often indirect, unpredictable and take time to be realised. However, potential socio-economic benefits are extensive and include the creation of: new scientific knowledge; new science, technology and innovation opportunities; new technologies and instruments; spin-off firms and new industries; and jobs. Other benefits include: supporting existing industry; contributing to training and development; attracting research funds; attracting industry funding; improving management capacity; boosting local expenditure and raising tax income. This list of benefits demonstrates that the potential opportunity costs of *not* taking a strategic approach to biobanking are high, and could include the loss of the UK's global position in biomedical research and attractiveness to the industries that commercialise this knowledge and deliver it to our citizens.

The research reported here contributes to the overall aim of the STRATUM project by focusing on the financial arrangements for biobanking. This work package set out to recommend a viable cost-model for a national biobanking solution based on analysis of the *organisation, governance and processes* for a spectrum of biobank types. The emphasis was on defining the 'as is' situation and proposing the most cost effective way of organising in the future. A qualitative case-study approach was designed to capture the diversity of biobanks in the UK and enable a detailed examination of institutional arrangements. Eight case-studies were generated through 18 face-to-face semi-structured interviews, supplemented by telephone and e-mail discussions, as well as secondary data, such as press releases, reports, meeting minutes and other records. Existing economic and other social science research on biobanking and the funding of research was also consulted. Taking this methodological approach facilitated an exploration of biobanking processes, the effects of alternative financial arrangements and the identification of contextual and interdependent factors. The financial arrangements of biobanks are analysed in the context of on-going efforts to coordinate biobanking activities and support the creation of a national research infrastructure.

This report first characterises the heterogeneity of the biobanking population in the UK before summarising the eight case studies selected to capture this heterogeneity. Cases are compared to examine diversity in the organisation, governance and processes of biobanking, as well as the effects of alternative financial arrangements. Empirical analysis is combined with existing literature that contributes to our understanding of how to maximise the medical and socio-economic benefits of biobanking. Finally, some observations and general recommendations are made to overcome the limitations associated with the organisation of biobanking in the UK.

CHARACTERISING UK BIOBANKS

The purpose of establishing collections of HBS has evolved substantially over time. What started as private 'curiosity cabinets' became pedagogic museums of human pathology. HBS initially collected in small numbers are now demanded in very large numbers as the raw HBS for research in epidemiology, molecular and cellular biology and for research leading to new interventions and stratified medicines. The

¹¹ Social welfare can be understood as societal benefits, such as a healthy population.

need for large numbers of high quality HBS and associated data has led to a rapid expansion in international biobanking activities over the last two decades. There is no definitive list of biobanks in the UK¹². In 2013, there were 215 biobanks holding HBS for research purposes licensed under the HTA¹³: 58 hospitals; 98 academic and 59 industrial biobanks. However, this only represents a sub-set of all UK biobanks and HBS resources, as each licensed institution may have a number of individual collections, and, not all HBS collections require a HTA license.

Biobanks are also very heterogeneous. In their study for the European biobank network project, BBMRI, Technopolis (2010), described the 'sheer diversity of biobanks' (p78). A point echoed across many reports (e.g. BETA, 2010; Gibbons, 2009; Watson and Barnes, 2011). There is no universal classification system for biobanks and a body of literature has emerged to address this issue. The table below builds on the expertise in STRATUM and consolidates research by BETA (2010); Gibbons (2009); Gottweiss and Zatloukal (2007); Tutton (2007); and Watson and Barnes (2011). The large number of categories in the literature has been reduced and broadened (Table 1) to reflect this report's focus on costs and the identification of suitable financial arrangements to support a national biobanking solution.

Characterising biobanks		
Purpose, Location & Ownership	Size, Scale & Scope	Nature of Contents
Financing Arrangements		Access Arrangements

Table 1 The main classification categories for characterising biobanks

It should be noted that terms are not used consistently in the literature, often reflecting the particular disciplinary background of the authors. Neither can taxonomy incorporate all real or possible variations between biobanks. Most of these classifications suffer from the limitation that definitions do not always have discrete boundaries (e.g. how to define a 'large' biobank). In addition, many biobanks fall within more than one category for any specific typological classification (e.g. funding from multiple sources). For example, no two biobanks in the Technopolis case study of 8 biobanks using 6 variables (year of conception, region, HBS numbers, organisation, outreach and funding sources) were similar. Finally, all of the biobanks investigated continue to evolve over time, shifting across boundaries. Generating an accepted typology of biobanks is problematic as these categories are ultimately artificial constructs and subject to reinterpretation by different members of the biobanking community. Yet capturing some of the diversity in organisational forms facilitates an analysis of main characteristics and how these are interrelated. This knowledge is critical for informing decisions around the financing, governance and access arrangements of an emerging RI.

Purpose, Location & Ownership

Biobanks can be classified according to the stated purpose for their existence (and their perceived ongoing role, which may also evolve). These categories (though somewhat fuzzy and open to re-negotiation) demonstrate the functional variety in biobanking operations.

¹² Or at the European level. A Nature (2010) report stated that there are over 400 biobanks in Europe and if small collections are included this figure is significantly larger.

¹³ <http://www.hta.gov.uk/licensingandinspections/listoflicensedestablishments.cfm>

- Academic research: e.g. often focused towards aspects of a specific disease, condition or population, at a molecular or cellular level. This category can include biobanks informed by hypothesis-driven studies and designed to answer a specific research question, and biobanks for longitudinal and population-based studies, i.e. cross-section and prospective studies. Publicly funded biobanks may also collect HBS routinely left over after surgery and surplus to diagnostic requirements, often with additional blood HBS from each donor. Such publicly (government or charitably) funded biobanks routinely provide HBS for academic and industrial research.
- Industrial research: HBS are used throughout the drug discovery and development life cycle, including during target identification, target validation and as an essential part of safety and efficacy evaluation. HBS are also required in the development, testing and QC of general and companion diagnostics to facilitate personalised or stratified medicine. HBS are now routinely collected as part of clinical trials to facilitate biomarker exploration and other R&D aims.
- Diagnostic and therapeutic purposes: Biobanks that store HBS intended for transplant are not within the scope of this report as they do not provide HBS for research. Hospitals pathology departments routinely archive HBS removed for therapeutic or diagnostic purposes for 30 years or more and these HBS may be accessible for research¹⁴.
- Teaching purposes e.g. anatomical collections for medical education and training.
- Commercial exploitation: a few biobanks have been constructed primarily for this purpose. Many commercial firms source HBS either through clinical collaborations or by paying the appropriate fees to public biobanks in order to acquire specimens. Commercial biobanks may also be created to bridge a gap in public funding and so support the maintenance of HBS collections.

The function of a biobank informs its location and ownership. A diverse range of institutions, organisations and groups own or manage biobanks, including government departments (e.g. DoH and MoD), non-governmental organisations (including universities), charitable bodies, hospitals, and a variety of commercial organisations, such as pharmaceutical, biotechnology and HBS sourcing firms. Gibbons (2009) notes that the location and ownership of biobank HBS and data are not static characteristics, and emphasises that data and HBS are re-located for strategic and tactical reasons through collaborations and networking agreements. This can be through legacy collections being used in new ways.

Biobanks with different functional aims will have different institutional, governance and funding structures. They are also likely to vary in their access arrangements. For the purpose of constructing a biobanking RI (and exploring different financing arrangements) this report includes cases of biobanks that have been constructed for academic research, pharmaceutical/biotech R&D, and commercial exploitation, and therefore includes biobanks that are housed in pharmaceutical firms, universities, hospitals and for-profit or cost-recovery organisations.

Size, Scale & Scope

The size, scale and scope of biobanking collections reflect the diversity of biobanking activities in the UK. Gibbons (2009) defines size, scale and scope as the total number of HBS; the quantity and extensiveness of data; organisational structure (how many personnel, stakeholders, collaborators, sites, IT systems, networked datasets, and/or jurisdictions are involved); geographical spread; and participant population size. The size of the biobank may be a function of the purpose of the biobank and the host organisation,

¹⁴ <http://www.cellpath.co.uk/archive-solutions.61.html>

for example, a population biobank by definition will involve HBS from thousands of people, a biobank supporting research on a rare disease is likely to be smaller, and biobanks that serve more than one collector (and thus have at least one feature of a network) tend to be larger.

Networking is important for this analysis. A national biobanking RI would be constructed (i.e. operationalized) as a network. The benefits associated with distributed RIs can be understood as network effects. Key benefits include increased transparency, information sharing, efficiency, consistency and quality as well as reduced duplication and transaction costs. Critical mass, in terms of the number of biobanks participating in an RI, is required to realise the benefits associated with networking, as is standardisation, which is necessary to facilitate interoperability. Standardisation of quality management, and traceability of processes, not only promotes quality and encourages consistency, but also enables HBS from discrete biobanks to be combined into research-ready collections.

Some partially networked biobanks have been established in the UK; these are usually based around disease or tissue types. All involve some type of common standards and aim to increase visibility and therefore access to HBS. The oldest is the UK DNA Banking Network (UDBN) that has evolved with common standards for consent, access, HBS accrual and processing plus a minimum core set of phenotypic data. Similarly, the MRC Stem Cell Bank implements common standards for stem cell lines. The Motor Neurone Disease (MND) Association (with Wellcome Trust support) is accruing MND HBS and data from patients seen at 20 UK clinical centres, storing them centrally and enabling distribution by making the resources visible through the European Bioinformatics Institute's (EBI) European Genome-phenome Archive (EGA). The Innovative Medicines Initiative (IMI) U-BIOPRED project in severe asthma, based in approximately 20 clinical centres across the EU, is accruing, storing and distributing a wide range of HBS types and data using common procedures and a single knowledge management system with central storage of HBS. The aim is to provide visibility and access to high quality HBS for U-BIOPRED consortia members across academia and industry, as well as third parties. The Manchester Academic Health Science Centre (MAHSC) partners are developing research biobank networks where initial HBS stabilisation processes can be undertaken in the spokes (e.g. hospitals), while final processing, storage and distribution may be undertaken at the hub (e.g. the University). More recently, the MRC Brain Bank Network has been funded and is implementing common standards across their national biobank partners. The MRC Brain Bank Network has invested in developing a web-based database for the cataloguing of HBS held by the constituent biobanks. The Confederation of Cancer Biobanks also aims to increase the visibility of samples by providing collated information on the NCRI Biosample Directory¹⁵ about samples held at member's biobanks and as part of other collections. They are also leading a harmonisation project that aims to improve quality and facilitate combining of samples from different biobanks. Another initiative is the Breast Cancer Campaign Tissue Bank that covers four separate sites that operate to shared guidelines and have a combined interactive on-line sample finder.

In industry, biobanks are often established because of disease strategies within a company, so are top-down in origin. However, in the academic setting and public sector, they frequently exhibit bottom-up conception and evolution, and are often initially funded through individual projects rather than as a strategic resource or RI. Although collections are increasingly associated with several research groups or with larger collection programmes for multiple users from different scientific disciplines, this has not removed the biobanking bottleneck in the delivery of stratified medicines. A harmonised biobanking system has not been created at the national level. There are efforts to pursue this internationally, for example a national registry is being built in Sweden and, at the European level, the FP7-funded project, Biobanking and BioMedical Resources RI (BBMRI), has successfully negotiated a network of national

15 (<http://biosampledirectory.ncri.org.uk>)

fundings across the EU to support a European coordination hub for biobanking. This model is being taken forward globally through the Global Biological Resources Centre Network (Human). However, the realisation of a transnational network relies on some level of coordination within the member states.

For the purposes of this report, the cases represented here include small collections, relatively large biobanks, and one evolving network. 'Large' biobanks potentially provide economies of scale, as fixed costs decrease relative to the number of HBS processed. Large biobanks may also have more formalised operational procedures and processes, including clear access and costing structures. Smaller collections can offer value and face different financial issues. There are lessons to be learnt from each of these categories. Similarly, the experience of an emerging (tissue type-specific) national network offers insights into the organisation and financing of a national biobanking RI. The age of a biobank is also relevant. On one hand, older, still operational, biobanks are likely to have experienced different funding challenges and their experiences could provide valuable lessons. Alternatively, governance practices may be less robust, HBS quality variable and annotated data may not have been maintained or updated. These characteristics have implications for the development of a national biobanking RI.

Nature of Contents: HBS & data

A wide range of HBS are held in biobanks. These include different tissues, organs, body parts, bodily fluids, cell-lines, and bodily waste products, as well as associated derivatives such as proteins, DNA and RNA. Reflecting the huge diversity in biobanks and the necessary resource constraints of the project, the remit for STRATUM is limited to HBS types collected in respiratory research (those types which are common to other areas of research). This remit is relaxed in this report as useful case studies are found in biobanks holding non-respiratory or generic HBS (i.e. HBS that may be of interest respiratory or any other disease, such as serum) and because a national resource will necessarily move beyond disease- or tissue-specific networks.

The type of HBS (and rationale for collection) has an impact on acquisition, storage/processing and (potentially) distribution for use. Each of these factors is associated with varying costs: 1) HBS (e.g. healthy or diseased tissues) and donor type can influence the acquisition process, for example whether recruitment occurs through routine diagnosis and treatment or through specific interventional studies. Acquisition is also related to study or biobank design (prospective and/ or retrospective; disease based; clinical trials etc). 2) Solids and liquids are stored in different formats and may require different storage conditions. Processing can also vary significantly. 3) Conversely, the distribution of HBS usually has minimal costs associated (relative to overall HBS life cycle; See Appendix 1), although some HBS, particularly fresh tissue, may require rapid transportation in specific conditions (for example) and therefore considerable costs may be incurred.

Annotations (data) associated with (describing) HBS are diverse. Annotations can be drawn from a pre-existing database (e.g. electronic health/social care record; research databases containing individual research test results or environmental data) or introduced into a new database (e.g. an electronic lifestyle questionnaire or an electronic HBS history database). Integrating diverse data sets is central to the construction of a national biobanking RI. Maintaining the annotated data associated with HBS, where remaining portions remain for other researchers to use, where longitudinal studies are being conducted or where the availability of clinical follow-up data would be useful, is critical to maintaining their value, i.e. enriching data to develop a dynamic and sustainable (in scientific value terms) RI. Until relatively recently, all annotations were captured manually, and this could be associated with relatively high levels of human error, with high costs implications. HBS can now be accurately annotated from live electronic databases, and this makes it simpler to undertake longitudinal studies in real time. Although this option is only available in some clinics and in one primary and secondary care system in England, the scientific value of annotating HBS with live data is potentially of great value. To optimise the research value of HBS

annotated in a network or a multicentre setting, it is critical to implement common ontologies for each type of data, including ontology for HBS history. This is common in large studies, but not across studies. Any system should also consider the potential for future European or international standardisation.

Financing Arrangements

The financing arrangements and business models of biobanks vary. Typical UK funders include government departments, research councils, the NHS, academia, industry, and non-profit organizations including charities (House of Lords Select Committee on Science and Technology, 2001). The majority of 'public' (as opposed to commercial) biobanks rely on external 'mixed' funding from a variety of sources. For academic sector biobanks, this may include central government funding¹⁶, charitable funding and discrete funds from companies (for example through access and service fees or ring-fenced funding for e.g. research nurses). Biobanks located in industrial settings (including pharmaceutical companies) may be entirely financed through internal capital. In the case of 'for-profit' biobanking firms, collections may initially be financed by venture capital, business angel or other sources of private capital. The majority of biobanking activities are maintained by ongoing public funding or, if in industry, through private finance or by provision of HBS in return for a fee.

However, there is discussion (involving the scientific community, funders and policy makers) on the potential for biobanking to become self-sufficient, i.e. moving to a cost-recovery model. Although biobanks should not make financial gains¹⁷ from selling HBS, they are allowed to make gains from data about HBS (Evers et al, 2012) or through the provision of services. Researchers, institutions and commercial entities were acknowledged by the Human Genome Organisation (HUGO) in 2002 (Rec 1,6) to 'have a right to a fair return for intellectual and financial contributions to databases', but 'fees should not restrict the free flow of scientific information and equitable access'. The wider public (this includes donors) could react against biobanking if a perception emerges that HBS are being exploited for financial gain. In this context, many biobanks rely on some form of access fees (in parallel with grant income) to maintain or support their operating activities (particularly if initial funding has been reduced or withdrawn).

¹⁶ In the UK, public sector funding for science and research is organised via the Dual Support System into two main channels: 1) the Research Councils provide grants for specific projects and programmes; 2) the higher education funding bodies provide block grant funding to universities. The budget for science and research funding is allocated by Department for Business and Skills. <https://www.gov.uk/government/policies/investing-in-research-development-and-innovation/supporting-pages/science-and-research-funding>.

¹⁷ Financial gains in this context refers to making a profit (beyond operating costs including salaries) from the trade of HBS. This is a complicated area and not clearly prohibited, unlike the sale of organs for transplant for example. 'The status of biological samples is initially an unresolved question; they can be considered to be either completely out of the commercial sphere as body parts, or not if they are covered by property rights.....The issue of direct involvement of private companies in biobank projects may also create ambiguities regarding financial benefits derived from the use of free donation.... biobanks intermingle notions of property shared by all of humanity with population and individual considerations. The participation of companies is more developed in terms of conditions of access to patients' samples and data. In case of benefits being generated, it is very unclear with whom and by which mechanisms they should be shared; various models have been proposed but even guiding principles remain unclear. This concept of benefit sharing must be balanced with the notion of "public good" and population health that constitute biobanks' (Cambon-Thomsen et al., 2007, p379). In the UK, the MRC state: 'The human body and its parts shall not, as such, give rise to financial gain. Researchers may not sell for a profit samples of human biological material that they have collected as part of MRC funded research, and research participants should never be offered any financial inducement to donate samples. Payment of reasonable expenses or costs is however acceptable'. (MRC, 2001, p3). Similarly, in the US, The University of California (SF) states: 'Although UCSF banks and investigators are not allowed to sell specimens for profit, investigators involved in specimen banking are permitted to recover the costs within the UCSF re-charge system for expenses associated with collection, processing, storage, and distribution.' (UCSF, 2005, p25). Although a complex ethical and legal area there is consensus the public are more likely to donate if they know their research is publicly-funded and contributes to research with societal and medical benefits.

Table 2, summarising revenue models, is compiled from a variety of sources including an IBM (2004) report based on two World Wide Biobank Summits and an ESA report (2010) on a workshop in the USA that sought to identify sustainable strategies for biological RI.

Biobanking Revenue Models	
Centralised public funding for RI	Creating endowments
Project funding from multiple sources	Collecting royalties on intellectual property
Charging membership or user fees	Build fees into a product or service
Charging a tiered system of access fees depending on whether the request is from academia/ industry	Associating RI with existing institutions (fixed costs)
Include RI costs in all grants	Mixed model (most likely)

Table 2 Biobanking revenue models

Each of these revenue models has implications for knowledge creation and innovation. For example: the structure of membership and user fees could impact on access; the inclusion of RI (RI) costs in all grants requires coordination across projects and funding bodies; collecting royalties on any resulting intellectual property (IP) could increase costs through royalty stacking¹⁸; associating RI with existing institutions fixed costs or with one main funder could result in inequity through free riding¹⁹. Identifying an optimum way of financing a national biobanking RI is informed by the viability of *revenue* models and the viability (and desirability) of different *operating* models. Transaction costs²⁰ have an impact here. Managing a diverse range of biobanks and financial streams takes time, management and accounting skills- activities with associated costs that need to be factored in. Also, sustainability is critical and unpredictable revenue streams make long-term planning, expansion, and improvement of infrastructure a challenge.

The capacity to preserve content and services in biobanks, and to increase their value to the user community over time, is critical (e.g. ESA/NSF, 2010). A national biobanking RI should be viewed as a dynamic resource that is evolving over time. There are costs associated with renewing and maintaining the data associated with HBS, as well as with improving or creating new biobanking methods (e.g. innovations in HBS acquisition, storage and processing techniques and protocols, as well as organisational or service innovations). To date, in the UK, although many general biobanks are based in hospitals & routinely collect HBS surplus to diagnostic requirements, biobanking is often funded through discrete investigator-led projects so funds tend to be time restricted; this has implications for the maintenance of collections, and optimising the use of surplus HBS. A related issue is that biobanking does not directly produce the types of indicator that facilitate second grants for the biobank although there are some examples of long-term funding, most funding bodies prefer to fund something new and novel, rather than maintain an existing resource (e.g. ESA/NSF, 2010). Financial discontinuities impede the maintenance of collections, as well as strategic oversight (necessary to reduce resource duplication for example).

The case studies outlined here include biobanks that are funded by charities, government, pharmaceutical companies and venture capital or private investment. Mixed models are seen in a few cases. In this report, we consider where costs and benefits accrue during the biobanking process. Access arrangements are

¹⁸ The concept of royalty stacking arises from the risk that multiple patents may affect a single product. Such risks are said to be particularly high in the biotechnology field, which is dominated by patent filing (Adhikari, 2005).

¹⁹ A free rider refers to someone who benefits from resources, goods, benefits, or services without paying for the cost of the benefit.

²⁰ Transaction costs are all the costs (other than the price) that are incurred during economic transactions (e.g. search costs, information processing).

Transaction costs are sometimes called coordination costs.

positively correlated to the realisation of benefits; the biobanks analysed as case studies include different access arrangements, including HBS access fees, service fees and centralized public funding for RI.

Access Arrangements

Access to HBS, data and services varies across biobanks. The level of access to a biobank has obvious implications for the scientific, social and economic impact of that biobank, as well as the potential to raise revenue from users. Gibbons (2009) identifies three archetypal access models observed in existing biobanks.

1. 'Closed' or exclusive access. In this case, third parties could be excluded from using the data and HBS collected.
2. 'Controlled' access by approved third parties, on application, subject to conditions. This is the most common access arrangement for publicly funded and commercial biobanks, while industrial internal Research Tissue Banks²¹ work similarly. Access to the biobank could be granted according to pre-defined criteria, for example type of user, type of research, type of sector or fields of use. This model could include the provision of services, so a biobank (or independent service provider) does not release HBS to users but conducts the experiments and releases the resulting data. The latter, where applicable, has the benefit of conserving HBS, may improve data quality and may ensure annotations are continually enriched, but may restrict the range of HBS analyses.
3. 'Open'²² or 'public' access, possibly at a fee. This could include copyleft type²³ solutions where research results are granted back to a common pool (Beta, 2010). This approach reduces the risks of free riding and fragmentation of the resource. It also has the benefit of enriching annotations and therefore the value of existing HBS.

The level of user access directly contributes to the innovation potential of the infrastructure and arguably open access generates the highest number and widest variety of positive impacts (assuming sub optimal use is minimised through some type of quality control). The more accessible the RI, especially if operating with an obligation for users to update associated annotated data (where applicable & not commercially sensitive) the greater the benefits. Indeed an open model where users are actively contributing (private collective model; von Hippel and von Krogh, 2003) has the potential to support a dynamic resource that increases in value over time²⁴. BETA (2010) associates this 'enrichment effect' with an efficient network structure that leads to a new generation of benefits.

However, HBS is often a finite resource that needs to be equitably distributed. Most biobanks are concerned with maximising the research value of the HBS in their care, and agree that donated HBS should be put to the 'best possible use', i.e. access to finite HBS should be granted according to the quality of a research proposal and the value of the expected outcomes. This model is widely accepted by the biobanking community; as demonstrated by the creation of 'access committees' to evaluate HBS requests. There is clearly a balance between open access (more suited for data and knowledge) and controlled access (more suited for finite resources). Conversely, selling research access could conflict with the 'best possible use' principle (Evers et al, 2012). How to grant access, who to, and if/how to charge for this access

21 In the context of this report a Research Tissue Bank (RTB) is defined as a collection of human tissue or other biological material, with ethical approval which is stored for future research use. Some RTBs have ethical approval to authorise use via a Access Committee, others do not.

22 Open access does not mean that all data is visible. For example, in the case of biobanking, no actual or potential patient identifiers would be accessible (all data is deidentified).

23 Copyleft is a method (often through licensing) of making data (most commonly computer programmes but including other work) freely available (not necessarily free of cost) and requiring all modified and extended versions of the data (programme/work) to be free as well.

24 If the cost of making knowledge public is less than the benefits, it is appropriate to disseminate knowledge (von Hippel and von Krogh, 2003).

is clearly a critical issue. It is important to note that access to HBS for purposes that are not strictly classified as research, such as assessment of the performance of diagnostic tests under development, is currently limited, even though such performance assessment may be essential to guarantee high accuracy and safety of such a test in patient care.

The cases presented in this report include biobanks that have exclusive access (e.g. pharmaceutical biobank), and controlled access (some with features of open access). Access and financial arrangements are often related, for example, the type of financing may affect the appropriation rules imposed on the network, for example public subsidies may imply open access (BETA, 2010). This issue is explored further in the case-based analysis.

EMPIRICAL CASE STUDIES

The aim of this report is to make explicit some of the costs and benefits associated with biobanking by documenting the *organisation*, *governance* and *processes* across a spectrum of biobank types. This workpackage was designed in this way for a number of reasons; 1) to capture the heterogeneity of biobanking activities and increase understanding of the organisation of biobanking in the UK; 2) to enable the identification of the main cost drivers²⁵; 3) to compare institutional arrangements at a variety of existing biobanks (and one network), and hence provide insights into the costs and benefits associated with different organisational forms, financial and access arrangements; and 4) in combination with existing research, to provide an evidence base for recommending solutions to overcome the problems currently associated with biobanking in the UK (and indeed, globally).

A case study methodology is most useful for addressing these issues. Case studies enable a detailed and in-depth examination of a variety of biobanking models. Taking this methodological approach facilitates an exploration of processes and effects, as well as the identification of contextual and interdependent factors. Case studies can also reveal how biobanks are evolving, and help to identify the contextual factors informing this evolution. For example, Technopolis (2010) report how the weight of project based funding in the UK system is partly responsible for the structure of UK UDBN, with multiple funding sources and cost recovering procedures. Additionally, quantitative data alone cannot give an accurate picture of the organisation, activities, benefits and costs associated with biobanking.

The empirical cases draw on both primary (semi-structured interviews) and secondary (minutes; press releases; evaluations etc.) data. For each case study, interviews were held with senior managers, principal investigators and in some cases finance officers and funders. Background information was collected prior to and following interview. Interviewees were identified by STRATUM stakeholders and a one page summary was shared with the main contact prior to interview, with a request to identify additional interviewees. The interview questions and the spreadsheet that interviewees were asked to complete can be found in Appendix 2: Semi-Structured Interview Questions. A full list of interviewees can be found in Appendix 3: Case study interviewees. The following section provides a short summary of each of the biobanks (in alphabetical order); the full cases are located in Appendix 4: Full Empirical Cases.

Summary Case study 1: Abcodia

Abcodia is a biomarker validation company with exclusive access rights to an extensive and unique biobank. The firm was created in 2011 and is a university spin-out (USO) from University College London (UCL) with support from UCL Business and a venture capital firm, Albion Ventures. Abcodia has exclusive access rights to over 5 million prospectively collected serum HBS aliquots in liquid nitrogen from over

²⁵ A cost driver is a factor that can cause a change in the cost of an activity.

200,000 female donors with an associated comprehensive database of phenotypic, demographic and disease incidence. A substantial sub-set of these HBS have longitudinal follow-up of up to ten years. The custodianship and management of the HBS is retained by UCL.

The collection was established in 2000 using HBS obtained from the UKCTOCS (UK Collaborative Trial of Ovarian Cancer Study) and funded by the MRC, NHS (National Health Service), Department of Health (DoH) and various charities. The Principal Investigators saw an opportunity for valuable HBS to be collected alongside the study, which was looking at the impact of ovarian cancer screening on mortality, together with performance characteristics for screening options and the morbidity, resource and psychological implications. Marginal costs are associated with collecting additional HBS alongside a study of this size, as the majority of resources necessary for acquisition and storage would be financed through the study. HBS processing and initial storage was undertaken at UCL and was supported by University and charitable funding. Long-term storage is now contracted to a commercial facility.

Abcodia is a for-profit firm operating a 'value generation model' and is product focused with the aim of leveraging the £30m spent on HBS accumulation to support the commercialisation of diagnostic tools. Abcodia was created to overcome the re-occurring problem of attracting long-term external funding for storage and maintenance of the biobank, as well as to achieve maximum academic and commercial use of the HBS resource. The scientific aim of the company is to support the discovery and validation of biomarkers thereby improving disease diagnosis and screening, primarily in cancer. The business model is designed to realise an income stream for the research unit and a return on the initial investment.

Abcodia has an exclusive commercial licensing agreement with UCL Business and the rights to commercialise any resulting intellectual property (IP) generated from the use of this serum biobank. Abcodia's services extend beyond the supply of HBS and data, and include numerous project management, networking and consultation services for their collaborating customers through to product development and subsequent progression through regulatory milestones and commercialisation.

The company has received support and funding from the technology transfer office of UCL (UCLB) and from venture capital, and has also received (undisclosed) commercial income from collaborative or commercial customers. Future income is likely to include upfront license payments and subsequent payments linked to milestones as well as royalty revenue from the sales of any products. The company has disclosed a number of commercial partnerships since 2011, and achieved other recent success including a number of business start-up awards.

Although details of expenditure could not be interrogated the company operate with modest overheads and minimal staff; notably the practical aspects of the biobanking are contracted out (to Fisher BioServices). The four senior staff and one project co-ordinator handle other professional services themselves, or contract out to external experts as required. There are few overhead expenses in terms of buildings and facilities.

The primary commercial advantage leveraged by Abcodia is that their HBS were collected from then-healthy women, some of whom, in the time since elapsed, have developed disease & for most of whom, follow-up clinical data is available. This collection therefore represents a valuable resource for the investigation and identification of biomarkers. The company is also uniquely positioned to provide an organisational interface and maximise potential collaboration opportunities.

AstraZeneca (AZ) is an international pharmaceutical and biopharmaceutical company with its corporate headquarters in the UK. It has an active research and development pipeline requiring access to large numbers of well characterised, appropriately consented and specifically annotated HBS. AZ's Global Biobank consists of an international network of internal collections, primarily containing HBS which have either been purchased from carefully vetted external suppliers, or have been obtained via their own research collaborations and clinical studies or trials.

The biobank holds a wide variety of HBS, including formalin-fixed, paraffin-embedded (FFPE) and frozen tissue, plasma, serum, whole blood, urine, sputum and DNA. HBS processing tends to occur prior to inclusion in the biobank, with some processes, such as DNA extraction, contracted out to external organisations. Across the two sites included in this analysis (UK and Sweden), AZ holds over one million HBS, of which 50% are biofluids and 40% are DNA, with the remainder mainly solid tissue. A range of data is held on the biobanked HBS, including demographic, pathological, clinical and genotypic data. A customised off the shelf Laboratory Information Management System (LIMS) is under development which is fully searchable and allows interaction with their clinical trials databases.

HBS and data are almost exclusively used internally by AZ research staff; in the UK it is registered as an ethically-approved RTB. Priorities for HBS use tend to be driven by project priorities which have been subject to internal scientific and commercial scrutiny. Use of HBS outside of the company is limited, but tends to be driven by collaborative interests, with commercial contracts in place. Between 2010-2012, 400,000 HBS were collected and 90,000 were issued for research.

Collection and storage is driven by the need for continuous access to HBS for drug development and research. There is a general move towards obtaining broad consent at the time of collection to facilitate unspecified future research. Overall, there is a shortage of appropriate HBS for research, partly because those taken internally alongside clinical trials are collected in relatively small amounts and collected primarily for pre-determined diagnostic purposes and the measurement of specific biomarkers. The vast majority of banked HBS are provided as needed to internal research users. For this reason reliable, external sources of high-quality HBS are critical to enable research and rapid drug development programmes. To facilitate this supply, strategic collaborative links exist with a number of external organisations and biobanks. There is recognition that external collaboration will be fundamental to the successful provision of high quality HBS in the future. Successful collaborations are already in place, for example, through the provision of salary support for HBS collection, e.g. research nurses and biobank resources, strategically located within the NHS.

Biobanking at AZ is considered to be a corporate-wide enabling activity with high quality, well annotated HBS recognised as a key asset for their business. Operationally the Global Biobank is funded through the Discovery Biosciences division as an infrastructure, and investments in IT hardware and software is funded through AZ Research, Development and Innovation (RDI). The initial investment, footprint and non-staff running costs for the biobank are relatively modest in relation to the research spending of the company as a whole. Staffing costs are significant, but many staff are appointed at a high level, and provide a range of services including quality control and advice on HBS accrual, costing and long-term strategy.

Summary Case Study 3: Biobanking Solutions

Biobanking Solutions is the biobanking group located at the Centre for Integrated Genomic Medical Research (CIGMR), part of a research school within the Faculty of Medical and Health Sciences at the University of Manchester. CIGMR functions as a genomics translational research centre, offering expertise, facilities and storage of HBS, including the UK DNA biobanking Network (UDBN). The creation of

Biobanking Solutions in 2012 reflects a broadening of biobanking operations, which had initially focused on the storage of DNA and the UDBN collections. CIGMR continues to support both this biobanking in addition to a number of project-specific biobanking services.

Biobanking Solutions supports mainly academic researchers locally and nationally through collaborative research and offering paid services. There is little involvement in HBS acquisition, but Biobanking Solutions provides a central service for their receipt, logging, labelling, processing, replenishment, storage and distribution. The biobank has a focus on genetic epidemiology, with the main specialism being for DNA HBS management, but it now holds a broad range of other HBS types (especially biofluids). Biobanking Solutions currently holds around 250,000 aliquots in freezers or liquid nitrogen, from over 50,000 donors. The facility operates to ISO 9001:2008 accreditation, operates a fully customised LIMS and has a significant capacity in HBS handling robotics.

The finances of Biobanking Solutions are incorporated into the larger, complicated funding streams associated with CIGMR. The main capital support funding came from the MRC, with some further core funding awarded for successive 1-3 year periods. Cost recovery, from the supply of HBS and services, is generating an increasing proportion of their income, and CIGMR is actively trying to reduce its dependence on grant funded income. However, this is complicated by the lack of appropriate financial and administrative support within a research environment set-up primarily to deal with grant funding.

Biobanking Solutions has estimated the costs associated with its main services. These costs are highly variable (DNA extraction costing significantly more than many other biobanking processes). The prices charged are dependent on parameters such as the quality of the product or service, the level of collaboration and resource involved, the current market price, the financial arrangements of the customer and the likelihood of further work. As an example, storage may historically have been provided at no charge if future DNA processing or analysis was anticipated. The finance arrangements are also complicated by indirect and institutional costs which are not clearly identifiable. In addition, there is significant cross-subsidisation between biobanking and other specific project work to improve overall efficiency. Technical time tended to be recouped through applying for salaried staff posts within grant proposals; staff costs account for the major proportion of all expenditure.

Although Biobanking Solution costs do not include donor recruitment or HBS collection, they are increased by the nature of the genomic work they undertake and the investment and maintenance of robotics. In addition there is significant time, and therefore staffing, costs associated with running both their LIMS and the quality management standard (which incurs additional license and inspection fees).

Biobanking Solutions allows numerous individual researchers or research groups to use DNA extracted in a regulated and consistent manner with quality assurance that the processes adopted are consistent and will maximise the value of the HBS for future research. They have a strategically important role within their academic environment, and the ability to advise and influence external partners directly or through their position within the Manchester Academic Health Sciences partnership.

Summary Case Study 4: Fresh Tissue Supply

The Nottingham Arthritis Pain Centre (NAPC) is funded by Arthritis Research UK and hosts a biobank which stores a range of human HBS with associated clinical data. In addition to the provision of this biobanked HBS, and facilitated by the overall infrastructure that has been developed, the facility also supplies fresh HBS for research purposes. Only the supply of fresh HBS was the focus of this case study, as it provides an essential resource for many pharmaceutical companies for research and drug development, when frozen

or fixed biobanked HBS are not suitable. Key users include local research groups at The University of Nottingham, pharmaceutical companies and external academic researchers.

The provision of fresh HBS originated as part of a collaborative project in 2000 with AZ; this enabled the basic procedures for the supply of fresh HBS to be established, initially from donors undergoing surgery, but later also post mortem. Using existing biobank staff and infrastructure has meant that a relatively cost effective mechanism for obtaining fresh HBS has been established. This mechanism negates the normal main expenses associated with collecting HBS that is erratically and unpredictably available. Crucial to the service has been a flexible approach that allows development of new protocols according to researchers' requirements, but that also utilises staff who can adapt their priorities to fit in around HBS availability.

Contracts are drawn up individually and fresh HBS are only supplied when needed. The supply of fresh HBS is inherently expensive, especially for external researchers, due to the need for rapid processing and despatch of HBS, without any of the economies of scale associated with handling large batches. In addition, it may require out of hours working and specialised resources, skills or facilities and by definition has to be used immediately, so has limited potential for sub-dividing.

The full costs associated with the provision of fresh HBS are calculated for users on an as needs basis. Due to the commercial status of many collaborators, there was a reluctance to share specific cost, charge and income data (commercial sensitivity). The general strategy was to aim for cost recovery amongst commercial users, which would include a contribution towards the running of the facility as a whole. Other user charges depended on the nature of the work (for example pilot work for larger studies may incur a minimal fee) and the association with the research team, for example, through collaboration. The sustained operation of the infrastructure is financially supported by the NHS Trust via salaried staff time appointed primarily for the more routine biobanking.

The Pain Centre biobank has an effective network of partners and works especially closely with the Nottingham Health Sciences Biobank. The provision of fresh HBS is a specialist niche service that supports research both locally and externally, and provides extra income for the biobank.

Summary Case Study 5: Nottingham Health Sciences Biobank

The Nottingham Health Science Biobank (NHSB) was set up in 2010 to support translational and clinical research across the Nottingham University Hospitals (NUH) NHS Trust, and is a key component of the Trust's research strategy. The NHSB facility has a relatively large number of staff including scientists, technicians and volunteers. There is strong leadership and the management are implementing a very clear and medium-long term business strategy.

The facility has ethical approval to obtain informed generic consent and collect HBS from any inpatients and outpatients within the Trust. The biobank has a team of extensively trained donors to approach patients for consent. To further minimise the costs associated with acquisition, the HBS is primarily residual material, which is excess to diagnostic requirements. Solid HBS is collected by NHS pathologists (within their existing quality assured framework) whereas blood is collected by clinical staff or biobank phlebotomists in parallel to the patient's routine clinical care. The NHSB committee can approve work utilising these HBS and archived pathology HBS.

The facility currently holds over 20,000 HBS as frozen aliquots, FFPE blocks, or slides. These numbers include HBS taken as part of the Breast Cancer Tissue Campaign biobank, as Nottingham is one of four regional centres. The majority of these latter HBS are solid tissue. The biobank manages the tracking of all HBS through a customised commercial LIMS, which the Trust supports. The NHSB is investing significantly

in procuring a full management system that will provide live downloads from the Trust electronic patient records system, while ensuring confidentiality. To enhance functionality, an informatics system is being developed to enable consistent and accurate coding of medical records for research use.

The biobank offers open access to HBS for commercial or academic research use. Users of HBS are asked to acknowledge the biobank in publications, and feed any enriching data back into the NHSB databases. Data enrichment is carried out by biobank staff to reduce user costs associated with this activity. The NHSB has no intellectual property rights over the data.

Capital spending on the biobank has been relatively modest, partly because little refurbishment was required. Spending on freezers and HBS storage was less than on laboratory analysis equipment which in turn was less than spending on the HBS tracking/IT system. The largest spending relates to the development of the HBS data linkage and coding system. In terms of annual running costs, the staffing bill is over five times higher than all the spending on space rental, consumables, reagents, equipment maintenance, stationery, and health and safety.

The biobank is heavily subsidised from grant sources and through NHS R&D funding. Although it operates on a not-for-profit basis, NHSB aims to be fully self-funding from 2015, by recouping all costs, including overheads, mainly through HBS distribution. The facility has interrogated the costs associated with biobanking and demonstrated that full costs are higher than generally acknowledged, with at least half of the charge relating to 'overheads' (mainly Trust overheads and pathology support costs), and in some cases only 12% directly attributable to HBS consent, collection, processing and storage. They have adopted a tiered charging structure for access, with local researchers who contribute HBS to the biobank potentially accessing HBS free of charge, and commercial users paying an individually tailored fee which may be influenced by market pricing, supply of associated data, rarity of HBS, and quality control procedures. The NHSB have undertaken a comprehensive analysis of the biobanking environment to inform their business strategy.

Summary Case Study 6: Small Research Collection

The Scleroderma research collection was established in 1996 by a consultant rheumatologist at Salford Royal Hospital with an active research programme in this field. The rheumatologist felt it was important to collect HBS, which could potentially aid future research, from this specific group of patients with relatively little inconvenience while they were attending clinics. The collection originally focused on serum or plasma HBS, but later expanded to include whole blood for genomic investigations and skin for histopathological analysis.

Since 2009, the collection has been registered as a RTB with ethical permission to collect and distribute HBS for research, through an internal steering committee. Patients are identified from clinic lists and approached by the clinical team to seek informed consent. Blood is collected by members of a small research team, and processed within communal laboratory facilities, before being aliquoted and stored in freezers at -80°C. Skin and whole blood HBS are processed and stored at the Arthritis Research UK laboratories at the University of Manchester. Over 450 patients have been recruited and sampled, with over 2500 separate longitudinal serum HBS collections.

The costs associated with the collection of the HBS have never been accurately calculated. The extra time and effort taken to consent and obtain blood samples from patients, outside their routine clinical care, is minimal. The HBS processing was historically undertaken by university funded research staff, although these posts are steadily being lost in favour of short term appointments for specific grant funded projects.

Consumables, equipment and storage facilities are funded from the general research funds of Professor Herrick as the principal investigator (PI), with some overall facility support provided by the host Trust and University.

Although information about the collection is publically available via the University research profiles, the HBS are not actively marketed. Despite this, DNA HBS in particular have been used in a variety of research projects and have contributed to a number of high-quality publications. HBS are provided on a collaborative basis, without seeking any cost-recovery.

Recent changes and developments within 2013 mean that HBS are now collected as part of an NIHR portfolio funded study and are stored within a formalised biobanking facility.

Summary Case Study 7: UK Biobank

UK Biobank is a very large, high profile, prospective collection that recruited 500,000 people aged between 40-69 years from across the UK between 2006 and 2010. The biobank now houses an estimated 10 million HBS. The aim of UK Biobank is to build the world's largest information resource on the genetic and environmental factors that cause or prevent human disease. Initial grant funding of £62 million came from a range of sources including the Wellcome Trust, MRC, Department of Health and the Scottish Government, and is supported by the NHS and hosted by the University of Manchester. Additional funding (approximately £31M) has been secured for further measurements, to develop online access and to operate the storage facilities until 2016. A range of committees, advisory boards and working groups advise and support the facility in various capacities. The UK Biocentre was opened as a wholly owned subsidiary of UK biobank in 2012 to promote secondary use of the equipment and facilities through external contracts.

Donors who enrolled in UK Biobank undertook a range of physiological measurements and tests, completed detailed lifestyle surveys, provided a clinical history and provided a range of biofluid HBS (including blood, urine and saliva). They also agreed to allow future access to defined personal records and data, and in some cases to allow longitudinal (future) visits and sampling.

Since the end of March 2012, users have been able to request access to HBS data and/or physical HBS. The biobank is a resource for anyone doing health related research in the public interest anywhere in the world. Data enrichment of HBS from research that has been undertaken will occur after a time delay to allow patenting or publication by researchers. Although users will access HBS in order to perform analyses, a panel of core baseline tests will be conducted on all HBS. Access is via a cost recovery model, but this only aims to recoup the costs associated with distribution of HBS or data, it does not aim to recoup original collection costs.

The main capital expenditure of UK biobank was on specialised storage facilities at two sites, robotics, refurbishment and IT. Approximately £15M was spent on a comprehensive pilot study, but it was estimated that of the original £62M at least half was spent on the salaries of the staff involved in recruiting donors and collecting HBS at the various centres throughout the UK. The major ongoing running costs relate to salaries, rent and equipment maintenance.

The costs associated with different stages of biobanking were not available, but using a top-down calculation, the total initial funding represents a figure of approximately £124 per donor, each of which provided approximately ten different HBS types. This covers contacting donors, transport, consent, sampling and HBS storage, together with the completion of the associated questionnaires and physical tests. The current NHS system was used to identify possible participants.

Summary Case Study 8: UK Brain Bank Network

The UK Brain Bank network is an initiative led and sponsored by the MRC to coordinate a national network of UK brain tissue collections. The constituent members of the network include four MRC funded brain banks or archives, and six charitable or NHS partner brain banks, all of which have their own collections of brain or related HBS, as well as ethical approval to release it for research. The network was established by the MRC, and supported by the UK Clinical Research Collaboration, to realise a strategic approach to UK brain biobanking. Coordination was perceived as important due to the significant levels of funding the MRC was investing in this field (almost £1M p.a. to the current MRC brain biobanks and the archive collection). The main objective was to enhance the availability of quality brain tissue for research through increased operational efficiency and coordination of the brain biobanks.

Creation of a steering committee led to a period of consultation with potential and current research users of brain HBS, the outcome of which was a number of key observations and priority areas. A network director was appointed to develop and drive the proposals with an initial three year budget of £410,000, and this led to the creation of the co-ordinating centre at the University of Edinburgh with a small number of core staff, including an IT manager.

The constituent biobanks of the network collect a range of HBS including whole brains, tissue sections and slides, blood and blood derived products (including DNA), most of which come from specific disease areas. Historically, the biobanks have operated in isolation with different access policies; however, the consensus of the network was to move towards a standardised model which provides HBS for research projects and pilot studies based on scientific merit. The intention was that standardised access fees would only recoup the marginal costs associated with access and supply of HBS but not the accrual and storage of HBS, or the overall network infrastructure. It was intended from the start that all researchers should have access to HBS, facilitated by investment in a single searchable on-line databank (launched March 2013), which brings together the key data for all the HBS held by the individual biobanks. The database is accompanied by the development of a standardised coding system for all the HBS and standardisation of key access paperwork (for example, material transfer agreements).

The Brain Bank Network has since made a successful bid to enhance funding. In 2010, the MRC awarded a grant for the collection of brain material from the underrepresented 'control' group (i.e. donors with no known underlying neurological conditions). Additional funding of £1.5M over three years has also been made available to the networked biobanks since 2012. This funding is to facilitate the transport and pathological diagnosis of brain HBS, a service which was inconsistently supported through normal NHS funding routes and has resulted in an 18% increase in brain donations in 2012 in comparison with 2011.

The MRC indicates that brain biobanking is not intended to be financially profitable, but should facilitate the very large amount of research funded on neurological and psychiatric disorders. Traditional grant-based funding mechanisms for brain biobanks have historically offered limited long-term stability. By demonstrating cost efficiencies, higher quality, reduced duplication and enhanced access to HBS through a network, the case for future funding for each of the brain biobanks is enhanced. The MRC brain biobanks are now coordinating their bids for further funding, rather than each presenting their own competing cases.

CROSS-CASE COMPARISON

The biobanks summarised above demonstrate the diversity of biobanking activities in the UK. This section identifies the key drivers of the costs and benefits associated with biobanking, and examines the implications of different financial arrangements.

Institutional Setting			
Biobank	Location & Ownership	Age** (yrs)	Function
Abcodia	University Spin Out (venture capital, private, university)	2	Support the discovery & validation of biomarkers
Astrazeneca	Corporate (pharmaceutical)	50+	Support R&D development of personalised & other medicines & companion diagnostics (exploratory research; QC; storing clinical trial HBS)
Biobanking Solutions	University	12+	Supports genomic research
Fresh Tissue Supply**	Hospital (Project-based)	12	Sourcing of fresh tissue for academic and commercial research on-demand
Nottingham Health Sciences Biobank	NHS Trust University Hospital	2	Supports translational & clinical research
Small research collection	University Research Group, & Hospital	16	Unspecified future disease orientated research
UK Biobank	Independent charity	6+	Unspecified prospective studies

Table 3 Institutional setting for each of the biobank cases

*From initial HBS collection (except Abcodia where age is from inception of firm) ** The sourcing of fresh tissues is often dependent on the presence of a biobank infrastructure

Most of the biobanks in the HBS are affiliated with an existing institution and the majority are located in public organisations, including universities and hospitals (Table 3). The HBS broadly reflects recent research funded by the National Human Genome Research Institute in the US which found that ‘most biobanks are affiliated in one or multiple ways with other entities: 88% are part of at least one or more larger organizations (67% of these are academic, 23% hospitals, 13% research institutes²⁶)’ (Henderson et al, 2013, abstract)²⁷. In the same survey it was found that only 5% of U.S. biobanks are for-profit organizations and only 7% are incorporated (Henderson et al, 2013, p14). Although no such similar survey

²⁶ This is the first national survey of biobanks in the USA.

²⁷ ‘Clearly the most frequent affiliation of a biobank is within an academic institution (78% of embedded banks). Hospitals were reported as a parent organization for 27%, and 15% were part of a research institute. About a quarter (28%) of all biobanks are part of more than one larger organization.By far the most common situation of multiple-affiliation is for a biobank to be affiliated with an academic institution and also with another organization—a hospital being a second affiliation for more than half (73%) of academic biobanks with multiple affiliations. The next most common multiple affiliation is within an academic institution and also a research institute (34% of biobanks affiliated with academic institutions are also part of a research institute)’ (Henderson et al, 2013, pg 16).

has been conducted in the UK, expert interviews suggest the US ratios are likely to hold in the UK. From our research we believe that our case studies can be considered *proportionally* representative; capturing the majority of UK biobanks types. A notable omission is that of intermediary agents, for example Human Focused Testing²⁸ and Tissue Solutions²⁹; “virtual biobanks” that do not hold physical HBS, but source them through a network for their research clients.

In addition to the individual biobanks above, this report also reflects on the experience of an existing biobank network that coordinates access to HBS from a specific organ (brains). Existing biobank networks, and those under development, tend to focus on disease areas or tissue types. The emergence of these networks demonstrates how biobanks and HBS users are self-organising ‘from the ground-up’ to address HBS access and funding issues.

Network	Location & Ownership	Age (yrs)	Function
UK Brains Bank Network	University Hospital	4	Co-ordinate national brain banks

A national biobanking RI will need to integrate a heterogeneous population of organisations and emerging networks. There are challenges associated with this, including high management and coordination costs, and overcoming barriers to communication and interaction. There are also valuable benefits to be realised, as discussed in the introduction, including: increasing visibility of and access to HBS; raising quality and comparability through the promotion of best practices; financial savings through pooling of resources; the potential to strategically review and plan collections; and maximising opportunities for knowledge creation (knowledge creation and more radical innovation tends to occur at the intersection of disciplines and organisations). A biobanking RI will exhibit increasing returns (benefits) as more biobanks join, more researchers contribute and more researchers use the RI (these benefits are referred to by economists as ‘network externalities’). The construction of a national biobanking RI therefore requires that particular attention is given to the different operating modes and strategies of this diverse population.

COSTS

This report has identified the available data on costs in each of the case studies (see Appendix 2 for the interview questions and costing spreadsheet; this spreadsheet could be used by individual biobanks to interrogate their own costs). For each study, respondents were asked to complete a questionnaire about initial set-up costs (refurbishment, freezers, other storage systems, automation, robotics, test equipment, IT and LIMS) and annual operating expenses (salaries, rental, facility maintenance, service charges, IT systems, equipment maintenance/servicing and consumables). The response rate and level of detail was variable across the institutions. Overall, detailed, comparable data has not been available for four main reasons;

1. Hidden costs and cross-subsidising; for example, the use of services, resources or facilities are not solely attributable to the biobank, but are shared or provided by a larger, over-arching organisation.

²⁸ <http://www.humanfocusedtesting.com>

²⁹ <http://www.tissue-solutions.com/>

2. Opaque financial systems; these include complex models and accounting systems used by the NHS and Universities.
3. Inability to provide financial data; for example, detailed figures have not been prepared previously (in many cases there is no institutional or regulatory obligation to breakdown the figures relating to biobanking)
4. Unwillingness to provide financial data; for example, for commercial or confidentiality reasons.

Where detailed figures are available these are not comparable because of differences in; 1) HBS types³⁰, for example, figures provided by Nottingham Health Sciences Biobank indicated that there can be a six fold variation in the cost of processing and biobanking HBS of differing type (based on comparing processing of serum with a frozen fresh tissue HBS); 2) stages of the HBS life cycle undertaken by the biobank (for example, specific processing and storage only; See Appendix 1 for the stages of the HBS life cycle); and 3) the individual biobanks' cost calculation methods (for example diverse definitions of full costs, direct costs, indirect costs, depreciation, etc). For these reasons, this report does not specify the cost per HBS at individual biobanks and is unable to suggest a universal cost model for individual, or networked, biobanks). However, the cases do enable us to identify some of the main variables affecting costs. Table 4 captures the main cost drivers for HBS collection and processing. Note that these are representative examples only and in some situations they may be reversed (for example, robotic processing may prove more expensive than manual processing where there is a low HBS throughput).

	Process		Examples*	
	<i>Project specific variable</i>	<i>Facility specific variable</i>	<i>Less expensive</i>	<i>More costly</i>
Collection	HBS type		Saliva	Solid tissue
	Donor type		Patient	Control
	Location		Local clinic	Home visit
	Time of day		Morning	Night
	Time-point		Longitudinal	Single
Processing	Processing method		Aliquot liquid	FFPE section
	Final concentration		Not specified	Normalised
	Number of aliquots		One	Multiple
	Size of aliquots		Microtube	Block of tissue
		Technical resource	Robotics	Manual
		Quality	Not specified	Externally audited
Storage	Storage conditions		Room temperature	Liquid nitrogen
	Replenishability and		DNA	Fresh tissue

30 An added difficulty relates to the interpretation or definition ascribed to 'a HBS' when looking at costs – for example in the case of serum, the term can be interpreted as a single 'aliquot' of serum from one tube of blood, or, as a single tube of blood obtained from a donor prior to processing. From a costing perspective, the situation is further complicated as a number of HBS from a single collection time point (e.g. a series of blood tubes from one venepuncture) or even a number of HBS collected longitudinally from one donor, are likely to be cheaper to collect and process, than HBS from discrete donors. The type of material also determines the relative costs associated with sub-dividing – a serum HBS would normally be divided and aliquoted only once when the HBS is centrifuged, whereas a wax block of solid tissue can be frequently revisited to prepare new sections and slides as needed. In our analysis, the HBS cost has generally been ascribed to one portion of material collected at one time point for one patient.

	HBS stability			
		Emergency back-up	<i>No spare capacity</i>	<i>Reserve facilities</i>
		Consumable costs	<i>Bulk discounts</i>	<i>List price</i>
		Data entry	<i>Single</i>	<i>Double</i>
		Labelling	<i>Hand-written</i>	<i>Integral 2D barcode</i>
		Tracking	<i>Paper records</i>	<i>Customised LIMS</i>
		Alarms & environmental monitoring	<i>None</i>	<i>Remote alarm and auto temperature logging</i>

Table 4 Key cost drivers, and representative examples, for HBS collection, processing and storage

Some biobanks have well defined costs, as exemplified by the UK Biobank, who were established with a clear remit and with a defined budget covering all aspects of biobanking, including physical construction, HBS collection (accrual), storage and some processing. The UK Biobanks target demographic was drawn from the normal population and identification was facilitated through access to NHS records. Successful recruitment levels (5.5%) reflected the large target population (9 million people invited to attend; Allen *et al.* 2012), the publicity, the perceived ‘common good’ and public altruism. Although it could be expected that a prospective study collecting HBS from the general population, outside of an existing infrastructure would be expensive, cost per HBS are relatively low reflecting scale economies. The large scale of the project justified a substantial investment in resources (most notably robotics and freezer storage) and also enabled highly efficient recruitment; co-ordinating centres could be arranged with high throughput of donors so staff were recruited at an appropriate level of expertise and for a relatively short time.

In comparison to UK Biobank, most biobanks have a relatively vague cost model and may even be unable to analyse specific costs retrospectively. However, there was evidence that there is a shift towards trying to elucidate ‘real’ costs in the future possibly relating to increased financial instability and the consequent need for accountability. In particular, Nottingham Health Sciences Biobank has invested significant resources in identifying their costs and developing a business plan. NHSB and other biobanks located in hospitals/university hospitals are likely to play increasingly important roles in translational & clinical research (also seen in US study by Henderson *et al.*, 2013). NHSB are actively planning to recoup the full cost of their biobanking (including the institutional and infrastructure costs) primarily through the provision of HBS to commercial users.

The extensive analysis undertaken by NHSB for the preparation of their business strategy has highlighted some of the key costs associated with biobanking. For example, they have indicated that when taking into account all of the costs associated with the preparation of a fresh frozen tissue HBS, only about 12% of the total is directly associated with the collection, processing and storage of a physical HBS (with a similar proportion attributable to data collection), whereas almost half of the overall cost is attributable to overheads (for the biobank, pathology, R&I³¹ and Trust as a whole). The figures for Nottingham may be representative of other similar biobank models. Nottingham have employed some interesting processes to reduce their costs and increase the efficiency of HBS accrual and processing, for example, by using donors to seek consent in clinics, as well as using generic consent, as is now common amongst generic biobanks that routinely collect surplus patient HBS, to maximise opportunities for future research.

31 The NUH Trust’s Department for Research and Innovation.

Nottingham have also committed extensive funding (over £1M) to the development of IT infrastructure in the form of both a LIMS, but more significantly, an informatics system that helps code and link the phenotype data to the stored physical HBS. This highlights the importance that is attributed to searchable and well annotated HBS associated data. All the biobank case study interviews highlighted that good quality associated data contributes significantly to the research value of HBS. Indeed, if R&D is based on poor quality data this has significant cost implications in the medium-long term, if inaccurate results (and poor commercial decisions) are the outcome. The provision of poor quality HBS and associated data can also result in reputational losses for the biobank. Like NHSB, some were investing significantly in collating data manually or automatically into a comprehensive and searchable database, while others preferred a simpler system, possibly dependant on future manual access to clinical records or via a currently unspecified electronic mechanism. In all cases it was clear that there were significant resource implications either in the short (creation of a 'system') or long-term (in retrieving the relevant information). Where a database already exists, perhaps for an associated study (e.g. with the Abcodia serum collection, or the AZ clinical trials data) or through retrieval from an electronic NHS database, there is an obvious cost saving to be made, albeit with the associated precautions associated with quality and accuracy of the information held.

The construction and equipping of biobanks can incur large costs. This is exemplified by the high specification, purpose-built facilities established across two sites by UK Biobank, costing well over £10M. Although an exceptional example with particularly advanced systems for robotics, frozen storage, security, and fire suppression, it does highlight the potential costs involved. In contrast, and as already mentioned, other establishments may have incurred costs progressively (for example in facilities previously converted or allocated to laboratory work) or over a longer period of time through a slowly expanding facility, and these costs will frequently be 'hidden' within larger scale facility support. This is true of many of the cases examined (e.g. AZ, Biobanking Solutions, NHSB, small collection case, fresh tissue). In some cases, even the purchase of associated equipment may be linked to previous budgets or centralised facilities (for example, as seen in the small collection case). It is important to realise that these 'hidden' costs still exist, even when they represent a reuse of otherwise underutilised facilities or resources.

In contrast to the UK Biobank (and some longitudinal studies), many biobanks have historically received project specific funding to facilitate research activity in a specific disease area. This has led to facilities that are funded for an initial three-five year period, but discontinued, so biobanks must creatively search for new funding streams to continue their operations and replace or update critical equipment. In the case of BioBanking Solutions this discontinuity problem was exacerbated as the new financial model was unfamiliar and not supported by the existing university finance system. Conversely, in an attempt to maximise use and safeguard a valuable collection, Abcodia developed a commercial business model. Although, there is clearly a tension between committing open-ended funding to individual biobanks or research projects, discontinuity of funding is a serious issue and could undermine initial investments, as well as the safeguarding of collections. Additionally, funding according to disease area means there is potential for duplicated or under-utilisation of the resources across disciplines.

Running costs are diverse and highly variable depending on the model employed, but salaries represent a very large outgoing for all biobanking models. The figures are difficult to untangle; even UK biobank with its relatively transparent model had highly variable salary outgoings depending on the stage of recruitment. The HBS collection teams were frequently recruited on fixed term contracts, worked in specified geographical areas and operated with a high donor throughput to maximise efficiency. In contrast, the acquisition of fresh tissue at Nottingham operates effectively by utilising staff that work in a flexible manner within a broader job remit. This maximises efficiency, but again relies on effective time management and an underlying facility support (that can utilise the staff effectively when no HBS need processing).

Biobanking Solutions (BBS) also utilises a flexible staffing model with skills utilised across both the biobanking and non-biobanking aspects of the over-arching company (CIGMR), for example in terms of overseeing Quality Assurance or IT, as well as with role flexibility to deal with peaks and troughs of HBS throughput. Over half the running costs for BBS relate to salaries with the second biggest expenditure being maintenance and depreciation (and therefore planned replacement) of core equipment. This reflects the relatively specialised area (genomics) in which they work, together with their use of robotic liquid handling, which they see as being critical to HBS quality and reliable HBS handling. Illustrating the diversity across the cases, but the continued dominance of salaries, AZ has a core team across the two main sites who are assigned to biobanking and drawing salaries of nearly £1M, yet its calculated capital resource equates to approximately £50k p.a., and its spend on consumables less than £20k p.a. This reflects a likely high level of 'hidden' financial support within the company, including the fact that individual research teams may incur HBS collection costs when obtained from external sources and the fact that many services (for example DNA processing) are contracted out.

Aside from salaries and equipment maintenance (including IT/LIMS), the other on-going annual costs associated with biobanking are relatively low. They include consumable supplies, licensing and administration (for example to ensure regulatory compliance), energy, training, marketing, transport and courier costs. However, these costs are also highly variable; for example, UK biobank spent a significant sum on HBS transport as it operated a model with a central storage facility and outlying satellite collecting sites.

In addition to the cost analysis for individual biobanks, the UK Brain Banks Network (UBBN) was interrogated as a model for enhanced networking. This network was introduced by the main grant funder in this area (the MRC) to promote brain research through the introduction of a more co-ordinated strategy for the biobanking of brain HBS across both the MRC and the charitably funded brain banks. At the individual biobank level, cost savings and benefits are realised through, for example, the use of a centralised database to promote research uptake of their biobanked HBS as well as increased justification for future funding as they can demonstrate increased collaboration and less duplication of HBS. This coordination benefits the MRC (and the other, charitable, funders) by reducing overlapping funding requests. Furthermore, the network has also enabled the banks to have an enhanced, unified 'voice', in order to seek further funding in specific priority areas (e.g. illustrated by the allocation of £1.5M award for the retrieval, transport and pathological assessment or diagnosis of brain tissue). Creation of centralised administrative and IT resources can clearly provide a key cost saving for relatively small biobanks with individually limited resources.

The small scale collection included in the analysis demonstrates that enthusiastic individual researchers or clinicians targeting specific valuable patient groups can collect with very little additional resource by using existing systems that provide access to patients (usually via the NHS). However, these individual researchers have little resource available to process, store or distribute HBS. If these facilities were made accessible to them and HR practices rewarded these activities, then individual researchers and clinicians could collect and distribute more HBS relatively cost effectively.

The data on costs that could be collected has highlighted the diversity of biobank models and enabled the identification of the main cost drivers. It is clear that prospective, carefully planned, large-scale collections such as UK Biobank can recruit in a relatively efficient manner, although it could be argued that this has the potential to lead to underutilised resources and equipment if a relatively short-term funding phase expires. Similar scenarios exist across other grant and publicly funded resources, whereby a lack of guaranteed maintenance funding leads to insecurity and, ultimately, the potential failure of initially expensive resources. For all biobank funding it is important to identify a strategy that ensures long-term utilisation of resources, i.e. to move away from the dominant model of short term funding for biobanks

through specific projects only. In order to maintain a sustainable biobank operating to appropriate standards, there is a need for long term core funding that ensures that such facilities will be appropriately staffed and that equipment will be maintained and replenished. Without this, there will always be an uncertain future for the HBS and the research potential that they hold.

Information Communication Technologies (ICT)

The costs of developing ICT systems are underexplored in this work package but are obviously key expenditures, as demonstrated by the dedicated funds allocated to this by the NHSB (£1.2m), Biobanking Solutions (£65,000 per annum) and UKBBN (1 FTE) cases. Investment in ICT should cover HBS tracking, annotated data management (including any coding or classification projects) and provision of an access portal for internal and external users. Related to this, annotation is fundamental to the value of HBS and standardisation of ontologies is necessary to realise the full value of a national biobanking infrastructure. Development of national coding strategies for disease, HBS classification and other elements is ongoing and resource consuming. A review of existing coding and classification strategies may be necessary and decisions required, for example whether to invest in ICT that overcomes these variables and/or how to encourage convergence in practice. Ideally, the system should enable the linking of HBS with clinical data; a critical bottleneck in biobanking.

As the number and diversity of biobanks increase, interoperability between biobanks is also an increasingly important issue. Similarly, because of the global nature of R&D, international interoperability is desirable and the UKBBN is building on existing European systems to enable HBS sharing and to avoid the high costs associated with custom designed ICT solutions. From a political perspective, there are clear signals (e.g. RCUK FfCI, 2012) that ICT development should build on existing complementary infrastructures. Those relevant here include e-infrastructure and bioinformatics facilities. Opportunities exist to construct a biobanking infrastructure alongside a biomedical informatics infrastructure. As the UK has exceptional biomedical, healthcare and social data, high quality HBS could be associated with this data, and this would give the UK a global competitive advantage and act as an incentive for research to be conducted and exploited here. The European Bioinformatics Institute initiative ELIXIR and the Department of Health's investment in health data sets are particularly relevant.

FINANCING & ACCESS ARRANGEMENTS

Biobank	Financing	Access Arrangements	Access Fees
Abcodia	Mixed public funds, including charities → VC, private	Controlled Access: by access committee	Flexible contractual and financial arrangements
Astrazeneca	Corporate	Controlled Access: internal project review or access committee	No charge at point of access: Free to internal users; external access via collaborations
Biobanking Solutions	Research council, project grants	Controlled Access: by technical committee incl. original collector	Tiered Access Fee: Lower price for academics Higher price for industry users <i>Fee to cover distribution not accrual or infrastructure</i>
Fresh Tissues	Biobank by NIHR via Trust Fresh tissue by projects and contracts	Controlled Access: Collaborative or contractual	Tiered Access Fee: Lower price for local academics Higher prices for industry users

NHSB	NHS Trust	Controlled Access: by access committee	Tiered Access Fee: Lower price for local academics Higher price for industry users <i>Fee to cover biobank & trust overheads</i>
Small collection	Project grants	Controlled Access: ad hoc	No charge
UK Biobank	Mixed public funds, including charities	Controlled Access: by access committee	Flat registration fee Flat data access fee Variable HBS Access Fee: <i>Fee to cover direct costs</i>
UBBN	Research council	Controlled Access: by access committee	Aim to introduce a standard access fee <i>Fee to cover distribution not accrual or infrastructure</i>

Table 5 Financing and access arrangements for each of the biobank cases

Financing

The biobanks in our case studies are financed by a variety of sources, reflecting their location and function. However, with the exception of the corporate biobank, they are predominantly supported (or have been supported) by mixed public funding. Data from this cross-section of biobanks analysed supports findings in a national US survey, where 78% of biobanks were funded by either the federal government, the larger host organisation (presumably including universities and hospitals), individuals or federations or the state government (Henderson et al, 2013). Public funding of research (including biobanking) is widely recognised as critical by both politicians and economists because; knowledge (the output of research) shares properties of a public good³²; the generation of knowledge stimulates the generation of new knowledge; the benefits of research are widespread, diffuse and unpredictable; and limited access to knowledge can significantly slow the pace of innovation. Research can also be a long way from market³³ which acts as a disincentive for firms to invest extensively in R&D unless it is clearly product related, except to maintain capabilities in the field³⁴. Additionally, public subsidies are justified in situations of market failure, i.e. when the market is not allocating resources efficiently. Market failure is expressed in biobanking (globally) as a lack of coordination between biobanks and poor visibility of HBS, combining to impede access to sufficient numbers of high quality HBS necessary to underpin applied R&D (as evidenced by the funding of STRATUM by 2 global pharmaceutical and 1 diagnostic company. The current situation in biobanking is inefficient and ineffective, and is negatively impacting on the delivery of stratified medicine and resulting in a loss of societal and economic benefits. Combined with evidence that public spending on R&D stimulates the private sector to invest (e.g. Cohen et al. 2002) there is a strong rationale for collective action to promote knowledge generation and sharing.

It is generally agreed that *‘the central public policy implication of public goods is that the state must play some role in the provision of such goods; otherwise they will be undersupplied. If firms cannot appropriate the returns to producing knowledge, then they will have limited incentive to produce it: in deciding how*

32 A public good has two critical properties: non-rivalrous consumption (i.e. the consumption by one individual does not stop another individual consuming it) and non-excludability (it is difficult to exclude an individual from consuming the good).

33 The commercialisation process from invention to a new product entering the market takes on average 15 years.

34 Clearly, industry also plays an important role in financing and conducting research. The type of research, the nature of the problem it addresses as well as the potential to appropriate value from it, are some of the factors that affect where research takes place.

much to invest, they will look only at the return that they acquire, not the benefits that accrue to others.' (Stiglitz³⁵, 1999 p.311).

It is highly unlikely that a biobank RI can be financed entirely by commercial funds; but rather, when commercial finance is sought, this should be clearly defined (e.g. for services; access costs) to promote equitable contributions and access. If individual firms are required to contribute directly to development and maintenance of RI, it is difficult to design and co-ordinate comprehensive and fair contributions across all potential industrial beneficiaries. Issues such as free-riding, the exclusion of organisations (including SMEs), as well as excessive transaction and management costs are likely to impact on perceptions of equity that are fundamental to the sharing of HBS, and ultimately the ability of researchers to access them. This could have a negative impact on innovation. However, industrial users of a coordinated national biobanking infrastructure must also make a fair contribution to any centrally funded scheme. Currently there is no national financial oversight or guidance associated with the provision of HBS to industry, and supply tends to be negotiated on an ad hoc basis or governed by the central philosophy of each individual biobank. Although there is a general consensus amongst the publicly funded biobanking community that HBS should not be 'sold for profit', a number of biobanks adopt a tiered fee system, generally led by the ability and willingness to pay rather than reflecting true costs (the price is not set by the market). Tiered fee structures are employed to enable a degree of cost recovery and subsidise academic users. They tend to be designed as access fees, i.e. at the point of exchange of samples, there are no examples in the cases of membership fees, though this could be one option for a national RI. Other possible options include companies contributing to the pot of central RI funding.

Construction of each of the biobanks has involved some form of 'strategic' investment, unless, for example in the small collection case, they evolved from smaller scale collections into larger or more formalised biobanks (this has frequently been driven by regulatory requirements). All the biobanks in our selection are dependent on either core or project funding and, in the case of corporate biobanks, are usually financed by the global budget of the institution (in line with Hirtzlin et al, 2003 and Henderson et al 2013). For example, the NHSB has invested in the development of a business plan that aims to recover the costs of running the biobank (this includes the Trust's overheads, but not the Access Committee or a return on the initial investment by the Trusts R&D budget). The business plan projects that the biobank can cover its own costs by March 2014, including pathology and overheads by March 2015, and the Trusts overheads by March 2016. These projections are based on the assumption that non-grant income is doubled each year and involves a significant shift in financing streams and activities. Over £3m of R&D funding is ring-fenced for the NHSB until March 2015.

Sustainability may only be achievable if researchers collecting HBS for their own projects are obliged by funders to use a recognised biobank for HBS and data management and where the collector's funder pays the biobank directly for that management. This resolves a conflict of interest between the Principle Investigator (PI) and the biobank (the PI is conflicted between getting funds for an investigation and getting funds for biobanking), and allows for maintenance, depreciation and endogenous development of the infrastructure.

Related to this, a critical juncture in the longevity of a biobank is the transition in funding from construction to maintenance and development of collections (including the related tools, technologies and techniques). Our case studies show that the maintenance of a biobank within a public institution is often largely dependent on research project income, where a proportion of income from projects is allocated to

35 Nobel Memorial Prize in Economic Sciences and John Bates Clark Medal, H. C. Recktenwald Prize in Economics

biobanking. In some cases, this is used to support additional development activities. However, project funding is erratic (discontinuous) and many biobanks are in receipt of funding from multiple sources, increasing the administrative burden of running the biobank, and resulting in the widespread cross-subsidising of biobank activities. Some of this cross-subsidising is transparent, much of it is not. This has a variety of effects, including a lack of information about real costs, distortion of the market and low morale amongst support staff who may experience job insecurity, particularly in the university sector. Innovation in biobanking technologies, processes and practices may also be negatively affected due to less 'slack' in the system for experimentation.

Any discussion about financing arrangements cannot ignore the current political or economic environment. Economic austerity has been felt across the UK, and science is certainly no exception. Current restrictions on capital funding (for Research Councils UK, an initial 53% reduction in capital funds in the first year, N8 Research Partnership, 2012) will increase competition between capital development projects, such as a national biobanking RI. The RCUK Framework for Capital Investment³⁶ (re-named Capital Investment Roadmap³⁷) replaces the Large Facilities Roadmap (RCUK, 2008) to inform the 'identification, prioritisation and timely realisation of key capital investments'. The Framework is organised around seven 'major research challenges and opportunities where the UK either has an international lead in research, or is poised to take this position' (RCUK FfCI, pg6). A national biobanking infrastructure supports research in three out of seven of these key areas; (1) Health, disease and aging; (2) Population change and diversity; and (3) Synthetic biology. As such, a strong argument could be made for public funding in this area.

However, the government is in favour of reducing the role of the state³⁸. In this context, the creation of a coordinated biobanking network may be dependent in part on a resource commitment by industry and charities in the UK. A coordinated approach across the public and private sectors will be critical to ensuring the design of a RI that meets the needs of stakeholders, as well as incorporating funding from a variety of sources in an equitable way. However, the research presented suggests that investments should be strategic and long term in order to sustain a coordinated national biobanking RI.

Access Fees

Access fees provide an additional source of finance, although they are presently highly variable. NHSB research reports that an extensively annotated HBS may be worth twice one that has limited data. Although price variation can be expected according to the type of HBS requested, the accompanying data and any extra service provision, these factors do not fully explain the variation. Some additional reasons have been identified. However, while many biobanks reported flexible financial arrangements, details about calculation methods were not usually provided.

- Some biobanks used flat rates (usually for data, sometimes for HBS), however, even UK Biobank couldn't/wouldn't give an average figure for *price* per HBS.
- The common use of tiered financing structures, based on the type of researcher, rather than the type of HBS, further complicated the picture. For example, the NHSB will charge local researchers the 'direct cost plus Pathology overheads' (reflecting rates achievable from funding grants, because main funding

³⁶ <http://www.rcuk.ac.uk/documents/publications/RCUKFrameworkforCapitalInvestment2012.pdf>

³⁷ <http://www.rcuk.ac.uk/media/news/2012news/Pages/121109.aspx>

³⁸ See, for example, the Wilson Review into University-Business Collaboration (February, 2012) making the case for increased funding for universities from the commercial and voluntary sectors.

bodies cover direct costs only, i.e. 33-55% of full cost recovery). Some local researchers are given access to HBS 'free of charge' for pilot work relating to research proposals. In a tiered pricing model aiming to recover full costs, industrial partners may be required to pay above cost in order to supplement local and academic research. However, there are no examples in the cases, or found in the literature, where full cost recovery is achievable (Chandras et al, 2009). A two tiered charging policy, where industry users are charged commercial rates, is also common for equipment sharing (N8 Sharing for Excellence and Growth, 2012). However, this research has shown that tiered pricing can cause tension, not only for industry users, but also for university researchers who can feel that commercial users are given priority of access.

- An additional influence for a biobank's pricing model is the stipulations outlined by the main funding provider

There are also significant differences in how price is calculated. Some biobanks calculate the price to cover supply costs (not including HBS, accrual, storage or infrastructure), some calculate price to cover direct costs only and some calculate to cover both direct and indirect costs (though on closer examination even those aiming to recover direct costs only have different criteria). Interviewees also reported that price often reflects the users' ability or willingness to pay, just as much as costs. Often this means that price levels are set by the market and are below cost. Profit generation may be possible in exceptional circumstances but there is limited evidence for this in the cases we examined. Indeed, even commercial biobanks may operate at low margins and are hence vulnerable to take-over (e.g. Asterand). This corresponds with market failure theories and may support arguments to subsidise biobanking (with public and private funds) as an activity whose outcomes generate economic and health benefits over time.

Access

All of the biobanks investigated provide access to HBS and visibility of HBS under conditions which are restrictive to some degree and can be characterised as 'Controlled Access'. Some restrictions are ethical or regulatory³⁹; some are legal; some are cultural; some arise from the business model. The dominant and most consistent restriction is the use of a committee to prioritise access and ensure the best possible use of HBS. Ensuring that HBS are used in scientifically and/or commercially valuable research contributes to the innovation potential of samples and the overall benefit they deliver. Once access committees are accounted for, some biobanks exhibit more elements of 'closed' than 'open' access, or vice versa. For example, the corporate biobanks (e.g. AZ) are more closed than open. In comparison commercial biobanks (i.e. for-profit) are more open than closed; assuming users are able to pay, which could operate as barrier for many. The biobanks located in universities and hospitals (as well as the charitable biobank) can be characterised as more open. Overall, level of access tends to reflect the host organisation, the function of the biobank and the related funding stream. In the cases we examined, publicly funded biobanks were more likely to support wider/external access; though internal and collaborating researchers tended to be prioritised. The corporate biobank was only accessible to internal researchers and contracting organisations; however, the development of a biobanking RI implies the mutual sharing of HBS (cross-access) between biobanks, and the firm supported this in principle. A commercial biobank (eg Abcodia) could participate in a cross-access arrangement if able to charge an access/service price inclusive of profit. There could still be a role for intermediaries and other types of companies when a RI exists.

³⁹ For example, some registered research tissue banks have permission to collect samples but not to distribute (except to studies with specific ethical approval) so there may be regulatory hurdles in relation to supply of material.

In all of the case studies, access to HBS is conditional upon mutual benefits (e.g. some form of research collaboration or financial transaction). This finding is very similar to the N8 equipment study and is not unexpected; it is clear that whatever access mechanisms are used they should be widely perceived as equitable and they should be inclusive rather than exclusive. The importance of perceived equity is also important in relation to the distribution of benefits arising from the use of HBS. Conflicting opinions about the ownership of outputs (including new knowledge, publications and products), were expressed by interviewees. At one end of the spectrum, interviewees argued that HBS are critical to the production of new knowledge and the biobank (or collecting individual) should be authored on any resulting publications (none of the interviewees asked expressed the opinion that IPR should be granted to the biobank). At the other end of the spectrum, no recognition was sought. A variety of arrangements are observed across the cases; for example, UK Biobank and the UKBBN do not conduct research so benefit for the biobank arises entirely from the enrichment of HBS annotation. Both organisations perceive their value to lie in supporting research undertaken by others. The NHSB also asks that users contribute to the enrichment of HBS and require published or patented data to be shared with the biobank as raw phenotypic data that can be associated with HBS. The NHSB does not require a stake in any intellectual property (IP) resulting from the research using HBS from their biobank, and is not authored on publications (it is necessary to acknowledge where the HBS came from). Overall, the consensus is emerging that data enrichment by users, combined with an acknowledgement for the biobank(s) in publications is best practice.

The data associated with HBS may be valuable to researchers independent of any physical HBS. However, this study relates primarily to the provision of HBS, so data is considered in the context of provision with HBS (the 'annotation'). It should be noted that well characterised, high quality data can be a valuable additional asset and this is indeed exploited by some of the biobanks. Apart from being an infinite resource (unlike the physical HBS), data increases in value through continual enrichment (i.e. the feeding back of research results and data into the database) and potentially, subject to appropriate consent, through follow-up to provide long term longitudinal information, including ultimate clinical outcomes. The individual biobank's guidelines relating to the provision of data were generally loosely defined; data was generally supplied as requested (with HBS). The organisation with the clearest approach was UK BioBank, who has open access policy and a set access fee for data with an additional charge based on the time and effort needed to retrieve the data. Others supplied associated data at no extra cost (essentially deeming it to be fundamental to the HBS as a whole price) or judged its value on a case by case basis (e.g. Abcodia).

A key issue is that access relies on prior awareness of collections; without knowing where HBS are held, it is difficult to access them. There is very little visibility of collections in the user community and this is a key concern for industrial and academic researchers alike⁴⁰. Many biobanks have limited strategies (or resources) for increasing awareness of collections, this is particularly true for smaller collections although less so for commercial biobanks and for discrete national biobanks such as the UK Biobank and the UKBBN. It is critical that a national biobanking RI addresses this issue, preferably through a single IT presence that enables researchers to search for quality HBS and related data across all affiliated UK biobanks.

IMPLICATIONS FOR A NATIONAL BIOBANKING RI

⁴⁰ One example of how these differences are being overcome is described briefly: the NCI is developing tools for interoperability that aid HBS resources in reporting and locating biospecimens, including OBBR and CaBIG efforts in the Specimen Resource Locator and the CaBIG Common BioRepository Model that enables deidentified biospecimen information via caGRID, and open source software platform" (National Cancer Institute's Best Practice for Biospecimen Resources, pg 21-32)

The cases and accompanying discussion above highlight a number of issues affecting the creation of a national biobanking RI. A strategic and coordination to UK biobanking has the potential to both increase the returns from biobanking (faster accrual of the right HBS in the right numbers and easier distribution of existing HBS) and to reduce costs (through standardisation and opportunities to reduce duplication). Conversely, the opportunity costs of not investing in a biobank RI are high.

A variety of benefits and opportunities have been identified that could be realised through the construction of a biobanking RI. Key benefits include increased visibility and access to HBS: 1) Access to large numbers of quality HBS and associated data should provide sufficient statistical power in research clinical trials (and performance assessment) enabling the rapid development of stratified medicine. This has the potential to accelerate the research cycle and strengthen epidemiological and experimental meta-analysis. 2) Access through a single portal could enable the planning of future HBS acquisition. 3) The creation of a biobanking RI could increase the value of HBS through the adoption of standards, ensuring consistency and promoting quality. 4) An RI could also increase the value of HBS through the enrichment of existing (and the provision of new) associated data. 5) A biobanking RI reduces costs for the: user (e.g. search costs across multiple biobanks); biobank (e.g. reducing speculative approaches and marketing costs), and funders (e.g. maximising the potential of existing collections).

However, there are significant challenges involved in creating a national biobanking RI. For a RI to operate most effectively it requires that many biobanks and existing project-based networks participate, this can be achieved over time by encouraging participation and highlighting the benefits of doing so. For this to happen, the benefits of participating must be greater than the costs of doing so. Encouraging participation requires careful consideration and relates to issues of trust⁴¹, intellectual property rights (IPR), and competition in science as well as across organisational types. It should be noted that academics are penalised for undertaking managerial and administrative tasks, as this interrupts their research and critically, individual HBS collectors' outputs. Although reward systems in industry are orientated towards organisational/project goals, similar issues exist. Reflecting this, guidelines on study co-design, publication practices and IPR need to be clearly defined at the outset. Recent research by the N8 on asset collaboration (N8, 2012) found that sharing (in this case of facilities) was contingent on reciprocity and perceptions of equity. The N8 research also found that sharing is most likely to occur for 'neutral assets' i.e. equipment acquired for collective use. Anecdotal experience within the biobanking and research community suggests that there can be reluctance amongst individual collectors to share HBS; however, a biobanking RI could be constructed as a shared asset, helping to overcome some of these issues.

Overcoming internal and intra- institutional barriers may also create significant new costs, associated with the required changes, for individual collectors and biobanks in an institution wishing to participate in a biobanking RI. A coordinated effort is required to design an overarching funding strategy that recognises the costs associated with maintaining local biobanking infrastructure if these institutional barriers are to be overcome. Activities associated with maintaining a RI include dedicated staff to interface with upstream and downstream users; management of information systems and their interfaces, especially systems concerned with HBS history; ensuring appropriate training of biobanking personnel; ensuring compliance with current consent and access governance policy; negotiating and implementing consensus standards with other biobanks. A form of coordinated (or aligned) continual funding for these types of activities could increase cost transparency and overcome barriers associated with funding. It is important that the construction of a RI maintains the diversity and independence of biobanks whilst enabling coordination across the biobank population.

41 For example, trust that HBS will be used in the best possible way.

CONCLUSIONS

This report has summarised the qualitative research undertaken by The University of Manchester for STRATUM. The aim of this research was to examine and develop a 'cost model' for a national solution to the lack of sufficient numbers of high quality HBS for research, and specifically for the development and adoption of stratified medicines. The case studies generated for this report (seven individual biobanks and one biobank network) have enabled the main cost drivers associated with biobanking to be identified. However, during the course of this research it became clear that most biobanks are not fully aware of their costs and many costs are 'hidden', often as a result of complex inter-institutional arrangements and mixed funding streams. Those biobanks that have invested in calculating their costs have found that the costs associated with HBS vary according to sample type, accrual and access arrangements, as well as institutional context. Overall, the cost of HBS is high. All the biobank case studies who charged access fees for HBS set the price according to the ability or willingness of users to pay, rather than to try to recover their full costs. The empirical data aligns with established principles for the public funding of science and strongly suggests that a full cost-recovery model is not viable.

The cases have also enabled the identification of existing financial arrangements that are contributing to the current situation of market and system failure⁴², as well as opportunities to overcome these failures. Public returns exceed private returns in biobanking and there is a strong rationale for public funding of core activities. The existing fragmentation of biobanks and the lack of HBS visibility incur high search costs for users, duplication of funding, underutilisation of existing HBS and limits opportunities for strategic planning (e.g. prioritising accrual of specific tissue types or disease areas; conducting multi-partner research projects). Fragmentation also undermines confidence in consistency of HBS and impedes the sharing of best practice, including quality standards, amongst biobanks. Gaps in financing the maintenance of collections and data associated with HBS can result in the loss of valuable resources and unnecessary duplication, for example, of equipment and HBS types within specific disease areas. Financial gaps also reduce cost transparency as biobanks create opportunities for cross subsidisation.

Overcoming these problems requires a strategic approach at the national level. In aggregate, our cases studies, combined with existing research, provide additional empirical evidence that there is a requirement for public funding of biobanking, and that it is useful to consider biobanking as a distributed national RI involving some form of coordination. Financing biobanking as a national distributed RI (i.e. coordinated network) could support a thriving academic and industrial R&D base in the UK. The opportunity costs of not developing a biobanking RI are high in medical, social and economic terms. A number of observations and general recommendations follow from this research:

Financial arrangements

There are benefits associated with biobanking being located within a broad policy framework, for example a top-down approach may be required where there is a broader disease strategy or an unmet public need. However, there are also benefits of biobanking being project-orientated and led from the 'bottom-up'. A national centralised biobanking facility is neither desirable (from an access, cost or innovation perspective) nor viable (operationalizing it would be extremely difficult if not impossible). The most efficient and effective way of constructing a sustainable biobanking RI is coordinating across existing and emerging biobank and biobank networks. The cases presented in this report illustrate that it is not possible (or desirable) to apply a standard cost model across such a diverse population.

⁴² This is an international issue. For an overview of problems experienced in the US due to fragmented and uncoordinated biobanking, see - <http://www.futurity.org/health-medicine/biobanks-worry-specimens-will-go-to-waste/>

Coordination requires dedicated resources, including funding for strategic management duties (e.g. 'buying' the time of representatives from stakeholder organisations); a permanent operational staff (e.g. Director, quality coordinator, IT manager, network development coordinator, any other necessary roles); a coordination centre (with appropriate facilities and IT equipment); and necessary activities (e.g. travel and subsistence, communication). Co-ordination should be financed centrally by public funds, most likely the research councils. This builds on existing efforts by funders and others to build an RI through networking across tissue/disease areas. Potentially, this funding could be supplemented with industrial sponsorship through a mechanism such as a tiered RI membership fee or contributions to the central funding stream. The details of such a structure would have to be carefully considered so as not to discriminate against potential users, particularly SMEs with fewer capital resources.

Simultaneously, the financial arrangements for existing individual biobanks should be reconfigured. Beyond the initial construction stage (the most expensive stage where, paradoxically, most funding has tended to be available) biobanks struggle to finance their operations (e.g. Chandras et al, 2009). Based on the research undertaken for this report, the recommendations for appropriate financial arrangements can be summarised in three stages:

1. Acquisition of HBS: acquisition can be organised in different ways, however, it is frequently project-orientated. The financing of prospective HBS accrual and storage (for a defined period) should continue to be costed (built-in) to project proposals⁴³. This approach supports diversity and competition whilst ensuring that acquisition is driven by research needs.
2. Facilities: These are the physical components of a biobank⁴⁴ that are currently funded through projects. Overcoming funding gaps requires on-going funding. A separate funding stream for facilities could support maintenance and enhancements of collections, innovation in biobanking technologies and techniques, as well as the uptake of best practice. Many biobanks are supported by institutional funds to some degree; this arrangement could be extended so that central public funds allocated to biobanking are distributed to host institutions in the public sector through the research councils and other routes (including the NHS)⁴⁵.
3. Access/Distribution of HBS: there are marginal costs associated with distribution and these costs should be paid directly by the (secondary) user through; a) project funding for publicly-financed R&D; b) project funding for public-private R&D partnerships, and c) an access fee for privately-financed R&D. These fees could be tiered so that industrial users subsidise academic/not-for-profit users.

Access arrangements

'Controlled access' with open access features supports the 'best possible use' of HBS and associated data. The majority of biobanks in the case studies control access through a committee or other mechanism designed to assess the scientific merit of project proposals. This arrangement reflects best practice and can support knowledge sharing whilst conserving valuable finite physical HBS. Open-access (with usual

⁴³ Financing accrual is complicated by regional variation in the ability of biobanks to access NHS service support costs. The UKCRC brain bank strategy report (2008, p11) recommends that brain biobanking should be designated as a research activity within the NIHR agenda and funding for tissue collection 'could be obtained directly as a research-relevant 'service-support' cost, or indirectly through cost-recovery from grant funding to individual banks/the coordinating centre' (Steering Committee, 2010, p12). The provision of financial support through the NHS is an important issue that could not be covered effectively by this report and requires further attention.

⁴⁴ Finance is required to cover the following costs; dedicated biobank staff salaries; non-staff costs including equipment, local IT systems, maintenance and consumables; estate costs, including rent and utilities; replacement cost depreciation, other.

⁴⁵ Charities and other major funders of research supplement RI directly (via the RCs) or through research projects where a specified amount is allocated to biobanking and paid to the host institution (but held by the biobank to ensure direct investment).

anonymity practices) for associated data (and software) has the most beneficial impact on knowledge creation and innovation. In order for a biobanking RI to operate as a dynamic and sustainable resource (i.e. increase in value over time) it is highly desirable that HBS is continually enriched with high quality annotations (both clinical and experimental). This data enrichment requires that users submit new knowledge created from the use of HBS (after publication or patenting) to the biobank or associated data controller. Ideally, the biobank could link the HBS to external data sources, e.g. donor's health records. To incentivise enrichment and minimise the resource costs to users, the biobank (or coordinating body) should undertake the data enrichment process. This will increase compliance by reducing the time and effort costs to the users, as well as maintaining format/ontological consistency and quality. Data enrichment could be mandated by funders.

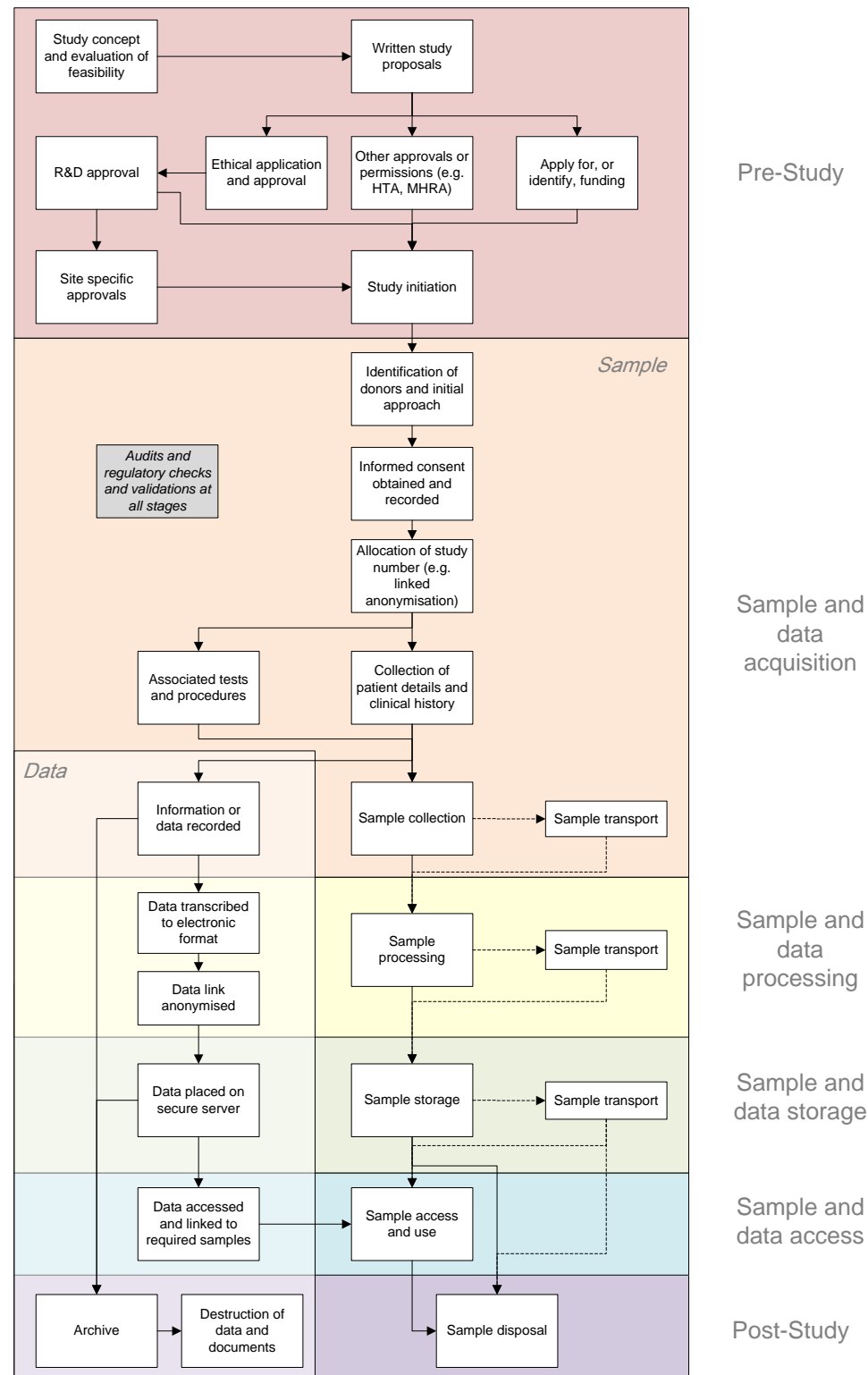
To reduce the high search costs for users (for samples to be visible and easily accessible), a national biobanking RI requires a searchable register of HBS (including associated minimum data set). The register should be easily searchable. Search results could identify batches of HBS with the desired annotations whilst maintaining donor confidentiality. Analysis of users and their searches on the portal has the potential to provide valuable data on changing national and international R&D interests and priorities.

The scientific value of HBS is optimised when HBS and data are consistent across the network and when policies are aligned⁴⁶. The emergence of a national biobanking RI should build on previous efforts (e.g. The Human Tissue Authority (HTA) codes of practice) and enrolment in the RI will be dependent on the adoption of a core set of policies and standards (See STRATUM WP3 and 4). Individual biobanks could benefit directly through the diffusion of best practice, and access to standardised policies that meet (or exceed) regulatory requirements. This will benefit users by increasing the quality and consistency of HBS.

The creation of a national biobanking RI has the potential to increase the medical, social and economic returns of biobanking (by achieving critical mass, optimising resources and increasing transparency and accessibility), as well as to reduce the costs of biobanking (through standardisation, reducing duplication, reducing transaction costs and enabling synergies). This report has focused on the supply side to examine the 'as is' situation for a variety of biobank types in the UK, and identifies issues with existing costing and funding arrangements. This research should support on-going efforts to design a coordinated approach to biobanking at the national level.

⁴⁶ The implementation of a national biobanking accreditation system would support standardisation; although this has cost implications (e.g. license fees, inspections, conformance), an accreditation system could overall benefit and reassure the wide range of stakeholders in biobanking.

APPENDIX 1: SIMPLIFIED HBS LIFE CYCLE



APPENDIX 2: SEMI-STRUCTURED INTERVIEW QUESTIONS

Questions were asked in a semi-structured manner using the following general guide/template:

Background

1. Who set up the **biobank**?
 - a. When?
 - b. Why? (*as a biobank? an extension of project?*)
 - c. Where is it hosted? (e.g. hospital clinical lab, hospital research lab, university research lab)
 - d. Who benefits from the biobank?
 - e. How has it evolved over time?
 - f. What is the overall governance structure? (personnel/organisational map)
2. What types/classes of **samples** are collected and stored? (*e.g. whole blood, plasma, serum, solid tissue, DNA, sputum, urine*).
 - a. How many samples? (*are these finite*) *How many tubes, containers etc?*
 - b. From how many donors?
 - c. Are fresh (unfrozen, unfixed) samples (e.g. tissue in DMEM) provided to researchers?
 - d. How is quality safeguarded?
 - e. Is the BB used for short or long term storage of samples?
 - f. What IT system (LIMs) does the BB use?
 - g. What are the associated costs for different sample types and processes?
3. What type of donors? (Patients, healthy volunteers)
 - a. Where from? (e.g. hospitals and other clinical care settings, other biobanks, commercial suppliers, other)
4. Is any associated **data** stored by the biobank? (i.e. donor information; sample information; sample tests/results/analysis)
 - a. Is this data in a standardised electronic format. Specify format
 - b. Is there a specified minimal dataset?
 - c. Are there any plans to review the storage of data?
5. What **stages of banking** involved? (*consent, collection, processing, storage, distribution*)
 - a. Does the BB operate a **QC/QA** scheme?
 - b. Are standardised **procedures** in place? (*e.g. SOPs, standards*)
 - c. Is BB registered under NRES/HTA?
6. Is the biobank linked to other biobanks or a member of any networks?
7. Samples, IT system, governance?

Samples

		Current	2011	2010	2009	2008	2007
How many projects do/did you collect samples for?							
How many samples did you receive each year?							
How many patient's samples do you currently store?	Low temperature freezers						
	Liquid nitrogen						
	Other (specify)						
	Other (specify)						
How many individual aliquots/slides/preps do you currently store?	Low temperature freezers						
	Liquid nitrogen						
	Other (specify)						
	Other (specify)						
How many samples did you distribute each year?							
How many samples did you dispose of each year?							
Please indicate the main types of samples stored as a relative proportion (%) of all those held:							
	DNA						
	RNA						
	Whole blood						
	Sputum						
	Serum or plasma						
	Solid tissue (respiratory)						
	Solid tissue (non respiratory)						
	Urine						
	Other (specify)						
	Other (specify)						
	Other (specify)						
	Other (specify)						
	Other (specify)						
	Other (specify)						
	Other (specify)						
	Other (specify)						
	Other (specify)						
Please indicate what percentage of samples are from normal/healthy volunteers: <input type="text"/> %							

Income

1. What funding does the biobank have?

- Research / research infrastructure funding? Why? For what? (*set up, maintenance, support, mixed revenue and proportionate distribution*)
- Other sources of income? (*Access fees? Service provision? Institutional support?*)
-

	£	Current	2011	2010	2009	2008	2007
What was the annual income?							
What percentage of income is attributable to biobanking?							
How much income comes/came from (extra detail on exact sources where possible):							
	Grants for biobanking						
	Grants for projects						
	Private finance						
	Cost recovery						
	Host support						
	Other						
	Other						

Please provide any further details of sources that funded your biobank:

Specify

Costs

- Does the biobank have a ringfenced budget? (*if so, are we able to view the budget?*)
- What are the costs of running the biobank (incl. any indirect/institutional costs?)

Initial set-up costs

	% attributable to biobanking	Cost £	% incurred by biobank	% incurred by host
Refurbishment (labs)				
Refurbishment (offices and other areas)				
Freezers				
Other storage (e.g. liquid nitrogen tanks)				
Automation and robotics				
Analysers and testing equipment				
IT equipment and infrastructure				
Other (specify)				
Other (specify)				
Other (specify)				

Annual operating expenses

	% attributable to biobanking	Cost £	% incurred by biobank	% incurred by host
Space rental				
Building and facility maintenance				
Electricity				
Phone, water, other services				
IT service and maintenance				
Equipment maintenance/service/calibration				
Equipment renewal				
Liquid nitrogen				
Reagents, chemicals, kits				
Tubes, boxes, other sample storage				
General consumables & H&S				
Other (specify)				
Other (specify)				
Other (specify)				

Expenditure

Please provide a breakdown of staff directly employed by the facility:

	Total salary cost p.a.	Number of employees	Proportion of time spent:		How many of these staff are employed for one specific project?
			Biobanking	Other activities	
Senior managers/directors					
Managers					
Technicians					
Administrators & support staff					
Specify					
Specify					

Please provide any information on other staff who support the facility but are not directly salaried by it:

Job titles, roles, contribution to biobanking facility, any other details
Specify

4. Costs across sample life cycle (Including percentage attributions; does this vary for type of project?)
- How much does each step cost?
 - Who incurs these costs (if not your biobank)?

"Typical study"

	Is the biobank involved in this process?	% of the costs incurred by biobank*	Typical cost in £s (fill in as much as appropriate)		
	1. Never 2. Rarely 3. Sometimes 4. Very often 5. Always		Cost per sample	Cost per patient	Cost per project
Overall (project as a whole)	5. Always				
Study concept and idea	1 2 3 4 5				
Obtaining or identifying financial support/funding	1 2 3 4 5				
Obtaining ethical approval	1 2 3 4 5				
Obtaining all other regulatory and site specific approvals	1 2 3 4 5				
Identifying donors/patients/volunteers	1 2 3 4 5				
Obtaining consent	1 2 3 4 5				
Collecting clinical and demographic details	1 2 3 4 5				
Electronically recording clinical/demographic details	1 2 3 4 5				
Allocating a study ID/number	1 2 3 4 5				
Preparing/supplying sample collection pack	1 2 3 4 5				
Obtaining a sample from the volunteer	1 2 3 4 5				
Transport of sample for processing	1 2 3 4 5				
Sample processing	1 2 3 4 5				
Transport of sample for storage	1 2 3 4 5				
Phenotypic/clinical data storage (per year)	1 2 3 4 5				
Sample storage (per year)	1 2 3 4 5				
Obtaining approval to access samples or data	1 2 3 4 5				
Sample access	1 2 3 4 5				
Linking sample with associated data	1 2 3 4 5				
Sample disposal	1 2 3 4 5				
Document and record archival	1 2 3 4 5				
	1 2 3 4 5				

Transactions

5. Who can access samples and/or data?
 - What are the costs associated with providing access to samples and data?
 - Is there an access fee?
6. How many samples have been distributed/not distributed? To whom? Any returned due to quality?
7. Can BB release samples without full project ethical approval? Other authorisation? Costs?

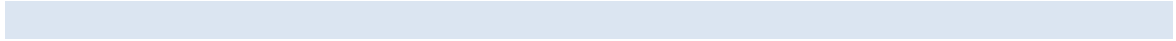
Constructing a research infrastructure

8. How would you **structure** a national infrastructure?
 - *e.g. a network? distributed samples and centralised IT?, centralised physical storage and IT? Anything in between?) Organised geographically? By sample/disease/type?*
 - *Should there be different roles for different components of an RI/ network (e.g. stabilisation in hospitals, storage at and distribution from a central facility?*
9. What would you expect / want from a national biobanking network?
 - *E.g. more collaborations, faster turnaround, quality & quantity of samples, value of samples access, lower costs, any added scientific or other value?*
10. What are the main barriers to network construction?
 - *e.g. fear of lower quality research? relinquishing control? funding? Diverse standards?*
11. What are the main enablers to network construction?

- *a coordinated quality management system?; a national catalogue of fully annotated samples; national access policies and procedures?; a standard national / international sample ID method?*

12. What are the main tensions, in your view?

- *e.g. access fees could impact on deposits and use, fees could reduce access? How to stimulate inputs/network participation? How to maintain a dynamic resource, i.e. increasing in value?*



APPENDIX 3: CASE STUDY INTERVIEWEES

Primary interviews were conducted between May and October 2012. Follow-up interviews and secondary data were obtained up until March 2013.

Number	Case Study Name	Organisation	Interviewees & contributors
1	Abcodia	Abcodia	Julie Barnes Ian Jacobs (by email)
2	AstraZeneca	AstraZeneca	Rachel Mager Chris Womack
3	Biobanking Solutions	Centre for Integrated Genomics Research (CIGMR)	Kate Dixon Bill Ollier Martin Yuille Melanie Lythgo Craig Sykes
4	Fresh Tissue Supply	Sherwood Forest Hospitals NHS Foundation Trust & University of Nottingham	David Walsh (by phone) Julie Corfield
5	Nottingham Health Science Biobank (NHSB)	Nottingham University Hospitals NHS (NUH) Trust	Balwir Matharoo-Ball Brian Thomson (by email)
6	Small Research Collection	Salford Royal NHS Foundation Trust and University of Manchester	Ariane Herrick Holly Ennis (by phone)
7	UK Biobank	UK Biobank	Paul Downey Pamela Moore
8	UK Brain Banks Network (UKBBN)	UKBBN	James Ironside Chris Tindal Joanna Jenkinson (MRC; by phone)

APPENDIX 4: FULL EMPIRICAL CASES

The full empirical cases are presented in alphabetical order.

Case Study 1: Abcodia.....	49
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Case Study 3: Biobanking Solutions (Biobanking component of CIGMR)	62
Case Study 4: Fresh tissue supply	72
Case Study 5: Nottingham Health Science Biobank (NHSB)	75
Case study 6: Small research collection	83
Case Study 7: UK Biobank	86
Case Study 8: UK Brain Banks Network (UKBBN)	92

FULL CASE STUDY 1: ABCODIA

Compiled from secondary data and interviews with;

- Interviews with **Dr Julie Barnes** (CEO). 25th June 2012 and subsequent email correspondence.
- Email correspondence with **Professor Ian Jacobs** (co-founder) from Oct 2012.
- Secondary data was sought from the websites of Abcodia; UCL Institute for Women's Health; and the MRC; as well as from press releases.

Institutional Context

Abcodia is a spin-out company from University College London. Abcodia was created to generate value from a collection of serum that had been created by UCL as part of a prospective screening trial. The establishment of Abcodia limited the need for long-term external funding for the biobank storage and maintenance, whilst also aiming to achieve maximum academic and commercial use of the biobank resource, an income stream for the research unit and a return on the initial investment. The aim of the company is to support the discovery and validation of biomarkers by commercial organisations and academics, thereby improving disease diagnosis and screening, primarily in cancer. Abcodia is a for-profit firm operating a 'value generation model'. The company is product focused with the aim of leveraging the £30m spent on HBS accumulation to support the commercialisation of diagnostic tools.

Abcodia was founded by a team of individuals that included Professor Ian Jacobs (now Vice President of The University of Manchester, Dean of the Faculty of Medical & Human Sciences, Director of the MAHSC) and incorporated in 2010. The company was formally launched on the 21st February 2011 with Dr Julie Barnes as CEO (ex-GSK, and BioWisdom) and Chris Hodgkinson as COO (ex-GSK, BioWisdom and National Lottery). Dr Andy Richards serves as the Chairman (business angel, biotech entrepreneur) and Prof Ian Jacobs (principal investigator for the UKCTOCS study), Andrew Elder (representing Albion Ventures) and Claire Hooper (representing UCL Business Plc) all serve as Non-Executive Directors. Wendy Alderton is Director of Science and Mike Fisher is Director of Business Development. The current shareholding of Abcodia comprises a mix of institutional and individual shareholders, with UCL, via UCL Business retaining a major share.

The company is registered at The Network Building, 97 Tottenham Court Road, London, W1T 4TP. However, this is a holding address as the company has no premises. The management of the firm is 'floating', with communication via smart phone or online communications, allowing the team to operate remotely, with occasional meetings held in the UCL department of gynaecological oncology or the offices of UCL Business. HBS were collected at 13 regional centres in the UK and are now stored in a commercial biobanking storage facility. All studies are conducted in accordance with ethical approvals, and the Abcodia/UCL Steering Committee oversees access to the HBS, thus ensuring the scientific quality of all collaborations.

Abcodia has an exclusive commercial licensing agreement with UCL Business and the rights to commercialise any resulting intellectual property (IP) generated from the use of this serum biobank. The

'custodianship' and management of the HBS is retained by UCL. On 24th May 2011 Abcodia announced it had raised £1m in funding from UCL Business (the technology transfer office of UCL) and Albion Ventures LLP (a venture capital company). This funding was to undertake translational studies using the pre-diagnosis and longitudinal serum collection that is exclusively licensed from UCL.

Historical Context

The longitudinal serum collection is the by-product of a prospective clinical trial - the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS); the world's largest ovarian cancer screening research programme.

The research programme commenced in 2000 and will be complete in 2015, with HBS collection between 2000 and 2011. It was funded jointly by the MRC, NHS R&D, Department of Health, Cancer Research UK and others, including the Eve Appeal; the fund raising section of the Gynaecology Cancer Research Fund. Prof Ian Jacobs is the PI; Co-Investigators include Prof Usha Menon who is the UKCTOCS trial Coordinator. The main aims of the study were; 1. to measure the impact of screening on ovarian cancer mortality; 2. to document the performance characteristics of ovarian cancer screening (sensitivity, specificity etc); 3. to investigate the morbidity, resource and psychological implications of undertaking ovarian cancer screening. Biobanking was not supported by the funding agencies but was recognised by the PI as being an important academic opportunity and resource beyond the focus on ovarian cancer; extensive efforts were made to secure support for the serum biobank to enable future assessment of novel tumour biomarkers. Donors were informed that HBS would be taken for future research studies focusing on the early detection and treatment of disease and gave consent for this purpose. UKCTOCS was originally based at Queen Mary's University London before moving to University College London in 2004.

Recruitment to the trial took place between 2000 and 2005, when UKCTOCS collected serum HBS from over 200,000 healthy, post-menopausal women donors. Donors attended one of the 13 trial centres at NHS hospitals in England, Wales and Northern Ireland. Each centre had a dedicated trial team lead by a consultant clinician, composed of; one research nurse, phlebotomist, clerk and ultrasonographers. Consent was requested, and in the majority of cases, given to use HBS for academic and commercial research. Of the 202,000 donors, over 50,000 women gave serial HBS over time (in some cases up to 10 years after treatment) and 150,000 gave a single HBS at the outset of the study. The HBS were then transported to a CPA accredited laboratory at UCL, centrifuged, and placed into sealed straws with unique barcode labelling. These were transferred for long-term storage in fully monitored liquid nitrogen commercial biobanking facilities at Fisher BioServices (ThermoFisher Scientific) in Bishops Cleeve. This facility is accredited to ISO9001:2008 and all staff screened to BS7858:2006.

The UKCTOCS serum biobank now contains over 5 million longitudinal serum HBS accompanied by a comprehensive database of phenotypic, demographic and disease incidence. All subjects were free from cancer for the previous year on entry, but many have since developed cancer, thus, these HBS represent a rare cohort of pre-diagnosis HBS. As the UKCTOCS trial recruitment phase approached completion, the question of use and long-term storage of the HBS was addressed. Collection of the HBS had taken place on the basis that there was a unique opportunity to store potentially valuable research HBS with relatively little extra effort while the donors were attending for the 'main' parts of the study. However, it was unclear where funding for this storage and research would come from. Further public and charitable funding was obtained from University and charitable sources to develop and maintain the biobank. As the

trial drew to a close, the need for a longer term sustainable solution for supporting and developing the biobank became a priority. The concept of Abcodia was developed by Professor Jacobs with assistance from and external consultancy (4D Biomedical, Cambridge) between 2006 and 2011. Eventually the business case was supported by UCL Business and attracted external investment.

Biobanking activities

Abcodia does not own the UKCTOCS serum collection but currently has the exclusive commercial rights to use it. They are not involved with the collection of samples as these have already been collected as part of the main study. They also do not directly store the samples; this is contracted to a commercial organisation, with the charges covered by Abcodia. Abcodia operate a flexible business model which they indicate allows access to samples and expertise, while sharing the risks and rewards of biomarker discovery and validation; essentially the firm is looking for collaborators to develop biomarkers. Their aim is to speed-up the commercialisation of diagnostic technologies (biomarkers) for a variety of diseases, focussing in particular on cancer screening. Every collaboration is negotiated on an individual basis to obtain mutually beneficial terms. Through technology partners, Abcodia is also performing its own discovery experiments that may lead to the discovery of biomarkers for cancer screening.

Abcodia works to make connections with academic and commercial groups who can benefit from access to the unique preclinical sample set available for biomarker development. The company also facilitates the distribution of samples and manages the flow of associated data. Any data that is generated is provided back to the company for research use. Access to data generated from the samples allows Abcodia to identify connections which may not be obvious to individual collaborators working on separate diagnostic areas. Abcodia stress that they are doing far more than a 'typical' biobank, by offering a perspective that facilitates progression through the product development regulatory landmarks.

In addition to commercial collaborations, Abcodia maintains working relationships with academic researchers. Financial returns are less clearly defined, but the profile associated with publications, the knowledge generated and the opportunity to offer a route to commercialisation, are important drivers in these relationships. Abcodia report that they also offer advice about any potential financial implications of related academic research, in particular encouraging the researchers to patent (before publishing). Importantly this model supports continued academic research at UCL, in addition to the firm's commercial activities, whilst also providing a 'bridge' between academia (particularly UCL researchers) and industry.

Income

In the year 2011-2012 Abcodia received initial seed funding, and £1m from Albion (venture capital firm) and UCL Business (technology transfer office). In July 2012, Abcodia had not sought any grant income but are in receipt of undisclosed income from commercial sources.

Revenue is primarily generated through collaborations with commercial partners. Partners pay Abcodia for access to the serum biobanks for a defined purpose and Abcodia support this through a variety of routes (see above). Fees could include initial upfront license payments and subsequent payments linked to milestones as well as royalty revenue from the sales of any products resulting from the collaboration. It is predicted that the commercially viable products will include CE marked products, laboratory derived tests and distributed tests developed and launched subject to regulatory (e.g. FDA) approvals. As many of

the milestones tend to be regulatory in nature, this provides clear landmarks allowing unambiguous assessment of the stages of progression of a product.

Disclosed partnerships to date include (chronologically):

- 1) Nov 2011 - Oxford Gene Technology: Abcodia provide data mining expertise to deliver optimal HBS sets from its large prospective serum biobank, to identify HBS taken from individuals up to 7 years before the diagnosis of pancreatic cancer. OGT apply its functional protein array platform and its Geneefficiency microRNA profiling array to identify pancreatic cancer specific biomarkers that can be used as diagnostic indicators of developing pancreatic cancer. Both OGT and Abcodia contribute expertise in experimental design and analysis.
- 2) Dec 2011 - Exploristics; optimising Abcodia's research programme through the application of study simulation capabilities.
- 3) February 2012 –VolitionRx; collaboration for the development of biomarkers for early detection of cancer (lung, colorectal and pancreatic). Cameron Reynolds, Chief Executive of VolitionRx, said: 'The collaboration with Abcodia is a key partnership for us. Access to Abcodia's samples will potentially expedite the development of our blood-based diagnostic technology, Nucleosomics. We believe that data from validation of thousands of samples, across multiple cancer areas, will help us to reach our goal of applying for European CE Mark approval this year.'
- 4) April 2012 –Biouniversa SRL; this collaboration with a spin off from the University of Salerno was formed to advance the development of the BAG3 protein biomarker for use in the early detection of pancreatic cancer.

Other partnerships exist but remain undisclosed.

Expenditure

Abcodia operate within a commercial environment and were unable to disclose data on expenditure. In line with other biobanks, the majority of costs are allocated to staff costs. Senior staff include a Chief Executive Officer, Chief Operating Officer, Director of Business Development and a Director of Science. Abcodia also remunerate a Chairman, and a number of Non-Executive Directors. Within UCL they support and pay for a single full time equivalent to help with project co-ordination, statistics, data-mining, experimental design, data generation and general liaison. The majority of the services that are directly related to the day to day running of the biobank are contracted out.

In terms of buildings and facilities, the company has limited liability. Senior staff tend to work from home, and meetings take place in individual's offices in (for example) UCL or meeting venues which are hired as required. Travel and related expenses are incurred, and consultants may be utilised for specific project collaborations. By contracting out the HBS storage, there are few hidden costs associated with the biobanking, although it is unclear whether they are charged at commercial rates (storage is negotiated by UCL), regardless, this should be balanced by the benefits of economy of scale.

The company will also have costs associated with its overall operation to do with communications, financial advisors, accountants, advertising and promotion. The company benefits from institutional

support offered by UCL, and the network of contacts that the individual senior staff have through their other (e.g. academic) positions.

Collaborations and networks

Abcodia maintains it is uniquely positioned to contribute to the overall diagnostic process. One of its key selling points is that it can provide an interface with other relevant organisations to maximise the potential collaborative opportunities. It is unclear, however, to what extent it combines resources with other biobanks; in many respects, it oversees such a large and unique collection that it is virtually self-contained and does not need to acquire extra HBS. If it does, these are likely to be obtained directly from source (i.e. by approaching donors), through its firm links to the UCL research teams. It is likely, that due to the commercial and sensitive nature of its clients and contracts, any ambitions to combine HBS resources would be entered into cautiously.

FULL CASE STUDY 2: ASTRAZENECA

Compiled from secondary data and interviews with:

- Interviews with **Rachel Mager** (Associate Director, Discovery Sciences Biobanks, and Global Head of Biobanks, AZ) and **Chris Womack** (Principal Clinical Histopathologist and Head of Oncology Translational Science Molecular Pathology group) at AZ, Alderley Park. 11th July 2012, with subsequent email and telephone correspondence.
- Secondary data includes: PPT presentations (provided by Julie Corfield, Rachel Mager and on the web) and information from <http://www.astrazeneca.co.uk/research-and-development>

Institutional context

AstraZeneca (AZ) is a global pharmaceutical and biopharmaceutical firm with corporate headquarters in the UK. AZ employs approximately 11,300 people across 14 principal R&D centres in 8 countries and invests over \$4bn in R&D globally. Despite a series of worldwide job cuts across all areas over recent years, there remain over 2000 R&D staff in the UK who, in 2010, accounted for approximately £1.3bn of the R&D budget. The Global Biobank section of the operations is funded through the Screening Sciences and HBS Management group of Discovery Sciences, which is a department within the R&D division 'Innovative Medicines'.

The Global Biobank is split across six main sites: Alderley Park (AP) (UK), Mölndal (Sweden), Shanghai (China), Bangalore (India), Boston (USA) and Sodertalje (Sweden). For the purposes of this case study, we have focused on the biobanks being managed by Discovery Sciences (AP and Mölndal), although all of the biobanks operate in global matrix organisation overseen by a HBS Governance Team. The biobank in Sodertalje is set to close, and management of the biobank in Boston will transfer from Oncology to Discovery Sciences.

The Global Biobank serves AZ globally and locally, and the running costs are funded by Discovery Sciences. Biobanking is considered a corporate-wide enabling activity, as demonstrated by its organisational proximity to the key areas of Screening Sciences and HBS Management, which includes the Compound Management group. High quality, well annotated HBS are increasingly recognised as a key asset for the business, and so subject to the equivalent quality, governance and cost issues as compounds. Notably, Global Biobanking also maintained their staffing levels in the last round of corporate restructuring (prior to 2013).

The aim of the global biobank at AZ is to collate, store and distribute annotated HBS, primarily to internal users. Principally, the global biobank acts as a curator for internal collections and as a broker for access to AZ approved external tissue biobanks and suppliers. This role reflects the organisation of R&D at AZ whereby clinical trials are outsourced through Contract Research Organisations (CROs) which co-ordinate the collection of HBS that are usually transferred to AZ at the end of the trial. The accrual of HBS for

internal projects is usually funded directly by the research group concerned, and normally obtained via external biobanks or collaboration agreements, with appropriate material transfer agreements (MTA) put in place. Over recent years, AZ has increasingly become involved in distributing HBS to external collaborators. For example, if undertaking method development for a project then AZ may provide HBS and antibodies to partners. Rather than act as an open access biobank, this is only undertaken as part of collaborative work under legally binding contracts; the Clinical Research Organisation (CRO) may access HBS on AZ's behalf. In addition, research collaborations with academics have been used to generate HBS for both parties, and collaborations have been fostered by the funding of post-docs.

The biobank serves to enable R&D, with the biobanking group work across the R&D and Clinical Interface for governance of HBS, including procuring HBS, outsourcing processing activities, auditing internal biobanks and quality controlling HBS that are brought in. The development of IT support systems such as the AZ BioBank Application (ABBA; see later) and GenoTyping LIMS at the DNA Biobank, has also been conducted across the interface of R&D and Clinical.

Like many pharmaceutical firms, AZ needs to access external HBS in order to obtain enough suitable research HBS that conform to strictly defined phenotypic and quality profiles. In order for any findings to be statistically valid, and for the development of personalised medicines, large cohort sizes as well as geographic and ethnic variation may be required. Developing companion diagnostics requires large numbers of HBS for screening because biomarkers and genetic mutations are only present in subsets of the population.

Historical Context

The aim of AZ's biobank is to make collections available for exploratory research. AZ has HBS dating back to 1953 that were collected when the firm was ICI (Zeneca demerged from ICI in 1993 and merged with Astra in 1999 to form AZ). HBS have been collected for clinical trials and are usually retained for 15 or 25 years, at which point they were normally disposed of, though the associated data are retained. Some HBS are also collected through research projects, and provided consent and protocols permit these may be retained in case they are valuable for exploratory research. The DNA biobank has existed since approximately 2000 and is now integrated with the biobank in Discovery Sciences.

In 2000, in response to an impending Swedish Law on Biobanking, the Human Tissue Research Project (HTRP) was instigated at AZ. The aim of this project was to pull together governance processes and develop procedures for HBS life cycle management. In addition to documenting and defining key procedures, the main output of the HTRP was the first AZ global policy on biobanking governance. This set out the company's strategic approach to future biobanking, in essence stating that their science policy would drive the collection of HBS. Major revisions to the policy which were implemented in January 2008 followed a project called Biological Samples Enabling Solutions (BIOSES) which from 2007 aimed to harmonise procedures globally⁴⁷ (not just those affected by or identified through the Swedish or UK biobanking legislation). The aim of this revision was to harmonise procedures in the research and clinical

⁴⁷ Globalisation of standards was initiated in 2003/04

parts of the organisation, that is, to move towards an overarching governance model. The most recent round of revisions has developed the policy, enabled development of the global biobank, and allowed the creation of a global IT system to support the biobank (including a system for the complete inventory management of HBS).

The BIOSSES project undertook an options appraisal of AZ biobanking in 2008/2009 to determine whether it would be more cost effective for AZ to centralise biobanking internally or whether to outsource the activity. The costing figures presented in the following section are based on the cost analysis process undertaken as part of this appraisal. As a result of the review, it was decided to set up two major hubs (Sweden and AP), with two smaller biobank sites (one of which has since moved to Sweden). During AZ restructuring in 2011 the Global Biobanking division was organisationally positioned in Discovery Sciences, which provides services across the organisation. The organisational location of biobanking within Discovery Sciences (rather than placing it, for example, within the oncology group, or the personalised health care group) demonstrates the wide remit associated with biobanking at AZ, and its perceived importance as a capability in the future.

High level policies are currently (2012) under review again, in response to a wider corporate strategy towards open innovation and outsourcing of some services and to ensure the internal policies support the new corporate strategy. In March 2013 AZ announced that it would be undergoing a major organisational restructuring.

Biobanking activities

The AZ Global Biobank in the UK has a Human Tissue Authority (HTA) licence and is ethically approved as a Research Tissue Bank. AZ is not directly involved in the consent or hands-on collection process, and involvement in other parts of the process varies depending on how the HBS are sourced.

HBS acquisition

One of the main strategic areas within AZ is oncology, and scientists working in this area are the main users of the Global Biobank resources. They are currently particularly interested in HBS from metastatic cancers, patients who have relapsed after treatment and longitudinal HBS (following disease progression). There is a dearth of these types of HBS because those taken are for diagnostic purposes, collected in relatively small amounts and frequently retained by pathology. HBS are also scarce from patients treated with medicines that have not been approved by NICE (e.g. Avastin); these may only be available from collections associated with clinical trials which thereby provides an incentive to collaborate with other pharmaceutical companies and to look for sources overseas.

Although the AZ Global Biobank does not acquire HBS directly, the biobank may advise on study design and provide advice regarding policies and procedures, HBS collection, labelling, processing and suitable storage arrangements. As previously indicated, most HBS are acquired by the CROs undertaking clinical trials on behalf of AZ and in recent years there has been a move away from specific consent towards more generic consent for research, in order to maximise the research potential of HBS collected during these studies. This is an ongoing piece of work, and particularly challenging when running global trials and working within the consent legislation and requirements in each country.

HBS being procured for specific research projects are generally acquired and supplied via external biobanks including commercial (for example, Asterand), academic and NHS suppliers. A HBS Category Group within AZ Procurement oversees applications from AZ researchers to source HBS. Policies and procedures are in place to assess potential commercial and public-funded suppliers against AZ requirements; this includes both a quality and financial audit. Once a supplier is approved, the Biobank Team may manage the request from the AZ researcher, place the order, liaise with the supplier, take receipt of the HBS and log them into the biobank inventory system, and then pass them on to the requestor. Further Quality Control checks on tissue HBS are carried out by an AZ pathologist. Assuming HBS are well characterised and of high quality, AZ may pay a premium to obtain the right HBS quickly, in order to maintain their rapid drug development programmes.

Amongst other things, HBS are used to measure targets in human tissue as well as the variability of biomarkers. This is partly to ensure methods in clinical trials are as valid as possible (robust, reliable and reproducible, with the possibility for patient stratification). HBS that have been acquired for research purposes are not available for external supply, not only because they are frequently exhausted through internal use, but also because of contractual limitations on their use imposed by suppliers. In July 2012 there were 209 projects providing HBS to the Biobank. Oncology alone supports 30- 40 projects at any one time. The oncology group tends to be particularly strategic in their approach to HBS accrual and biobanking and has allocated funds to a number of external biobanks (for example, Manchester, Nottingham and the Wales Cancer Biobank) in order to access a sufficient number of HBS.

HBS may be collected from both pre and post drug administration stages of AZ clinical trials. HBS from AZ sponsored trials are usually stored by the CROs (though Mölndal does have a policy for storing HBS accrued for research) and AZ pays for storage until the study ends and HBS are transferred to the internal biobank. Process improvements and optimisation of the inventory system are currently underway to evaluate incoming HBS more rigorously, allowing some surplus or lower quality HBS to be disposed of at an earlier stage. The new inventory system also incorporates an enhanced template so that HBS data from the CROs arrives at AZ in a standardised format, and consequently facilitates easier downstream identification of, and access to, the most appropriate HBS.

Types of HBS

AZ Global Biobank holds a wide variety of HBS, including FFPE and frozen tissue, plus HBS of plasma, serum, whole blood, urine, sputum and DNA. Many HBS have been collected for Respiratory, Joint Disease and Cardiovascular Disease. The biobank as a whole holds approximately one million HBS across the two sites. The profile of the HBS across the entire collection is roughly 50% biofluids, 40% DNA, with the remainder being mainly solid tissue HBS. Of this, there are a very small number (estimated 1%) of 'normal' HBS, and there is little easily obtainable information on the number of discrete/individual subjects that have provided the HBS (although this type of information will be more accessible once ABBA is implemented; see below).

A range of data is held on biobanked HBS, including demographic, pathology, clinical and genotypic data. The LIMS that will be used by the global biobank is called ABBA (AZ BioBank Application), and enables the full traceability of HBS as well as holding a set of key core data. The LIMS is searchable and enables integration with IMPACT, RAVE and CAVE, the in-house clinical trials databases. ABBA is an off-the-shelf product purchased from LabWare that has been highly customised over a period of years to meet AZ's

specific needs. This is a typical co-generation process, with ABBA expected to go live in early 2013. Users apply to register with the system and are then trained in its use. Although capital equipment for the biobank is funded through Discovery Sciences, IT and software are funded through AZ Research, Development and Innovation (RDI).

HBS processing

The main activity of the Global Biobank is curation; most HBS have been collected, processed and stored at an interim site, via a CRO, before arriving at the biobank. The type of processing that HBS undergo is primarily driven by the short term requirements of the clinical trials, although an increasing level of communication and co-ordination by the biobank means that processes are standardised wherever possible to maximise the long-term viability and compatibility of all HBS. HBS tend to arrive at the biobank in batches and they are then logged, tracked, quality verified and stored until required by research users. Where further processing is required, this may take place internally or be outsourced; for example, the DNA biobank outsources DNA extraction to an external company and coordinates the direct transfer of HBS from the CRO to the contracted processing company. The biobank then receives the aliquots of DNA ready for use. The number of companies now providing this service has been rationalised from three down to just one, in-line with the policy of process standardisation and simplification, as well as to reduce costs. Outsourcing to a company with expertise and experience in handling DNA ensures that processes can be rigorously maintained, and that expensive equipment does not need to be purchased or maintained. It also allows more flexibility in terms of keeping up to date with future advances in technology and equipment. In comparison, there are currently limited options for outsourcing solid tissue preparation.

Access

AZ's global biobank in the UK is an approved Research Tissue Bank with permission to authorise research on its own samples. HBS are only released internally or for AZ sponsored research; if external organisations are involved, HTA-compliant contracts/ MTAs are in place prior to supplying HBS. AZ do not currently have an internal access committee as all internal projects have already been rigorously reviewed and justified at the project proposal stage. An annual report is, however, submitted to the local REC outlining how HBS have been distributed and used. Requests are currently managed by the biobank team. This process involves gaining approval from the main AZ pathologist who has personal involvement and oversight of all research areas and priorities. As part of the DD&D review process, projects are prioritised; this facilitates access decisions if a number of requests come in together or if the HBS supply is limited. Approval for access is usually granted rapidly (within 24 hours), with HBS usually being issued within 5 days (with a self-imposed limit of 10 days). The relatively simple system for issuing HBS, involving individual key staff, may be formalised through the creation of an access committee, although it is considered essential that fast turnaround time for approval and supply should be maintained. Linking HBS to the appropriate database records and clinical/phenotypic data can take from one week to over a month, depending on the complexity and quantity of information that has been requested.

Although the main user group is oncology, there are a large number of groups using HBS; for example respiratory, cardiovascular, gastro-intestinal and neuroscience, as well as the safety assessment group. Most requests are from local sites and the oncology group in Boston, though some are from other sites. AZ acquired a therapeutic antibody company, MedImmune, in 2007. MedImmune is a wholly owned

subsidiary and the two organisations have worked relatively independently since the acquisition. Procedures are now being harmonised, but is currently impossible to transfer HBS between the two due to anti-competitive behaviour concerns.

Use of HBS at AZ is high; over the last two years almost 90,000 HBS were issued for research. In the same time period, about 400,000 HBS were collected, whereas only 10,000 were disposed of (Figure 1). This raises the issue of capacity; there are currently approximately one million HBS held in storage, so it is likely that in the future there will have to be more careful monitoring of the HBS that are collected and stored to ensure that HBS are not biobanked if there is little prospect that they will be used in the future. It's possible that there may no longer be automatic acceptance of large scale legacy collections at the end of clinical trials.

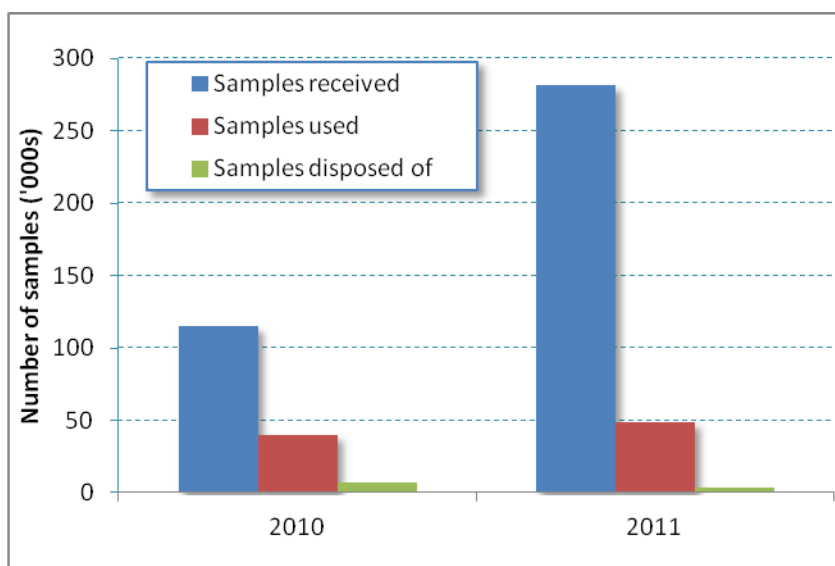


Figure 1 HBS received, used and disposed of by AZ global biobank

HBS are returned to the biobank in an agreed period of time (unless exhausted) and HBS repatriation or disposal is undertaken as required e.g. diagnostic NHS blocks may be requested by the original site, or HBS of Swedish origin may have to be returned to Sweden for long-term storage once analysis is complete (to conform to the Swedish Biobank Act). Repatriation (or destruction) of the highest priority requests (e.g. following withdrawal of consent) usually occurs within 24-48 hrs. HBS from clinical trials are usually disposed of after 25 years.

Income

The global biobanking budget is reviewed annually and funded centrally through AZ corporate funds (Discovery Sciences). Resources for biobanking vary annually based on the company's financial situation, commercial priorities, requests for capital investment or major development and the amount spent in the previous financial year. It was commented that the amounts needed to maintain and run the biobank are relatively modest, given the central role that it has within the research area of the company as a whole.

There is no additional income from users as access is free to internal researchers; in many cases they will have procured the collection of the HBS directly and the biobank will simply be acting as custodian of the

collection. External users only have access through collaboration with AZ on specific research projects, so any HBS requirements will be covered by broader contractual arrangements, with no money making its way back to the biobank directly.

Expenditure

As outlined above, biobanking activities are integrated into the organisation as a whole, with limited budgetary distinction from other departments for certain categories of spending. Capital expenditure costs were available for some dedicated biobank equipment (freezers) and for the refurbishment of the biobank laboratories, but there was no information available for the overall cost of the space occupied at the individual sites: the biobank occupies a very small footprint within a large research environment and it is supported by the overall research framework within AZ as it is considered to be an essential core facility. Between 2010 and 2012, across the Mölndal and AP sites, approximately £366,000 has been spent on facilities (including refurbishment, alarms and air-conditioning) and £118,000 on freezers. Using AZ's ten year lifespan model, this is equivalent to less than £50,000 per year on capital resources.

In contrast, the annual staffing costs are significant. Figure 2 shows the staff associated with the Global Biobank across the two main sites (including temporary and seconded positions). A dedicated associate director oversees both sites and staffs are split into main functions; IT; outsourcing; DNA biobank operations; and biobank operations (this last category represented at each site). These 17 staff span a wide range of salary bands, with total annual staffing costs of £922,000. The only other identified running costs for this analysis were consumables and energy costs, which were estimated as less than £20,000 p.a.

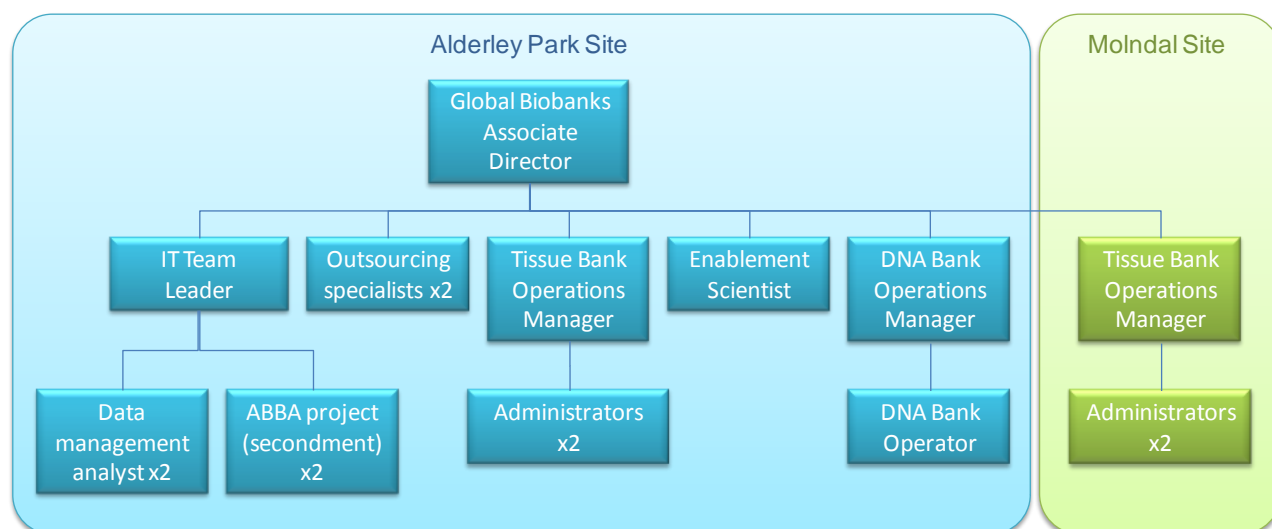


Figure 2 AZ Discovery Sciences Biobank staff across both the UK (blue) and Swedish (green) sites.

The hidden costs associated with the AZ model include building costs and the wider supporting services and staff (Human Resources, central IT, cleaners, reception staff, etc). In addition, the modest consumable costs reflect the fact that HBS collection (externally or via clinical trial patient recruitment) is covered by the individual research study groups that initially requires the HBS. In addition, there is significant outsourcing of services, including DNA extraction. Other aspects are covered by separate agreements or

funding streams; for example there is an internal Service Level Agreement in place between Discovery Sciences and Oncology to cover the work that the Clinical Histopathologist and Histopathologist technician (both based in Oncology) do for the biobank, e.g. quality control checks on externally sourced HBS.

Collaborations and evolving strategies

Over recent years, there have been major changes in the organisation of R&D activities at large pharmaceutical firms. In general, there has been a move towards more collaborative approaches to knowledge creation, sometimes termed 'open innovation'. This is in part a response to a number of inter-related factors; a reduction in R&D productivity, fewer New Chemical Entities (NCEs) that make it to market, an exponential rise in drug development costs, and the advent of molecular biology. AZ, like most other big pharma firms, has a high number, and wide range, of collaborations with a variety of organisations, including biotechnology firms, universities, CROs, and other major pharma firms.

HBS are donated and it is the ethical duty of the curator to ensure that they are used appropriately, with maximum research value achieved from their donation. This duty of care encourages HBS sharing.

Collaboration occurs for a range of reasons and takes a variety of forms, not only around HBS. Some examples of collaborative relationships that were discussed during interviews include;

- An increased willingness to allow academic researchers to work on novel or unique compounds with potential but where AZ has made a commercial decision not to develop the programme further. Increasingly, firms license out and/or donate compounds to other organisations to investigate alternative uses, including in neglected diseases.
- AZ have an existing collaboration through the Manchester Cancer Research Centre (MCRC) Network to create the MCRC biobank (www.mcrc.manchester.ac.uk/biobank). By providing salaries for tissue collectors, AZ has facilitated the collection of thousands of tumour and blood HBS, with associated clinical data, from five major hospitals within the Manchester area. The largest single disease area represented is lung cancer, which has led to selection as contributors to the CRUK stratified medicines programme. These HBS are available to a range of researchers (including those within the University of Manchester) to help develop knowledge, tests and treatments. The MCRC example demonstrates that pharmaceutical firms are willing to invest significant resource in RI to obtain high-quality, well characterised HBS.
- Two senior biobank staff at AZ are actively involved with the ABPI (Association of the British Pharmaceutical Industry) biobanking group, which includes representatives from CROs, biotechnology firms and pharma. The group meets to discuss a variety of shared issues and ideas e.g. the challenges of global legislation and regulations, and pre-competitive sharing of HBS.

FULL CASE STUDY 3: BIOBANKING SOLUTIONS (BIOBANKING COMPONENT OF CIGMR)

Compiled from secondary data and interviews with:

- Interviews with **Dr Kate Dixon** (Operations Manager), **Melanie Lythgo** (TRAC Manager, The University of Manchester) and **Craig Sykes** (Financial and Management accountant, The University of Manchester). 15th May 2012.
- Interviews with **Professor Bill Ollier** (Professor Immunogenetics and Director of CIGMR) and Dr. Kate Dixon. 10th May 2012.
- Followed up with **Dr Martin Yuille**, Dr Kate Dixon and Prof. Bill Ollier by email and telephone.

Institutional Context

Biobanking Solutions is the biobanking group located at the Centre for Integrated Genomic Medical Research (CIGMR), part of a research school within the Faculty of Medical and Health Sciences at the University of Manchester. CIGMR functions as a genomics translational research centre offering expertise, facilities and storage of HBS, including the UK DNA Biobanking Network (UDBN) for the MRC and the UK DNA Archive for Companion Animals for the University of Liverpool. Biobanking services are also provided for medical charities, including the Motor Neurone Disease association and Arthritis Research UK. In particular, the facility supports academic researchers locally and nationally through collaborative research or paid services. The biobanking aspects of the institution are represented as a discrete service, but as shown in the diagram below, the financial and organisational structure is closely intertwined with CIGMR and the whole structure falls under the umbrella of the University of Manchester. In March 2009, the University of Manchester and six NHS organisations (three acute trusts, two specialist trusts and one primary care trust) in Greater Manchester were designated by the Department of Health as one of the UKs five Academic Health Sciences Centres (AHSCs). The Manchester AHSC (MAHSC) was then established as a company limited by guarantee. The aims of this partnership include securing substantial funding and investment in RI and addressing aims in health benefits, translational research, teaching, innovation and international competitiveness. Biobanking is classified under 'Enabling Technologies and RI' within MAHSC. CIGMR's proposal for a hub and spoke network for biobanking was agreed by MAHSC in 2010 and a roadmap adopted. Its implementation has been piloted through a MAHSC-funded project and through cooperation with Salford Royal NHS Foundation Trust (SRFT).

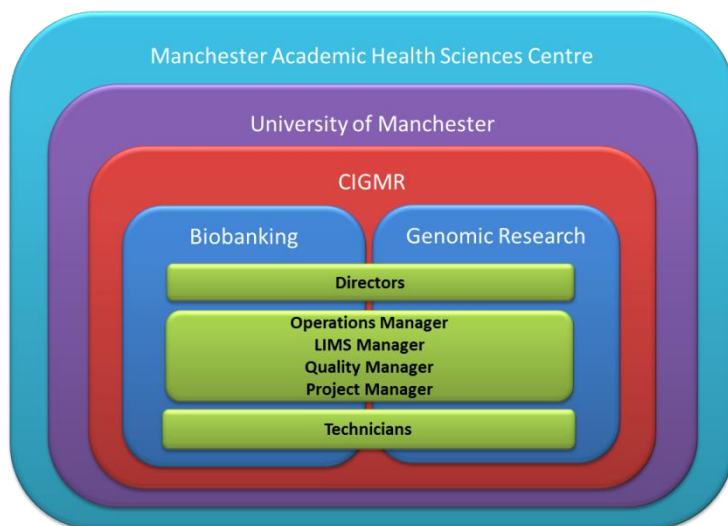


Figure 3 The institutional context of CIGMR

Historical context

Biobanking Solutions is the latest iteration of a biobanking organisation that has evolved via a chain of projects and funding streams over a period of two and a half decades. The original collection was initiated in the late 1980s as part of the Arthritis Research Campaign's (ARC; now AR-UK) need for HBS collection associated with genetic epidemiological⁴⁸ studies on rheumatic diseases. Their initial core funding of approximately £200k allowed the creation of a facility with capital equipment for both HBS storage (DNA processing and extraction facilities, freezers, etc) and genomic analysis (sequencers, analysers, etc). As a result of the success of this facility, the Centre for Integrated Genomic Medical Research (CIGMR) was established in 2001 to expand this as a service to the wider research community, primarily amongst other medical research disciplines within the University of Manchester. The expansion was enabled by a grant from MRC of approximately £6m that provided the facility with the equipment and capability to undertake large population studies to investigate multi-factorial diseases.

This initial investment was further consolidated when CIGMR (with the University of Cambridge) were awarded £2.7 million over 4 years to construct the UK DNA biobanking network (UDBN). UDBN was proposed and funded by the MRC to ensure access to the collection of blood and other HBS that had been collected between 2000-2003 in key disease areas from 40,000 patients and donors across 14 MRC grant at a cost of £8 million. The UDBN was agreed in 2002 and the funding commenced in 2003. The Cambridge site later closed and the human and material assets were transferred to Manchester in 2005. The network now comprises of one biobank and a consortium of 13 collectors. During this period, preliminary discussions relating to the development of a large scale national project, UK Biobank, were

⁴⁸ Epidemiology is the study of the distribution and patterns of health-events, health-characteristics and their causes or influences in well-defined populations.

held (see separate case), and biobanking experts within CIGMR also contributed significantly to this process. Furthermore the successful bid for The University of Manchester to be the 'host academic institution' for UK Biobank was written by individuals in CIGMR. Following award, CIGMR assisted in the development of the final HBS processing protocol and provided substantial R&D technical input into the development of novel processes such as EBV cell transformation of frozen Buffy coat samples, RNA stability studies and high throughput automated whole blood separation technologies.

CIGMR's biobanking operations continued to grow. New processes were introduced. New HBS types came under management. In 2012, partially to reflect this diversification and partly to reflect the integration of a wide range of activities, CIGMR's biobanking processes were branded as 'BioBanking Solutions' (BBS).

The analysis presented here focuses on the 'general human biobanking' aspects of the work undertaken within CIGMR. It does not include details of the financial accounts or staff time related to specific, separately funded projects, genomic analysis and research, or on animal biobanking.

Biobanking activities

Biobanking Solutions undertakes HBS management: it can supply bespoke validated HBS collection kits, and receives, logs, labels, tracks, processes, stores, replenishes and distributes aliquots of HBS, but it is not involved with obtaining HBS directly from donors or requesting their consent to provide a HBS. BBS undertakes data management in respect of the HBS itself but not in respect of the donor ('phenotype data') or in respect of experimental data on the HBS (e.g. DNA sequence data). However, where HBS collections managed by BBS are to be made accessible to third parties, BBS stores data about those parties and has developed and implemented links between some of the different types of data. CIGMR is currently funded by MRC to collaborate with the EBI to develop and implement links between all the types of data. CIGMR has developed the BBS website both to advertise existing accessible collections and to promote knowledge of and access to the processes it can contribute to research investigations.

CIGMR has a focus on genetic epidemiology and consequently processes were developed in BBS to manage DNA HBS. However, processes for management of other types of liquid HBS (plasma, serum, cell lines, white blood cells, urine, cerebro-spinal fluid, sputum etc) have been developed.

Biobanking processing including storage is undertaken within the University. There is also a secondary unmanned, off-site back-up storage facility. HBS are received in batches or individually by courier or mail, logged and labelled, and may be stored prior to processing. Automated or manual processes are used to extract and quantify DNA and a percentage of HBS are checked for quality. CIGMR currently has over 200,000 aliquots (from 58,000 donors) stored in -80°C freezers and 38,000 aliquots (from 14,000 donors) in liquid nitrogen; storage is temperature monitored and has a centralised alarm system. This accounts for over 90% of all stored aliquots, with a small number stored on card or in other formats. The purpose-equipped laboratories include a significant level of robotics associated with liquid-handling, and there is also a customised LIMS that provides full traceability of all tubes, wells etc. The facilities operate to ISO 9001:2008 certification.

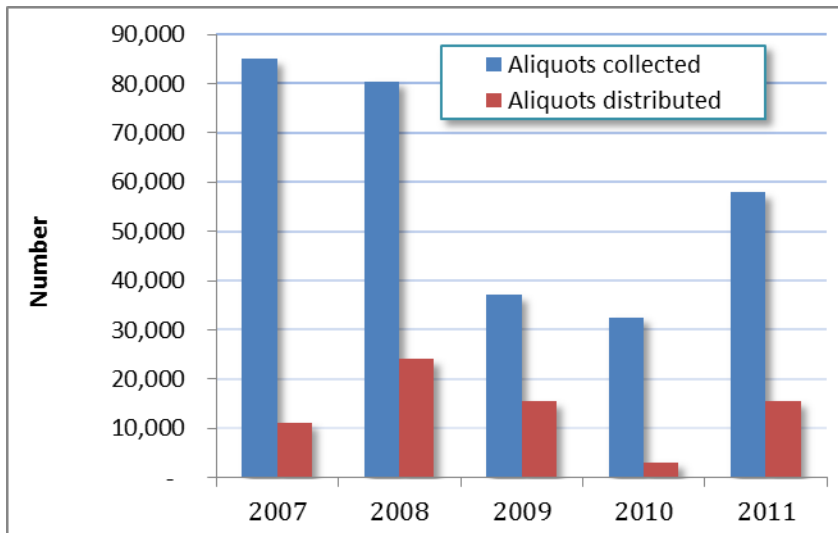


Figure 4 Number of aliquots collected (estimated) and distributed by CIGMR.

It can be seen from **Figure 4** that a relatively high number of HBS are distributed each year. As most of the HBS collected are DNA, it is also possible to prepare further aliquots as needed (these sub-aliquots are not included in the figures).

Income

The finances associated with the biobanking arm of CIGMR are complicated by the interdependency of the different aspects of its operations, the variety of funding streams associated with these, and the hidden or opaque costs associated with the University host. Early capital and support funding was from the ARC but an MRC grant of ~£6M in 2002 allowed the capital resources to be transferred to a stand-alone facility. MRC funding continued to offer the majority of the support through awards for 1-3 year periods, and this money was principally used for maintenance and the salaries of three core staff members. The interviewees indicated that the MRC awarding boards primarily consider funding for projects, rather than for longer term RI like biobanking. This represents a significant problem as the revenue stream is not secure. In general, funding bodies prefer to support hypothesis driven research rather than infrastructure projects (particularly the maintenance of infrastructure).

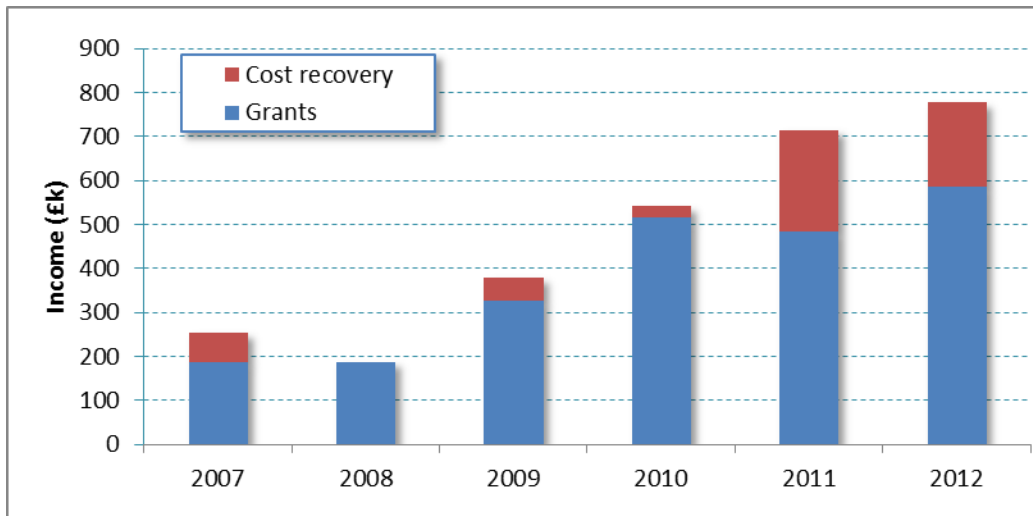


Figure 5 Annual income figures from grants and through cost recovery for CIGMR from 2007-2012

In order to overcome this funding problem, it has been necessary to cross subsidise biobanking activities from different grants and additional revenue streams in order to improve financial security and offer best value in terms of the utilisation of staff. Biobanking Solutions generate some revenue via a cost recovery model for the biobanking services they offer, but historically this income is relatively small compared to that generated from grants (see Figure 5). There is now an active strategy within CIGMR to significantly increase the proportion of income generated through HBS supply, partly to overcome the insecure nature of grant-based funding. Creating a cost recovery model requires full transparency as cost estimates are included on grants and project applications. Biobanking Solutions have previously separated processing, storage and distribution costs to calculate overall costs. The costs of processes are broken down to enable accurate and fair cost recovery. **Figure 6** shows the relative charges for different aspects of HBS processing and biobanking relating to the preparation of DNA from whole blood. The relative charges are highly variable with the most substantial resources relating to the extraction process itself. Importantly, these charges are not precisely calculated, but rather are developed based on a number of considerations, for example current market price for HBS and the quality of the processes and product attained (including charging more for technically demanding processes). In addition, there is flexibility in the application of costs, to encourage collaboration and to fit in with the nature of funding; for example, academic researchers may receive lump sums of grant money to use for specific projects and defined HBS processing, but have little reliable sustained income for the long-term storage of collections.

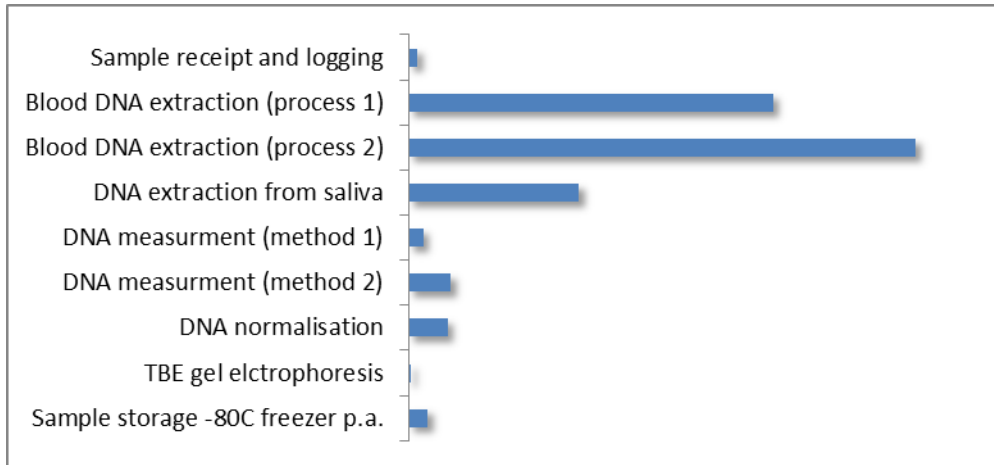


Figure 6 Relative charges associated with different aspects of DNA biobanking (actual figures not shown for commercial reasons)

Indeed, historically, the costs associated with storage have not been calculated or charged for (storage costs include energy, estates, core staff, quality management, consumables and depreciation). Distribution costs are charged to users separately (according to the predicted labour, logistics and consumable costs associated with distributing the HBS). In general, the interviewees estimated that 75% of the costs are associated with processing; however, they admitted that indirect and institutional costs were not always clear. There will obviously be significant variability from study to study, influenced by variables such as the number of HBS stored and distributed.

Processing is a physical activity with a set time; it can be quantified. Interestingly, when probed the interviewees were not accounting for the time taken by technicians for preparation or pre-processing activities or for transaction costs associated with operating a cost recovery model. Moreover, there was little mechanism for recovering costs for time that was not spent handling HBS – this is significant based on the erratic mechanism and nature by which HBS may be received. To compensate for this ‘down-time’ CIGMR tended to prefer to apply for salaried staff in new grant proposals rather than estimated costs based on procedures undertaken. The interviewees indicated that raising invoices was a labour intensive activity requiring a significant investment of time. Administering a cost recovery model was not supported by the central institution in practice as the university has historically dealt with grant based research income rather than cost recovery finance models.

The interviewees reported that implementing a cost recovery model has allowed the salaries of the technical and associated support staff to be maintained. However, within the accounting system adopted by the University, this has been problematic, as there has been no mechanism to accumulate funds across financial years. Essentially, surplus money at the end of the financial year has been lost (from CIGMR) thereby providing no long term stability for these staff.

Expenditure

CIGMR has a number of outgoings. The direct costs (i.e. those specifically associated with, and directly attributable to, CIGMR) were provided by the Operations Manager based on calculations of costs for procedures, services and techniques offered. To address the indirect costs (those associated with support

offered by the host) discussions were held with members of the finance office for the University of Manchester. These indirect costs relate to core services, facilities and support (for example, central staff functions, buildings and space)

Role	FTE	Proportion of time spent on general biobanking	Funding source
Co-director	1	50%	HEFCE
Co-director	0.2	50%	HEFCE
Administrator	1	10%	HEFCE
Operations manager	1	100%	MRC
LIMS manager	1	100%	MRC
Technician/Quality control manager	1	100%	MRC
Technicians	2	100%	Cost recovery
Technicians	3	100%	IMI
Project Manager	1	100%	IMI

Table 6 CIGMR staff employed to work on general biobanking and their funding sources (not including staff, or staff time, employed working on specific projects or in non-biobanking projects).

All CIGMR staff are employed by the University of Manchester either through HEFCE funding, cost recovery funds or on research grants. The “core” staff involved with general biobanking include an operations manager and a LIMS manager. Together with the two directors, they are involved with all the operations at CIGMR (i.e. both biobanking and non-biobanking activities, including research). There are also 5 technicians who are appointed for generic biobanking, with administrator support.

In addition to the staff covering the generic biobanking and HBS handling, there are a number of staff associated with specific projects hosted within CIGMR. In some cases, these projects are closely overseen within CIGMR and there may be shared and reciprocal use of staff (especially technician) time. In contrast, for other projects, their roles and work are theoretically separate from the main CIGMR structure, although there is still some overlap in terms of access to resources and equipment, and managerial oversight of activities.

	Direct costs: Project specific (variable)	Indirect Costs: Incurred by CIGMR	Indirect Costs: Incurred by the University
Salaries (CIGMR)	Technicians	Operations, IT, QC managers	All university support staff (security, cleaners, HR, admin, finance, etc)
Facilities		Laboratory infrastructure	Building costs and

		and refurbishment	maintenance
Equipment	Freezers	Robotics, LIMS	
IT		IT equipment and specific software and licenses	IT infrastructure
Quality control	Audit costs	Equipment calibration and servicing	
Materials	Reagents, tubes, labels, consumables	H&S, PPE, Stationery	
Services		Electricity, liquid nitrogen, dry ice	Heating, water, central services

Table 7 Summary of main costs for biobanking at CIGMR. Direct costs relate to project attributable charges, while indirect costs are general overhead costs that are incurred which may be attributed to either CIGMR or the University host.

BBS is not normally directly involved in the HBS collection stages of biobanking; its role is in receipt, processing, storage, promotion and distribution of HBS. The charges for these services are based on the calculated costs of specific procedures based on a breakdown of the HBS and chargeable labour employed. These costs are largely centred on the processing of HBS (normally the extraction of DNA from whole blood) and for access to HBS, with minimal charge (or even no charge) being made for the long-term storage of HBS. As such, the biobanking charges at CIGMR have historically been underestimated as a deliberate attempt to promote the use of the facility, encourage collectors and enhance use of the associated genomic facilities. In addition, certain indirect/overhead costs (for example electricity and services) have been left out of calculations as these are covered by the host institution. The charging structure is currently under review, with the intention that the costs associated with all stages of biobanking, including the storage of HBS, will need to be recouped more directly and fully in the future.

Estimating costs and charging appropriately is further complicated by the mixed funding model that the organisation employs. They are careful to ensure that staff time is not recharged where that member of staff is funded from another (usually grant-based) source. In addition, the erratic and changing nature of HBS accrual, with a variable work-load from day-to-day, means that staff are most efficiently used across a number of projects. This means that staff employed primarily for a specific project may be asked to undertake generic biobanking processes, and reciprocally, that staff employed for generic processes (including IT and quality control) may contribute to specific projects and tasks. This is the only way to utilise the staff and limited resources effectively.

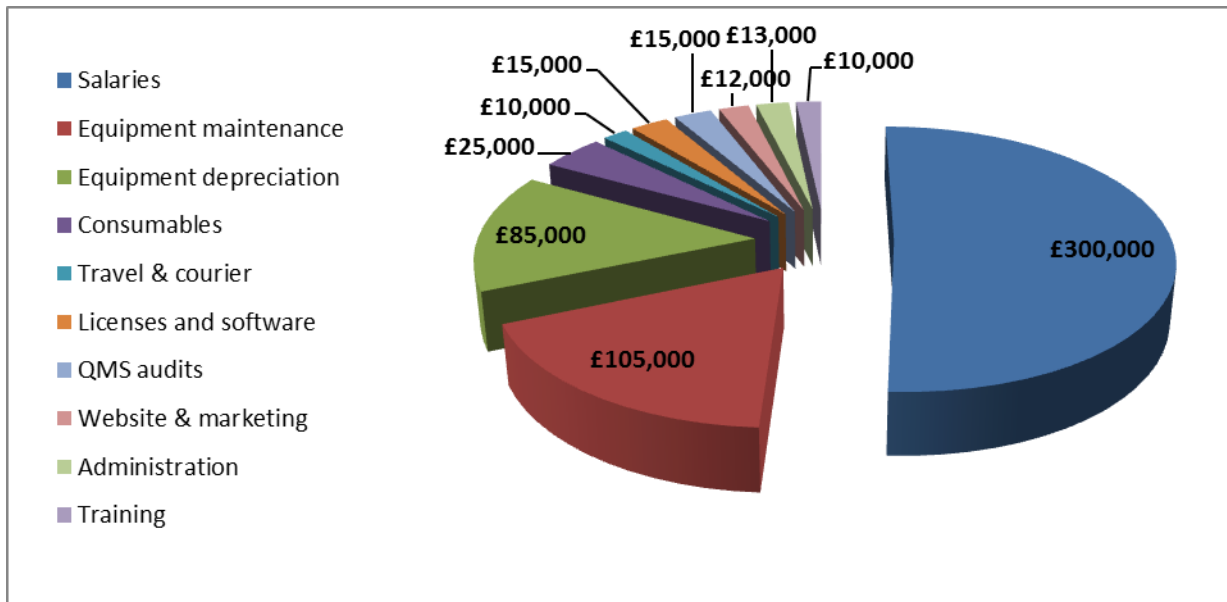


Figure 7 Predicted breakdown of the CIGMR biobanking annual running costs (from MRC funding application)

The costs associated with running the biobanking operations within an academic environment are complicated by the financial structure and regulations of the host as well as the funders. For example, when applying for funding, the research councils will only provide 80% of the full Economic Cost (fEC) with the expectation that the host institution will provide the remaining 20%. In addition, the process of applying for awards, needs to be conducted in accordance with the Transparent Approach to Costing (TRAC), which aims to identify the direct costs (i.e. those associated directly with the biobanking operations) and indirect costs (i.e. those 'overhead' costs that are shared with other activities). Academic institutions (including the University of Manchester) adopt standardised indirect costs based on the average figures of these shared resources throughout the organisation. In the case of biobanking at CIGMR it may be that some aspects of these indirect costs are an underestimate of the true cost (e.g. the large power consumption associated with -80°C freezers and the unusually high footprint for lab staff arising from this as well as from robotic and lab equipment).

Top-down (HBS) cost calculation

In order to work-out the average HBS cost, the income (CIGMR grant income and cost recovery income over five years) was divided by the number of individual donor HBS processed by CIGMR over the last five years. This gave a figure of £24 per HBS donor. The majority of HBS are received as a single whole blood tube, and processed to extract the DNA into multiple aliquots that are then stored frozen for an indeterminate period of time. This figure represents the average cost per HBS received at CIGMR; this tends to be a single blood tube from one patient that is then processed to extract the DNA which is split into numerous aliquots. This figure does not include any aspect of the consent or HBS collection process which is undertaken by the study research team.

Bottom-up (process) cost calculation

Although CIGMR have produced a charging structure for their services (Figure 4) this has been determined, to some extent, based on the anticipated cost that the market will be willing to pay rather than fully based on the true costs incurred (it is not a true cost recovery model). The most expensive processes CIGMR undertake relate to the extraction of DNA, and this is largely due to the reagents and specialist equipment that is employed; CIGMR's laboratory equipment cost in excess of £250k (freezers, liquid nitrogen, automation and robotics). As this represents an expert service, they can recoup the full costs from their customers to cover these processes, although they obviously incur costs associated with the maintenance of equipment even when it is not being used. The other processes related to biobanking are not as expensive (**Error! Reference source not found.**) and these may not even be charged in many cases. A true process calculation was not achievable, partly because no figures were obtained in relation to the salary costs which make up the majority of the operational costs of the facility. One of CIGMR's strengths relates to the high quality of its processes, its ISO accreditation and LIMS HBS tracking. Although such systems provide customers with reassurances about the consistency and quality of the HBS that is provided, they are expensive to operate both in terms of labour and the cost of licenses/software.

Benefits of this biobanking model

The CIGMR biobanking service allows numerous individual researchers or research groups to biobank in a regulated and consistent manner. In most cases, the individual researchers would not be able to carry this out at all, and certainly not with the level of quality assurance and efficiency offered by the biobank. CIGMR has identified key processes add scientific value to HBS, including: full HBS traceability, fair access governance ('Access By Collaboration: ABC'), enrichment of HBS annotations and the development of networks between collectors, biobanks and HBS users. CIGMR operate an industry standard LIMS, actively research and implement advances in HBS processing and biobanking technology wherever feasible, and provide training packages.

Central to CIGMRs objectives is the adoption and maintenance of a quality management system across HBS handling; the ISO-9001 framework provides assurances about procedures and processes in the absence of a regulated national biobanking quality framework. This provides reassurance to current collectors that their HBS are as likely as any to be considered acceptable for future (perhaps unknown) research use.

Furthermore, because they operate within an academic and research environment they are in a strategically important position in terms of education and research both within the host institution of the University of Manchester, but also across the wider MAHSC. This allows them to tap into a number of significant and important research active Trusts, although notably, and largely due to the nature of the HBS they collect, they have thus far had little opportunity to participate in potentially financially lucrative clinical trials.

FULL CASE STUDY 4: FRESH TISSUE SUPPLY

Compiled from secondary data and interviews with:

- **Professor David Walsh** (Director, Arthritis Research UK Pain Centre & Honorary Consultant Rheumatologist, University of Nottingham) interviewed by telephone 10th October 2010 and **Julie Corfield** (Director Areteva, ex-BioBank Head AZ, Project Lead STRATUM)
- Secondary data from various sources including presentations from AZ and Areteva, and <http://www.nottingham.ac.uk/paincentre/research/epidemiologyandbiobanks.aspx> (accessed October 2010)

Institutional Context

The University of Nottingham's Arthritis Pain Centre was funded through a £2.5 million award from Arthritis Research UK. Physically located within the University of Nottingham, but not directly funded by it, and in collaboration with Sherwood Forest Hospitals NHS Foundation Trust, a biobank is operated under the supervision of Professor David Walsh. The biobanking system facilitates the collection of HBS for either storage or immediate supply of fresh HBS, from both living and deceased patients. It is the supply of fresh HBS that is the focus here, although this is closely associated with the broader biobanking activities

Historical Context

Prof. Walsh has led the HBS collection programme since 2000. The original project was established through a collaboration between Sherwood Forest Hospitals NHS Foundation Trust and AZ to collect HBS with associated clinical data following joint replacement surgery, and this later progressed to also include post mortem material. Consequently, HBS were initially collected for specific studies relating to the mechanisms of arthritic pain. Over time, activities were expanded to cater for a larger range of studies in different research areas, resulting in a flexible model that could accommodate biobanking in general, rather than being limited to a fixed set of protocols or HBS types. A flexible biobanking model meant that it could accommodate the inherently specific requirements for fresh tissue collection in new collaborations relatively easily. The biobank has supplied fresh tissue to a range of collaborative partners (e.g. local research groups, the universities of Glasgow and Edinburgh, GSK and other pharmaceutical companies).

Biobanking activities

In aggregate, the banked biological resources include tissues from 2500 patients who have undergone joint replacement, as well more than 200 post mortem donors⁴⁹. The fresh HBS are obtained in parallel to

⁴⁹ <http://www.nottingham.ac.uk/paincentre/research/epidemiologyandbiobanks.aspx>

these HBS that are retained for the main biobank, and there is significant interdependency between the processes.

Fresh HBS availability is not generally predictable and staff with responsibility for accrual should be available throughout the day. To meet this need, staff are employed in flexible roles, which also incorporate, but are not restricted to, fresh HBS collection, enabling them to work around the availability of material. The type of fresh HBS collected is variable and the biobank takes a flexible approach towards requests for additional HBS types. Requests for fresh tissue have included bone marrow for stem cell extraction, or muscle HBS from post mortem for myocyte culture. Data are specifically collected by a trained nurse, and supplemented with medical records (current and potentially future) and radiographic images.

The fresh tissue aspect of the collection is only undertaken when agreements for specific projects are in place, whereas biobanked HBS are continually collected from all consenting patients. The ability to collect fresh material relies on the core structure that is in place for routine biobanking, without an existing biobank structure it would prove very expensive to retain dedicated staff and resources for fresh HBS that are required from time to time, according to unpredictable timelines. In this sense, research reliant on fresh tissue benefits from investment in biobanking infrastructures. However, fresh tissue invariably has extra and more onerous processing and transfer requirements, together with an obvious requirement for speed; the tissue is not stored but is immediately transported to the research group. The biobank performs a critical role to coordinate the supply and demand of fresh tissue. Processing requirements depend on the HBS type under investigation, but aspects such as transport are significantly more expensive as there is little scope to batch up material before transfer. The extra costs associated with transporting fresh tissue generally favours smaller studies and local collaborations. In addition, working with fresh tissue poses a greater risk of infection, and a need for specialist processing facilities, staff, equipment and extended cover outside normal working hours.

Collaborators may impose or suggest relatively strict supply structures to be in place for the supply of fresh tissue, particularly in relation to speed/time to supply material, however, research conducted by the biobank indicates that these requirements are often based on assumptions that are not fully justified. As such, the biobank distributes fresh tissue according to guidelines defined by their collaborators, but also actively evaluates the effect that these variables have on research. The biobank reported that an important element of their work is to extend the knowledge base in relation to both fresh tissue supply and general biobanking. The biobank reported that the ability to be flexible, and to develop and optimise protocols, ultimately increases the value of the facility and the service, as well as impacting on research outcomes.

Consent for all fresh samples is obtained via specific ethical REC approval (rather than through research tissue bank approval), with a relatively broad remit. Any extra procedures or activities need separate specific ethical approval. Consent includes the ability to access medical records in the future, as studies have frequently indicated that even with relatively extensive and thorough clinical histories, there may be unanticipated research questions that arise at a later stage. Moreover, follow-up clinical data on donor outcomes can provide very useful context for research studies.

Income

Financial support for the biobank currently comes from NUH Trust plus contributions from specific collaborative projects. The biobank works alongside the Nottingham Health Sciences Biorepository (see separate case).

It was not possible to obtain details on the income arising from the supply of fresh tissue, in part as it is so closely affiliated to the main biobank activities and partly because some studies are commercially sensitive. Staffing costs for donor recruitment and HBS/data acquisition and processing are paid for by the NUH Trust. As is Prof. Walsh's academic position and the position of affiliated researchers. The biobanking facility is seen as an important element of Sherwood Forest Hospitals NHS Foundation Trust's research portfolio, so the Trust supports internal staff training and professional development, as well as external research collaborations.

In line with the other publicly funded biobanks, profit is not sought through HBS supply. Instead, the biobank operates a cost-recovery model where possible, and each request is costed on a case-by-case basis. For example, a small-scale pilot study being undertaken in preparation for a research grant application, may not be charged for access to annotated HBS, on the proviso that a realistic cost is included in the grant application that is subsequently submitted. Early collaboration in the preparatory phase facilitates a two-way dialogue, which ultimately leads to an informed decision on the scale and suitability of the project, and the appropriate level of funding that needs to be factored into the grant proposal. Commercial/industrial projects tend to incur a higher charge reflecting full cost recovery, including an appropriate contribution towards the overall running of the facility. Fresh tissue in particular commands a higher premium due to the scarcity of supply and reflecting the higher costs involved in collection, processing and supply within tight timescales (normally hours to days). In addition fresh tissue can only be used once and is then gone, whereas biobanked HBS are usually divided to enable multiple use (e.g. in aliquots or sections). Obtaining fresh tissue through the model adopted by Prof. Walsh's team is likely to be substantially cheaper than if material were sourced directly through volunteer recruitment. The provision of fresh tissue for research is most cost effectively and ethically obtained through a research active hospital.

Expenditure

Biobanking activities are supported by NUH Trust through the employment of one specialist research nurse (for the identification of patients, liaising with clinical staff and obtaining consent), one technician (tissue processing and handling) and one administrator. These staff work flexibly, but spend at least 50% of their research time on biobanking-related activities, with a relatively small proportion of this time apportioned to sourcing fresh HBS. Their appointment and involvement in the routine biobanking allows a system to be in place that facilitates the flexibility needed for efficient and cost-effective collection and supply of fresh tissue for specific projects.

Collaborations and networks

The Arthritis Research UK Pain Centre in Nottingham has variable collaborative agreements in place in relation to biobanking (e.g. with Glasgow, Edinburgh, GSK and AZ). The Pain Centre is working closely with the evolving Nottingham Health Sciences Biobank to develop agreements that will allow them to work effectively together with minimal duplication, and to standardise their processes and procedures, including consent forms.

FULL CASE STUDY 5: NOTTINGHAM HEALTH SCIENCE BIOBANK (NHSB)
Compiled from secondary data and interviews with:

- Interviews with **Dr Balwir Matharoo-Ball** (Operations Manager for the NHSB). Interviewed 10th July 2012, and subsequent follow-up by email and telephone.
- **Dr Brian Thomson** (Director of Research and Innovation at Nottingham University Hospitals NHS Trust, Founder and Director of the NHSB). Email correspondence.
- Secondary data includes; R&D Annual Report (2011), Business Plan for the Nottingham Health Science Biobank (NHSB) for Nottingham University Hospitals NHS Trust, Freedom of Information (FOI) request template.

Institutional context

The NHSB was set up in 2010 to support translational and clinical research conducted by the Nottingham University Hospitals (NUH) NHS Trust, its key research partners and the wider scientific community. The NHSB was created as part of a drive by the Department of Research and Innovation (R&I) at NUH to systematically capture and align the resources of the NHS as a powerful platform for research. The NUH Trust is made up of Queens Medical Centre, Nottingham City Hospital and Ropewalk House. In partnership with the University of Nottingham, the NUH Trust hosts three Biomedical Research Units (BRUs⁵⁰), in Respiratory Diseases, Gastrointestinal & Liver Disease, and Deafness & Hearing. Funding for the BRU in Respiratory diseases ended in 2012. NUH is a teaching trust and has strong relationships with the University of Nottingham, and other regional universities. The NUH Trust was formed in 2006, employs 13,000 staff and has an annual income of £722.5million. The Trust has approximately 1,700 beds and serves over 2.5 million Nottingham residents. It also provides specialist services to an additional 4 million patients from neighbouring counties.

The existence of NHSB is in line with NUH Trust's research strategy. It is based in the Department of Pathology at NUH and is led by the R&I. It works primarily with leading researchers in the Trust, BRUs, and the University of Nottingham but also supplies tissues and linked data to commercial and non-commercial researchers outside Nottingham. The NHSB is based at the David Evans Medical Centre at the City campus and at the Queen Medical Centre. Initially the group consisted of 8 scientists, 2 data analysts and a research nurse (primarily to take consent). There are currently 21 employees, all employed by the Pathology Department, some of whom are on short term contracts. The team have regular meetings; there are also meetings at an operation level and higher level management meetings (these also involve the pathologists).

⁵⁰ BRUs were created by National Institute for Health Research (NIHR) in 2008 to translate fundamental biomedical research into clinical research in pre-selected priority areas. The aims of these bodies are to translate advances in science into benefits for patients. Achieving this aim requires BRUs to partner with a variety of organisations and use their infrastructure and facilities to attract external funding.

In response to the Carter Review⁵¹, it has been agreed that the NUH Trust and Leicester Hospitals NHS Trust will combine their pathology services. The new East Midlands Pathology Service (EMPATH) will have a new purpose built site between Nottingham and Leicester for all pathology services, except for cellular biology, which will remain at the existing hospital sites. The implication for NHSB is that new facilities will become available for expansion, facilitating departmental independence for the biobank. NHSB is likely to be closely associated with EMPATH and provide 'added value'. It is anticipated that there will also be opportunities for the NHSB to extend biobanking activities to include the Leicester Hospitals NHS Trust.

Historical Context

The NHSB was initiated through a 'programme of work force change' in Pathology in 2009. The project to establish the Biobank was approved by the Trust Investment Committee and Trust Directors Group in August 2010. Ethical approval was granted in November 2010. In January 2011, Dr Matharoo-Ball was recruited as Operations Director; she is a biomedical scientist and senior post-doctoral researcher. The project entered a pilot phase in 2010/11 (NUH Trust R&D Annual Report, 2011, p14) and during this time a project board was formed with the Director of R&I as the SRO. Ethical approval for generic consent for prospective collections and for the use of Pathology archival HBS has been granted by the Greater Manchester REC. Nottingham is one of four core centres contributing to the national Breast Cancer Campaign Tissue Bank (BCCTB). NHSB pilot projects involving Breast and Respiratory clinics at City campus, Liver clinics at Queen's Medical Centre and GI/Liver clinics at Nottingham NHS Treatment Centre were initiated in February 2011. Over 11000 HBS have so far been collected from 900 patients. A proportion of breast tissue collected by NHSB is donated to BCCTB. The Breast, Liver and Respiratory disease pilots are now nearly completed and it is intended to roll out these services to additional key clinical environments

Biobanking activities

The NHSB is an ethics-approved Research Tissue Bank, with permission to authorise research, which includes collections dating back to the 1950s. HBS that are excess to diagnostic requirements are collected for the bank thereby minimising costs and inconvenience. Most of this tissue is collected by NHS pathologists so all procedures are quality assured within the existing regulatory framework. Blood (serum and plasma) and other body fluids for the biobank are collected by phlebotomy or clinical staff during routine patient treatment and the samples are then collected by the biobank staff for processing and storage.

All donors give generic consent and patients are sent an information sheet and consent form prior to their routine clinical appointment. HBS collected pre-2006 do not require consent; however, all HBS collected since 2004 (that form part of an inherited biobank) have consent.

The NHSB operates an innovative consent process involving patients, public and carers, whereby members of the public are recruited as volunteers to approach potential donors. So far, there are 8

⁵¹ The Carter Review was an independent national review of Pathology services (2008). It made the case for the consolidation of pathology services to improve quality, efficiency and patient safety.

volunteers collecting consent in clinics and on Trust honorary contracts, and 12 others who help with posters and promotional campaigns. These volunteers undergo extensive and individually tailored training, incorporating role play, competencies, shadowing and observation. The biobank training and development package has been developed in-house and certification is valid for 2 years, at which point the volunteers are asked to renew and/or undertake the MRC online training. This consent process works effectively and clearly serves to reduce the relatively high costs associated with seeking consent for biobanking.

The majority of HBS (3488 donors) are in freezers in David Evans Medical Centre. FFPE blocks or slides (2126 individuals) lie within Histopathology. In terms of individual HBS/aliquots, there are over 14,000 in freezers, over 6,000 FFPE blocks, and over 1,000 slides (of these approximately 4000 are archive samples). These numbers include approximately 6,000 frozen breast tissue HBS. In terms of the sample types almost three-quarters of all those stored are solid tissue (Figure 8). All of these HBS are well characterised.

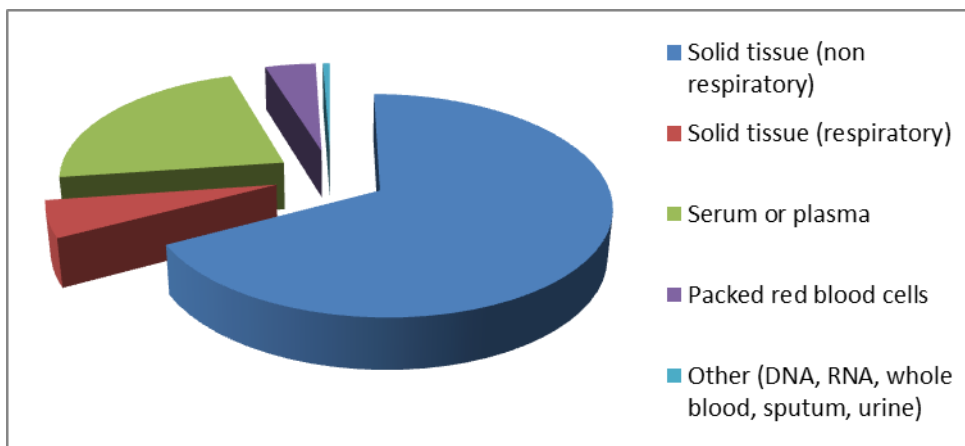


Figure 8 Distribution of HBS types held by the NHSB (2012)

NHSB was initially set up using a LabVantage Sapphire Biobank LIMS. The Trust provides IT support and backup facilities. The system provided a database resource with browser access, sample tracking, freezer storage management, sample processing data; research study accounts and data analysis. A full function biobank management system, including a searchable database, has now been procured from Achiever Medical. The database will be fully searchable and contain data from consented donors. It will be maintained by live downloads from the fully electronic data records at the trust (via ORCHID, see below). The isolation of this database from primary Trust records ensures compliance with data protection legislation. This new system will undergo iterative development and improvement cycles and will support the launch of the biobank to a wide range of researchers.

A novel patient coding and information strategy has been designed to capture and align patient data with the NHSB, as well as other major research programmes. The informatics system is called ORCHID (Ontology-based Research and Clinical Hierarchical Indexing Database), it and has been designed to link HBS to personal data and hospital records. ORCHID does this by capturing data and organising it in a searchable format. ORCHID has been co-developed by NUH Trust and Professor Chelsom from the Department of Health Informatics, City University, London. ORCHID is open source – so it can be used by

other organisations. Clinical input is critical to the design of this bioinformatics tool. These tools enable NHSB to exploit the market for provision of high quality HBS linked to exceptionally well characterised patient data.

An Access Committee has been formed with authority from ethics to review and approve applications for research to be undertaken without seeking further ethical approval. The committee is primarily comprised of researchers in the Trust and the University, with the option of asking specialists to review requests for access in particular areas of research, or to especially valuable HBS sets. Approval is anticipated to take 2 weeks, with HBS distributed within 4 weeks of approval. In 2011 (R&D Annual report, 2011) fifty five projects have been approved. Early industrial users checked the quality of HBS, including RNA quality and methodologies, SOPs and processes back to 1989 before entering into contracts with the biobank. These early users have thus demonstrated the quality and value of the biobank and serve as an important market signal.

The biobank does not require any intellectual property rights. All individuals and firms who access the HBS are able to publish and/or patent any knowledge created. The biobank and Trust staff are not named on publications; it is only necessary to acknowledge where the HBS have come from. After publication/patenting it is requested that researchers/firms provide their results to the biobank. Biobank staff will then upload these to ensure that the data associated with any remaining HBS portions is up-to-date.

Income

The Trusts Finance Manager has prepared a detailed Business Plan to help move the biobank to a self-funding model from 2015. Market research has been undertaken to inform this plan, involving a review of the grey literature, telephone interviews with commercial companies, FOI requests on NHS biobanks and meetings with potential customers. The Finance Manager has since left the team, however, this business plan is being used as a template for the emerging cost recovery model.

The NHSB operates on a not-for-profit basis, defined as only deriving sufficient revenue to cover direct costs plus Biobank, pathology and Trust overheads. The NHSB is mainly funded from existing R&D development and grant funded sources until 31st March 2015. After this date, all its recurrent and capital allocation will be used and it is predicted to be self-funding (Appendix 5; R&D Annual Report, 2011) as set out in their business strategy (see [Figure 9](#)).

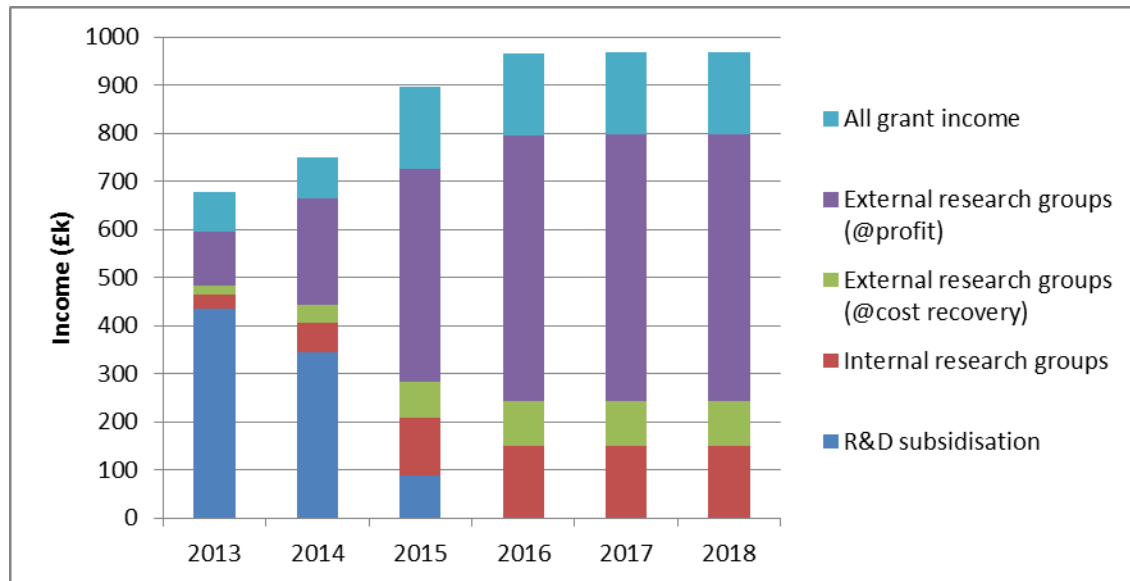


Figure 9 Income stream predictions to 2018, from the NHSB business plan. Key: External research groups @ profit include industrial users. External research groups @ cost recovery include academic researchers beyond Nottingham University. Internal research groups are academic researchers at Nottingham University and costed as subsidised by industrial users.

The self-funding model motivated the biobank to accurately evaluate the costs associated with biobanking. Costs were calculated primarily on the time taken for a given activity, and based on the minimum salary band of personnel required to undertake that activity. This review demonstrated that the actual costs associated with biobanking are significantly higher than recognised by most researchers and funding bodies. For example, overall, an average HBS could cost 5-10 times the amount estimated by the MRC. It was clear that internal (and external) academics were unable to pay these costs (Business Plan for NHSB). Any cost recovery would primarily come from commercial organisations, together with a block grant from the University of Nottingham in exchange for the provision of agreed services. The decision was made to employ PA Consulting Group to undertake market research with a variety of biobank users, including academics, CROs and pharmaceutical firms, to determine their needs. The NHSB is clear that their aim is to have a well-used biobank, so understanding the needs of users in terms of disease areas, HBS types and types of clinical data, has helped to prioritise their activities. It has also demonstrated that pharma wants a quick turnaround and this has prompted the biobank to prioritise the cataloguing of archives to enable them to respond to requests quickly.

Internal academic researchers can access the biobank for free, but may be asked to pay a nominal sum to recover the costs of accessing archive collections. Any internal researchers prospectively collecting studies are able to utilise the biobank at no cost but these researchers are asked to provide the Bank with a matched set of aliquots gathered for the purposes of their research. This innovative arrangement helps to promote access and is a cost neutral way of populating the bank.

In this tiered access structure, industry is required to pay a price designed to cover the cost of the HBS, including the biobanks and Trust overheads. However, once calculated the price reflecting cost recovery was reduced, primarily because the market was not prepared to pay the full cost. Costing is proportionally calculated according to the type and rarity of the HBS, the complexity of any processing required, the

associated data required and the QA/QC from pathology conducted in addition to that usually conducted as part of diagnosis. Quotes are provided on an individual basis. There have been more access requests from pharmaceutical researchers than academic researchers over the past year. One company has entered into a contract with a value of £500,000.

It is anticipated that the biobank will be operating at a loss and will need to be subsidised through R&D funding, for a number of years. The business plan maps out in full detail how it is anticipated that the bank will move from an overall loss towards breaking even after four years ([Figure 9](#)). These figures anticipate that in the early years of the model, almost two-thirds of necessary income will be derived from R&D subsidy, whereas at the point at which the model is operating 'without loss', two thirds will come from external researchers paying to access HBS (the vast majority of whom will be charged at the higher rate). However, the outcome of a recent exercise to actively annotate and market archival indicates that break-even point may occur sooner than the anticipated four year deadline.

It could easily be argued that business models are notoriously unreliable or inaccurate; however, perhaps the interesting aspect of the NHSB business plan is that they have one at all. This clear and (internally) transparent approach to biobanking is rarely seen.

Expenditure

The set-up costs for the basic infrastructure associated with the biobank are indicated in [Table 8](#). The costs for the physical facilities and resources associated directly with the collection and storage of HBS were relatively modest (e.g. £64,000 on freezers and other storage facilities). This reflects the fact that some laboratory facilities were already in place, with a relatively small proportion of the HBS requiring frozen storage and a strategy of building up HBS collection gradually. The most significant level of capital spending was on IT infrastructure and support.

Initial set-up costs	£
Refurbishment (offices and other areas)	5,000
Freezers	44,016
Other storage (e.g. liquid nitrogen tanks)	20,000
Analysers and testing equipment	141,711
IT equipment and infrastructure	217,546

Table 8 Main initial set-up costs for the NHSB

The annual operating costs (excluding staff; [Table 9](#)) amount to a relatively modest £45,000 and this includes significant expenditure on rental of the space (including associated energy and maintenance costs) and the equipment service/maintenance costs. To place these figures in context; this equates to just 15% of the annual current and anticipated future staffing budget facility (2011-2012).

Annual operating expenses	£ p.a.
Space rental	12,000
Equipment maintenance/service/calibration	9,000

Liquid nitrogen	2,000
Reagents, chemicals, kits	5,000
Tubes, boxes, other HBS storage	6,000
General consumables & H&S	2,500
Travel, subsistence	3,000
Catering	700
Printing and Stationary	5,000

Table 9 Estimated current annual operating costs (figures were not available for maintenance, electricity, services, IT maintenance)

Estimated future expenditure as shown by the business model indicates that salaries make up the largest percentage of the non-developmental costs in the short and long-term (see Table 10). As the biobank develops, there is a planned increased contribution towards other departments. The vast majority of this is to support pathology services, which are integral to the success of the biobank through their provision of both infrastructure and service support.

Predicted costs	Year end 2013 (%)	Year end 2016 (%)
Salaries	80.7	65.7
Non-salary related expenses	10.5	11.9
Equipment depreciation	4.0	3.2
Contribution towards other departments' costs	4.8	19.2
Total	100	100

Table 10 NHSB business model predicted costs (shown as % of total)

The other significant area of expenditure is in terms of developmental costs – these largely consist of investment costs associated with a LIMS, the ORCHID patient coding database and early stage project management fees. These represent an anticipated cost of over £1.5M to their completion in 2015.

Bottom-up cost analysis

The NHSB business plan breaks down the full predicted costs by department or process, for a prospectively collected fresh frozen tissue HBS. Only 12% (approximately £30) of the overall cost has actually been directly attributed to the process of taking consent and collecting, processing and storing the HBS. This percentage includes staff time, and is relatively low due to the use of volunteers for collecting consent from donors. A similar cost is associated with the preparation of the associated data (including a pathology report). In fact, numbers (Figure 10) indicate that the most substantial costs relate to overheads. These are attributable to the biobank itself (mainly support staff), the Trust as a whole (facilities, strategy, governance, estates, facilities, finance, procurement, HR, ICT), pathology (contribution to organisational costs) and R&D contracts (arrangement of contracts, MTAs, SLAs, etc). These overhead costs together account for 47% of the estimated overall cost associated with the collection of this relatively complicated HBS; for simpler HBS (e.g. serum) the overheads are likely to make up a larger proportion of the cost.

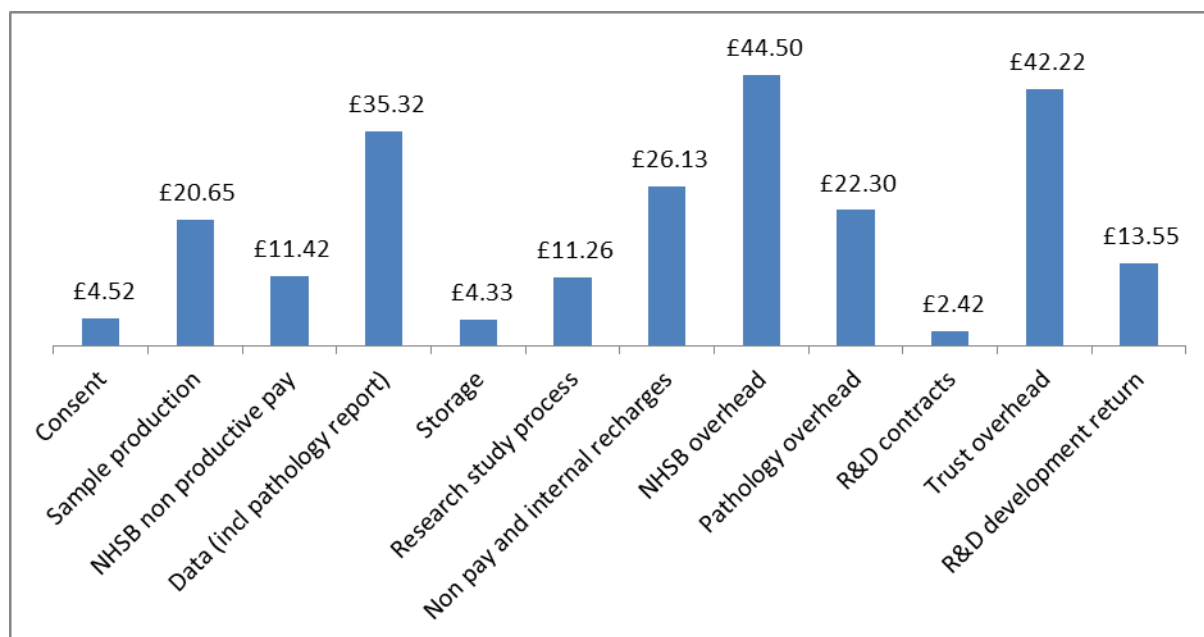


Figure 10 Departmental breakdown of the costs associated with the prospective collection of a fresh frozen tissue HBS (from NHS business plan)

Top down cost analysis

Figures quoted for 2011 indicate that approximately 15000 HBS were collected. In comparison to the overall spend for 2011-12 of approximately £416,876 (i.e. excluding overheads and substantial fixed asset or developmental investments), this equates to approximately £28 per HBS. Due to the early stage of development of the biobank, and the various provisos associated with the overall spend, and the uncertainty about how many of these HBS were actually newly acquired (as opposed to legacy collections), it is extremely difficult to put this figure into context.

As a comparison, their own business model projecting forward to the year 2018 suggests total costs of £968,000, which would require 17,334 HBS (from 4727 patients) to break even. This suggests an average cost per HBS of £56 (£204 per patient). Some HBS will be more expensive.

Summary

Nottingham health sciences biobank is an innovative project with ambitious and clearly defined plans. They have thoroughly researched the national and international biobanking market to develop a comprehensive business model, which they admit may not financially break even until 2015. They have used innovative techniques and resources to identify their potential strengths and their niche in this field – this has included the use of external consultants and FOI demands. Due to their ambitious plans and relatively early stage of development, it is comparatively difficult to gain an insight into their current HBS collection efficiency, but they do provide an interesting perspective on the potential hidden and overhead costs that need to be addressed when costing out HBS collection. Interestingly their focus appears to be primarily on justifying their costs and charges, with relatively little emphasis put on the non-financial benefits that their biobanking facility will inevitably achieve, although it is likely that this key aspect will be emphasised in future strategic plans.

FULL CASE STUDY 6: SMALL RESEARCH COLLECTION

Compiled from interviews with:

- **Professor Ariane Herrick** (Professor of Rheumatology and Honorary Consultant Rheumatologist, Salford Royal NHS Foundation Trust). 12th October 2012.
- **Dr Holly Ennis** (Institute of Inflammation and Repair, University of Manchester) by telephone, October/November 2012.

Institutional Context

Prof. Herrick is a University of Manchester academic researcher with an honorary clinical contract at Salford Royal Hospital. She has an active disease-based research programme that investigates different aspects of the pathogenesis, measurement and treatment of the autoimmune diseases Raynaud's phenomenon and systemic sclerosis (scleroderma). Prof. Herrick is the Principal Investigator in a number of clinical studies and is involved with several groups, facilitating collaborative work on systemic-sclerosis spectrum disorders.

Historical Context

Prof. Herrick established the Scleroderma research collection around 1996, shortly after being appointed as a consultant rheumatologist in Salford. With an active research interest, and access to patients attending rheumatology clinics for Raynaud's and sclerosis-spectrum conditions, she felt it was important to build up a collection of HBS that could enable future (unspecified) research. The collection originally focused on serum/plasma HBS, but has undergone various revisions and renewals since its inception. Most notably, around 2001, the decision was taken to include the collection of whole blood for DNA extraction and later, to collect skin HBS for future histopathological analyses. During 2012 the collection has undergone further development, and the management of the collection of serum HBS now falls within the remit of an internal Trust-led biorepository facility. Importantly, the samples are also no longer collected under a generic research tissue bank approval. The analysis presented here examines how the collection operated prior to these most recent changes.

Biobanking activities

Since 2009, the collection had been registered as a research tissue bank with permission to both collect samples and also to distribute them for research (within defined guidelines and subject to approval of a formal application by the local steering committee). Prof. Herrick co-ordinated and oversaw all aspects of the HBS collection, while all stages (from identifying the donors through to distribution of the HBS) were undertaken by the research group and affiliated staff.

Potential new donors and those due for follow-up sampling were identified by a research nurse during the preparation of clinic appointment lists. Consent was sought by trained research staff, and bloods were collected by clinic staff in parallel to the collection of routine clinical HBS. Serum HBS were processed immediately within research laboratories based at the hospital and stored in one of two -80°C freezers

located within the research laboratories at Salford Royal Hospital. These freezers (one of which was inherited at no cost from another research group) were approximately 20 years old but fully serviced/maintained and linked into a larger scale in-house alarm system. Whole blood samples were transported immediately after collection to the Arthritis UK (ARUK) Epidemiology Unit based at the University of Manchester where they were frozen prior to DNA extraction.

Since its inception, approximately 450 patient donors had been recruited and had blood collected for DNA extraction. In addition, these same donors have provided around 2,500 separate longitudinal serum samples. All HBS were collected in accordance with standard operating procedures and equipment was maintained and serviced regularly. Back-up and contingency plans in relation to the safeguarding of HBS are based on good-will and the fact that the collection was managed within a larger research environment where resources could be called upon if urgently required.

HBS are not actively marketed to external users, but information about the collection is openly available via the research group's university web-page. Use of the DNA samples comes through academic links or contacts and most HBS are used for collaborations, usually with no charge to the end-user, other than reimbursement of transport costs. The DNA samples have been used in a range of collaborations and contributed to 14 high-quality publications between 2010 and 2012, including in Nature Genetics.

There has not been extensive use made of the serum HBS to date beyond a limited number of small-scale collaborations. There are plans to seek funding for specific projects, as proteomic analysis of this type of HBS is considered expensive.

Income

No income was received in relation to the biobanking of these HBS. No grant funding specifically supported HBS collection and no revenue was generated from HBS supply.

Recent changes (late 2012; not covered in this case study) have sought to revise the ethical permissions, and recent changes have been put in place that mean that HBS are no longer collected for a research tissue bank, but under a project approval that has NIHR portfolio status approval; this should enable additional resources to be obtained to financially support some aspects of the collection process.

Expenditure

The overall costs associated with the collection, storage and distribution of these HBS have never been fully analysed or identified. The activities tended to take place alongside routine clinical care, with specific extra charges generally being addressed individually as they arose. The costs associated with the collection and storage of HBS were relatively modest. Freezer maintenance costs and consumables were funded from 'soft' research funds held by Prof. Herrick. The serum HBS were processed and held within a research active area of this teaching hospital; the Trust actively promoted research and in turn benefited from the overheads associated with successful research funding applications. DNA HBS extraction, storage and distribution costs were covered by the ARUK epidemiology unit, as part of its overall remit to provide infrastructure that will facilitate and support research that aids the understanding of the epidemiology of rheumatic disorders.

The most significant costs were linked to staff time, although even here the commitment was actually relatively modest as these HBS were collected alongside routine clinical activities. Some research nurse

time was available which was funded by a specific charity related to the disease area, and this time was primarily used to screen clinic lists and patient notes for suitable donors and seek consent. Historically, the research group also had dedicated research technicians for collection and local processing of HBS; these were University-funded and available to support any research taking place within their research theme. Progressively, these posts are being lost and replaced with staff appointed on short-term contracts supported by grants for specific studies. This inevitably means that providing staff time for these unfunded general biobanking projects will be more difficult in the future, and may reflect the change in approach that has been adopted for this collection, where the biobanking is now managed within a formal structure.

Collaborations and networks

All research collaborations to date, in relation to these samples, have been identified through direct academic and personal contacts as the resource is not actively publicised. The access committee that considers applications for release considers any approaches to use the samples based on scientific merit.

FULL CASE STUDY 7: UK BIOBANK**Compiled from secondary data and interviews with:**

- Interviews with **Paul Downey** (Operations Director) and **Pamela Moore** (Financial Consultant). 2nd July 2012 at UK Biobank, and subsequent email correspondence.
- Secondary data includes; the original funding application, minutes from the advisory board and annual financial statements.

Institutional context

UK Biobank Ltd is a major biobanking initiative and registered charity. UK Biobank is housed in a large warehouse situated in Cheadle Hulme, Stockport. The site is leased and the facilities have been purpose built to specification. An additional site is located in Wythenshawe, Manchester. Between 2006-2010 there were approximately 6-7 collection centres operating around the country collecting HBS from up to 1000 people per day. Over 500,000 individuals have contributed and it is estimated that by 2022, 10,000 of the cohort will have breast cancer, 9,000 will have Alzheimer's disease and some 28,000 will have died from heart disease (Nature, 2012). The biobank now houses an estimated 10 million HBS.

The aim of UK Biobank project is to build the world's largest information resource on the genetic and environmental factors that cause or prevent human diseases, including cancer, heart diseases, stroke, diabetes, arthritis, osteoporosis, eye disorders, depression and forms of dementia. It is a very high profile study, as a result of the substantial level of public funding and the high level of public recruitment that was required for it to be successful.

UK Biobank was established by the Wellcome Trust, MRC, Department of Health, Scottish Government and the Northwest Regional Development Agency. It has also had funding from the Welsh Assembly Government and the British Heart Foundation. In total initial funding was approximately £62 million. UK biobank is hosted by the University of Manchester, centrally supported by the NHS and has links to a range of British Universities.

In addition to the Board and Executive Team, UK Biobank has a Steering Committee that acts as an advisor to Professor Rory Collins and is comprises 8 leading scientists from a variety of health research backgrounds nationally. There are also four expert working groups with over 35 members (imaging, enhancements, outcomes, follow-up) that support the Steering Committee. The biobank also has an International Scientific Advisory Board composed of 14 world experts who meet annually. Finally, there are a number of Sub-Committees, perhaps the most important of which is the Access Committee that was set up in 2012 to review access arrangements. The Access Sub-Committee verifies the identities of individuals requesting access, reviews and supports their applications. The Access Sub-Committee is chaired by Tara Camm and is composed of Mrs. Lorraine Gillions (Administration), Dr Naomi Allen, (Senior Epidemiologist) and most of the senior management team.

Historical Context

UK biobank was initially conceived during formal discussions between the Wellcome Trust, MRC and Department of Health, all of which agreed that a large prospective study would provide a useful resource for biomedical research in the UK. McKinsey undertook the original scoping study and a draft proposal for a large UK biobank led to a series of discussions with international experts between 2001 and 2002. These discussions were complemented with engagement and consultation activities, partly to evaluate the feasibility of successfully engaging the public in such proposals.

The first press release confirming the joint funding for UK Biobank was made on 29th April 2002, and this was supported by a number of high profile statements from the Wellcome Trust, MRC and government ministers stressing its value as a tool for evaluating the role of genes and lifestyle in the development and progression of disease.

There then followed an extended period of discussions, planning and research to evaluate the best methodology by which to proceed. Other planning included a number of pilot studies aimed at identifying and ironing out potential problems, for example in relation to recruitment, and to identify and optimise high-quality collection procedures (Elliot and Peakman, 2008).

In 2002, the organisation of the proposed biobank was confirmed as a 'hub and spoke' model, with invitations for Universities to host the single hub (with financial management and overall HBS control) and the six spoke components (with local recruitment and HBS/data collection responsibilities through primary care). It was a regional recruitment model involving regional collaborating centres (RCCs). The University of Manchester (led by Professor Bill Ollier) was chosen and announced as the hub centre in March 2003 (together with the six regional spokes, and the CEO).

In 2005, following some disquiet amongst academic researchers and some ambiguity about central leadership and the role of the spoke centres, a change of approach was taken by the new CEO and PI (Sir Professor Rory Collins). A federated governance model was implemented to overcome the difficulties encountered by dealing with a large number of stakeholders, as well as variability in partner's collection methods. At this time, UK biobank's relationship with the University of Manchester became more arms-length, although the charity still uses some of the university's human resource capacity (e.g. pay roll).

The UK Biocentre was opened in March 2012 as a wholly owned subsidiary of the UK biobank. The aim of the UK Biocentre is to provide storage services for outside organisations. In addition to HBS management, it is able to support the development of the information systems necessary to run large, population based studies. The UK Biocentre currently houses approximately 10 'external' collections, including those of large pharmaceutical firms. In addition to HBS storage, the UK Biocentre offers consultancy advice to organisations to ensure their collections are compatible with back end processes. This type of consultancy is necessarily provided prior to HBS collection, and includes helping to design the study. For example, the UK Biocentre worked with the National Blood Service to design their collection project, which they subsequently housed. A tiered charging system operates, with projects from academic organisations being charged less than commercial firms. Profits from the UK Biocentre are appropriated by the parent company (i.e. UK biobank).

Biobanking activities

UK biobank is been involved in the design, collection, transportation, storage, processing and distribution of HBS. The resource was created specifically to collect HBS from 500,000 individuals from across the UK

aged between 40 and 69 years, between 2006 and 2010. As such, it is the only example amongst our case studies that provides a 'true' overview of the costs associated with biobanking when conducted as an isolated activity. Donors consented to have a series of HBS (including blood, urine and saliva) taken for unspecified future scientific analyses, undertook a series physical tests, and provided detailed information about their lifestyle and clinical history. In addition, they consented to allow future access to personal data (including for example, NHS records) and in some cases to participate in longitudinal follow-up HBS, visits and tests. The UK biobank has achieved both data breadth and depth (The Lancet, 2012). The Chief Scientist is currently exploring how to increase the value of HBS by linking to death registries, GP databases and HCRS. The project was designed to maximise the quantity of HBS collected with a defined budget, so minimal processing has been done. Recording the blood count was necessary prior to freezing but other processes, for example DNA extraction, have been deferred until requested.

Since the end of March 2012 users have been able to request access to HBS data and/or physical HBS. The biobank is a resource for anyone doing health related research in the public interest anywhere in the world, subject to the costs of processing the requests (Science, 2012). An online DataShowcase will allow scientists and the public to see a summary of the information collected so far (PharmaTimes, 2012). Up to July 2012, most requests had been for data rather than physical HBS, and no requests for physical HBS had yet undergone a full access cycle. The biobank suggested that most data currently being requested was for meta-analysis, and the organisation expects to see an increase in requests. Unlike some investigator-led biobanks, UK biobank will not act as a co-investigator for academics or firms who want to access the HBS (British Medical Journal, 2012). Any knowledge created as a result of research involving UK biobank HBS will be shared with the biobank after an initial secrecy period of six months to give researchers time to patent or publish the results.

UK biobank currently tracks the number of publications and patent registrations that arise from research using the biobank's data and/or HBS. In the medium term, UK biobank intends to evaluate the wider socio-economic impact of the biobank.

Income

From its inception, the funding of UK Biobank was considered controversial by many academic researchers as the funding mechanism was very different from the norm in public research (Langan, 2007). Some academics reported that this type of large-scale funding for construction of infrastructure was competing unfairly with their own traditional research funding requests for shorter-term disease-orientated collections. This mistrust may have been enhanced by the way the project was organised, with UK Biobank Ltd as a (not-for-profit, charitable) organisation at its centre.

Initial funding of £62 million has been supplemented recently by another £25 million from the Wellcome Trust, MRC and Department of Health over five years (2011-2016) to maintain the collection and facilitate and promote HBS access by researchers (Table 11). The biobank is actively exploring ways to add value to the collection and making decisions on what activities to do ad hoc, and what should be done for all HBS. As a result of this process, selected biochemical analyses are now being conducted for all HBS, and have been paid for by the current funders as well as Arthritis Research UK and Diabetes UK, who have provided a further £6 million for this purpose. The latter charities have contributed funding to enable measurement of parameters of particular interest within their disease areas.

Phase	Funding source	Time period	Income (£M)
Planning & Pilot	DoH, MRC, WT, Scottish Exec, NW	2002-2006	15
Recruitment, HBS & Data Collection	Regional Development Agency, Welsh assembly & BHF	2006-2010	47
Extra Analyses	DoH, MRC, WT	2012-2014	6
Storage & HBS Distribution	MRC, WT	2012-2017	25
Total			93

Table 11 Overview of main income sources associated with the UK Biobank

A proposal is also being considered that would provide additional grant funding of £40M to undertake extensive imaging studies of the heart and brain for a subset of 100,000 of donors.

Income is also being generated through access to UK biobank. The HBS access costs were under review at the time of writing this report. However, as of July 2012, a registration fee of £250 was being charged per application. This fee covers administration costs and also discourages applications that are not genuine, well thought-out proposals. The request is then considered by the access committee, who evaluate whether the proposed project is a good use of HBS. The biobank then creates an indicative quote intended to recover direct costs associated with accessing HBS and associated data. Indirect costs, for example, overheads, managerial salaries and rent, are not included. Indicative quotes vary significantly according to the individual application, but the highest quote to date is estimated at £1million for HBS access and DNA extraction. As DNA has not yet been extracted from the HBS, later genomic users are likely to benefit from the processing undertaken by earlier users.

In comparison, access to data is charged at an initial standard flat rate of £1,750 per access request; extra charges, depending on the time taken to identify or process the information that is requested (rather than, for example, a cost per patient), may be applied. Again this is purely cost recovery with no profit factored in and no recoup of the initial data collection costs. The IT group at the biobank extract the requested data and provide it (in a deidentified form) to the researcher. Amounts of data are usually quite small and easy to transport and store. Image data are larger. Any new knowledge created as a result of accessing UK biobank data is also shared with the biobank after a 6 month moratorium to allow publication or patenting.

Expenditure

The majority of the initial capital expenditure at UK Biobank related to provision of specialised HBS storage facilities (two sites), associated robotics, refurbishment, and IT systems (equipment and specialist software for handling collected data). The estimated figures, provided at interview, are shown in Table 12. The central storage and processing facility is a rented warehouse unit that had to be custom refurbished to accommodate specialist requirements relating to HBS storage facilities, including adequate fire-suppression and security measures.

	£M
Main site robotic -80°C storage	5.0

HBS handling robotics	3.0
Second site -80°C storage	2.5
Laboratory & office refurbishment	1.5
Data management software	1.5
Other IT infrastructure	0.9

Table 12 Estimates of the main capital expenditure associated with the establishment of UK Biobank

Of the £62 million initial funding, £15 million was provided for a pilot to test the efficiency of the high quality procedures envisaged. Once the pilot proved that the project was feasible, the remaining funds were released. In total it was estimated (interviews, 2012) that approximately half of the initial £62 million funding was spent on salaries for staff to recruit donors and collect HBS. This was due to the scale of the recruitment and the costs associated with operating 6 collection centres around the UK.

Annual running costs relate primarily to rent and salaries. The salary bill (2011 financial report) was £1.1 million p.a. This includes three senior staff (>£60,000 p.a. each), two other managers, and 16 other staff. Staffing of the biobank is highly flexible depending on the recruitment phase, but includes managers, administration, lab technicians, IT staff, security staff and equipment engineers. This includes staff at the core facility and collection centres.

Depreciation and impairment was listed as £0.7 million, with other resource costs listed as £2.2 million. It was estimated (interviews, 2012) that the minimum expenditure to maintain the UK biobank (i.e. without new HBS collection or volunteer recruitment) is in the region of £2 million per annum. This would cover the core staff, rent and essential facilities (for example, liquid nitrogen alone costs almost £0.3 million).

Assets held by the charity were recorded as £9.4 million in 2011, but these are subject to significant depreciation.

Despite the overall transparency of the project, and the enclosed nature of this biobanking model, we were unable to obtain detailed estimates about the costs associated with the different stages of biobanking the HBS. If we consider the project as a whole, crudely we can say that 500,000 patients were recruited for a total cost of £62 million; this equates to £124 per patient. With this top down approach it is important to establish what is included, and in the case of UK biobank the list is extensive: donors were identified, approached and consented; they undertook fitness tests and other physiological and clinical measurements; numerous questionnaires and medical histories were completed; blood and urine HBS were collected, processed, labelled, centralised and biobanked. Significant exclusions relate to the use of the NHS system to identify patients, the planned extraction of DNA from HBS and the donors' time (although their travel expenses were reimbursed). In terms of HBS, each of which is highly annotated and profiled, there are at least ten different HBS types per patient (with further sample collections possible), with up to four aliquots prepared from each. This means that each physical, annotated HBS 'type' cost around £12 to collect.

The post collection spending at UK Biobank (of £25 million over five years) will facilitate HBS storage during this period, advertising and promotion of the resource to researchers, and the measurement of a

number of key core biochemical parameters. This adds around £5 per HBS type (£1 per HBS type per year).

International researchers are able to access this resource at the same cost as UK researchers.

FULL CASE STUDY 8: UK BRAIN BANKS NETWORK (UKBBN)
Compiled from secondary data and interviews with:

- Interviews with **Professor James W Ironside** (Professor of Clinical Neuropathology and Director UKBBN) and **Chris Tindal** (Database Manager). 9th July 2012 in Edinburgh.
- Secondary data includes; minutes UKCRC Board meeting (7th June 2007); UKCRC Brain Bank Strategy Advisory Committee; Towards a national framework for brain biobanking in the UK; report to UKCRC(2008); MRC award letter (14th December 2009); application for fund the Network Co-ordinating Centre; minutes of the first UKBBN Steering Committee (25th January 2010); and information from the MRC website.
- Telephone interview with **Dr Joanna Jenkinson** (MRC) 22nd November 2012.

Institutional context

The UK Brains Bank network (UKBBN) is an initiative led and sponsored by the MRC on behalf of the UK Clinical Research Collaboration (UKCRC). The UKBBN aims to coordinate a national network of UK brain and brain tissue collections by means of an independently constituted and funded coordinating centre currently located at the University of Edinburgh. In order to remain independent, the centre does not conduct research itself. It is led on a part-time basis by Prof James Ironside as Director, with his current term running for four years to October 2013. It also has a part-time administrator and a full-time database manager. The UKBBN co-ordinating centre, including the director, is accountable to a steering committee that consists of external experts offering strategic and scientific advice and guidance in areas such as ethics, law and biobanking. The steering committee is currently chaired by Professor Christopher Kennard. In addition, a user group, largely made up of research active UK professors and chaired by Professor Paul Francis, offers direction to the management and steering groups on the needs of the scientific community. The user group also advise on strategy in relation to HBS quality, technical developments, national research activities, the requirements for control tissue and the requirements for associated data. Both bodies include invited observers from key organisations including UK charities, the HTA and industry. A management group made up of the Principal Investigators from each of the constituent brain banks, together with a layperson and the network director, addresses the running of the network, including the creation of policies to do with seeking consent, HBS requests, data access, HBS acquisition and handling, quality measures and defining performance assessment criteria. The group also advises on legislative requirements and technical developments and prepares the annual report.

Formal links extend beyond the major UK brain banks that are members of the network to other relevant research groups, as well as to similar brain bank networks outside of the UK, in particular BrainNet Europe (a consortium of 16 European brain banks). In addition, the management group have consulted other (non-brain) biobanks for input and advice on strategy and potential future collaboration.

The constituent biobank members of the network are either predominantly MRC funded banks (Edinburgh Brain Banks, London Neurodegenerative Diseases Brain Bank, Newcastle Brain Tissue

Resource, Oxford Brain Bank) or mixed funded charitable or NHS partner banks (Cambridge Brain Bank, Manchester Brain Bank, Multiple Sclerosis Society and Parkinson's UK Brain Bank at Imperial, Queen Square Brain Bank for Neurological Disorders at UCL, South West Dementia Brain Bank in Bristol, Sheffield Brain Bank). All these are Research Tissue Banks with their own ethics approval.

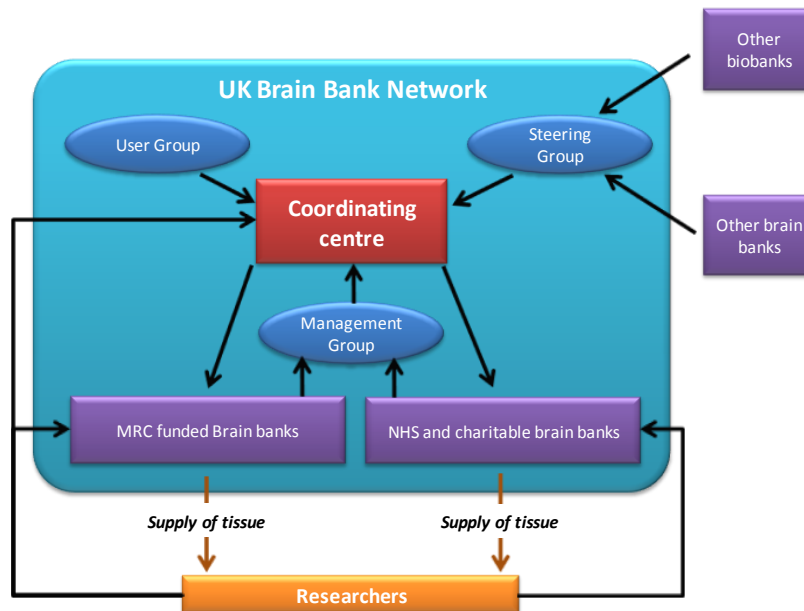


Figure 11 Overview of governance and strategic links

Historical Context

Systematic biobanking of human brains and brain tissue has been taking place for at least half a century, but until recently, biobanking has tended to be a localised activity with little coordination or central oversight. In the UK, there are 10 main brain banks that historically collected HBS based on the research interests and disease speciality of the principal investigators. In 2005, a number of these biobanks were reapplying for funding to the MRC. Biobanking proposals were competing with project proposals, and the MRC began to express concern about HBS sharing and whether there was any overlap with the activities of the other biobanks.

The MRC held a scoping workshop in London in 2006 for interested stakeholders involved in brain biobanking and research. Participants also included individuals from BrainNetEurope. Discussion took place around defining a variety of standards for brain biobanking. It was also discussed whether to form centres of excellence and it was agreed that a brain biobanking strategy should be developed. In June 2007, the UKCRC board endorsed a proposal for the establishment of a 'national network of brain banks to improve co-ordination and efficiency' (UKCRC, 2007). The MRC established a steering committee to consult researchers, with the aim of identifying reasons why, and areas where, researchers had trouble sourcing brain tissue, and highlighting the reasons (perceived or genuine) why some researchers did not undertake research using brain tissue. A report was produced with a number of key observations, most notably, the need to avoid HBS collection duplication, the proposed benefits of standardisation in methodology across the biobanks, and identification of a shortage of brain HBS from (assumed) healthy donors. The MRC was particularly interested in a forward thinking strategy because of the significant

amount of funding that it already invested in individual brain biobanks. There was also a general perception by funders that the biobanks were expensive to operate, without necessarily having the level of direct research impact desired. A report was submitted to the UKCRC in 2008 which contained a number of recommendations that were positively received. The UKCRC agreed that that brain biobanking in the UK should be networked.

The post of Network Director was advertised and James Ironside was appointed following interview, in part due to his experience in setting up the CJD biobank and his involvement in the Sudden Death and HIV biobanks. It was his role as the Network Director to devise a vision for how the UKBBN would operate and develop over the next three years, and beyond. The recommendations of the MRC report informed this strategy, as did a number of consultations with brain biobanks. An effective dialogue with putative member biobanks was perceived as critical to constructing a viable network that the existing brain banks would want to participate in.

Biobanking activities

The constituent biobanks of the network collect a diverse range of HBS, including whole brains, tissue sections and slides, blood and blood derived products (including DNA). Most of the collected HBS come from specific disease areas. An exception is the Sudden Death Brain Bank that was specifically funded and constructed by Professor Jeanne Bell to address the lack of brain tissue that was available from people who died suddenly with no apparent underlying neurological disorder.

Although individual members of the network currently operate different HBS access policies, the consensus of the network is to move towards a single model. The overall intention is that HBS should be provided free of charge, but with an access fee to recoup the minimal costs associated with access and supply of HBS (not a cost recovery model). It is hoped that these costs can be standardised across the member biobanks, to reduce internal competition between the institutions. The costs associated with HBS accrual, storage and network infrastructure are not recovered. The access policy encourages applications from all researchers, including those from overseas, and it is intended that the network will facilitate and coordinate the access, and alleviate some of the bureaucratic obstacles that researchers may have encountered when previously considering working on human brain HBS. HBS access is being facilitated by the creation of a searchable on-line databank (launched March 2013⁵²) containing deidentified information, for example the diagnosis, and the brain tissue samples available for research. Some of the constituent biobanks already have such databases, although none had them available as a web-based externally searchable resource. The UKBBN database builds on existing database and coding systems used by BrainNet Europe and Brains for Dementia Research (BDR). To this end, the database manager has spent some time visiting each site and offering advice on how to standardise terminology and records so that the data can be usefully uploaded to a centralised database. These records will provide key data on the donations held within the individual collections and can be updated as required by the individual biobanks. In addition, the centralised nature of such a database will allow a single point of reference for raising awareness amongst researchers (for example at conferences and meetings), who still frequently believe that it is simply too difficult and long-winded to locate and source brain HBS

⁵² www.mrc.ac.uk/brainbanksnetwork

Individual biobanks currently still negotiate the supply of HBS, normally as a collaborative arrangement, but it is anticipated that these arrangements will become increasingly coordinated. For example, there is a drive to adopt a standardised MTA across the network, and discussions have taken place with various relevant parties (including pharmaceutical companies) to devise terms that would be mutually acceptable.

Income

Individual biobanks can have complicated funding sources, which often include funding from many different charities or organisations. The traditional grant-based funding mechanism for has historically offered limited stability, and funding for HBS accrual and storage typically has to compete with project specific research (which frequently has a more immediate and a higher profile outcome). It was reported at interview that the MRC acknowledges biobanking is not intended to be financially profitable, but should be seen as a means to obtain the most appropriately characterised brain HBS and help facilitate the large amount of research funded on neurological and psychiatric disorders.

In this area of biobanking in particular, one of the difficulties relates to perceptions of what should be supported by the NHS itself, rather than the MRC; if the ultimate goal is better patient treatment, then arguably the NHS should contribute appropriately. The regional variation in the extent to which brain banks had been able to access NHS service support costs was reported as an issue (Steering Committee, 2010, p3). The UKCRC brain bank strategy report (2008, p11) recommends that brain biobanking should be designated as a research activity within the NIHR agenda such that funding for tissue collection 'could be obtained directly as a research-relevant "service-support" cost, or indirectly through cost-recovery from grant funding to individual banks/the coordinating centre' (ibid, p12).

The UKBBN has been funded by the MRC, in part to address the fact that they were being approached by individual banks with requests for sustainability funding with little national oversight. By providing a relatively modest amount of centralised funding, it was anticipated that the enhanced coordination would allow less duplication and a better understanding of priority areas for the collection of HBS- an activity that stands to benefit both MRC and non-MRC funded biobanks.

The MRC has committed £410,000 of funding over three years (2010-2013) for the construction of the network co-ordination centre. This is in addition to funding of almost £1 million p.a. that is provided between the existing MRC brain biobanks. A further £1.5 million of service support funding from the MRC was announced in March 2012 (MRC, 2012) to facilitate the retrieval, transport and diagnosis of the donated brain HBS over a three year period.

The MRC has committed average funding of £137k per annum to support this co-ordinating centre over a three year pilot phase up to 2013, with some additional funding for the director's salary. The facility is being developed with a long term strategy, and applications for renewal of funding are expected on a five-yearly basis after this pilot (UKCRC, 2008, p10). Although individual brain banks remain accountable primarily to their own funding source(s) it is anticipated that their individual operations should align with the co-ordinating centre's strategy (UKCRC, 2008, p10).

The MRC also provides 'pre-banking' service support funding for the benefit of all ten UK brain banks. This allocation, of £1.5 million over three years is directly aimed at facilitating mechanisms for collecting and

transporting bodies, removing the brain HBS as rapidly as possible and for making a primary diagnosis (MRC, 2012)¹. Although provided by the MRC, this funding is allocated to all associated brain banks participating in the UKBBN; this enables the charity co-ordinated collections to reimburse the expensive pathology services. This funding has been calculated on a retrospective basis, based on the number of brains that tend to be analysed annually (e.g. total funding for the year 2012/2013 was £448k). As well as significantly increasing the value of the biobanked HBS, the funds allow a confirmed pathological diagnosis to be recorded in the clinical records for the benefits of GPs, clinical staff and relatives. In most cases, this definitive post mortem analysis would not be provided via normal NHS pathology services. This funding supported an 18% increase in the retrieval of brain donations in the UK in 2012 in comparison with 2011, when no such support was available.

Expenditure

The breakdown of costs associated with the first two years of operation of the brain bank network co-ordination centre are illustrated in Table 13. The MRC funding has allowed the establishment of the coordinating centre in Edinburgh, with salaries for the director (up to 0.2 FTE), a personal assistant (0.5 FTE) and a research database manager (1.0 FTE). This last post is directly associated with the development of a web-based database for the cataloguing of all HBS held by the constituent biobanks. Some additional funding was also needed for IT equipment and server support. The intention is to enable researchers to be able to visit a single site and determine what brain HBS are available for their needs..

MRC funds: UKBBN coordinating centre	Income (£)
Staff	91,115
Travel & subsistence	19,609
Equipment	5,760
Estates	25,766
Other directly incurred costs	82,390
Other directly allocated costs	2,987
Indirect costs	66,740

Table 13 Overview of initial MRC grant for the UK Brain Bank Coordinating Centre (24 months)

Network Benefits

The brain bank network was set up to address a number of objectives relating to the collection and use of brain HBS for research in the UK - principally to increase the availability of high quality brain tissue that is available to (UK) researchers, to establish 'gold standards' and avoid duplication of effort (UKCRC, 2008 op8-9). This is considered to be a staged process, but the primary steps have already been achieved *i.e.* to bring the current UK brain banks together within the network. This has raised awareness and understanding of the biobanks that exist and highlighted areas of duplication as well as indicating areas of priority and where there is a shortage of material.

Using a collaborative approach also facilitates sharing and develops best practice in biobanking. There are clear benefits in developing a standardised approach, for example in addressing regulatory requirements (e.g. Human Tissue Act, ethical approval) relating to consent, both to avoid duplication but also to avoid inconsistency, thereby simplifying HBS sharing. In terms of tissue processing and storage, the construction

of an interacting network accelerates the sharing of new improvements in processes, techniques and technology; the aforementioned online database, for example, should eliminate time consuming (and perhaps fruitless) speculative approaches to each individual biobank.

The network has already highlighted the need for increased donation of brains from healthy individuals. Whilst there was already a suspicion amongst researchers that this type of donation was underrepresented, the network has both allowed the problem to be quantified and enabled steps to be taken to address the situation. This has been possible because of the increased profile, impact and authority that a network has, in comparison to the effects of the individual efforts of the constituent biobanks. A good example of this relates to the increased profile and coverage created simply by the formal announcement (and associated press coverage) of the network in 2009. The network also has increased authority and influence when it comes to approaching the funding bodies for resources in key areas (who in turn are less likely to have duplicated applications for smaller and less well organised collections). This has been demonstrated through the successful recent funding of the two new brain banks that focus on the collection of control tissue HBS, located in the University of Edinburgh (Sudden Death Bank) and the University of Oxford (Oxford Brain Bank). As an additional step towards increased donation of normal HBS, the network plans to establish a donor programme that will include web-based resources to advise members of the public on how and where best to participate.

Another benefit comes from bringing together Principal Investigators and associated researchers from separate banks, and hence offering benefits relating to the increased prestige offered at an international level. In turn, this allows them to liaise with similar international brain biobanking projects, thereby providing an access point for linking into global networks. The UKBBN has adopted BrainNet Europe's coding structure for categorising brain HBS. This saves time and resource, but also provides an international level of consistency, and should simplify future access by researchers from other countries.

Stated benefit	Perceived importance (out of 10)
Facilitate research	10
Standardise methods	8
Impose quality standards	8
Highlight areas of deficiency	8
Provide central databases or other IT services	8
Increase collaboration	7
Increase profile	7
Save money	7
Lead to more funding	7
Provide support for administration and regulatory compliance	7
Increased efficiency	7
Increase status and power of research	5
Reduce duplication of work	5
Provide training	5

Table 14 Interviewee's interpretation of some of the key benefits offered by a network model for brain biobanking in the UK

One of the key roles of the network director has been to address the potential concerns of the biobanks' principal investigators and reassuring them that they are not expected to hand over their collections or data. It was highlighted that they needed to be able to see the advantages of being part of a network model, and to have a forum for expressing their concerns. Meanwhile, an advantage for the participating biobanks is the enhanced potential to 'gain longer term funding stability' (steering committee, 2010, p3).

As the director, Professor Ironside's involvement in projects such as STRATUM and the CCB Harmonisation project allow the objectives and outcomes from these projects to be shared with the Brain Bank Network, particularly in relation to standards of operation, access policies and quality control.

Conclusion

The majority of the funding received by the UKBBN has been to support the infrastructure and activities of the co-ordinating centre, in order to facilitate biobanking and research opportunities. The MRC sees the UKBBN as a valuable resource that provides oversight on brain biobanking across the UK and can feed this back via a formal network. This knowledge informs the MRC in relation to the allocation of future funding within this field, with some reassurance that priority areas will be addressed with minimal duplication of resources. This has been highlighted through the modified mechanism of funding that is being rolled out to the four MRC brain banks, i.e. that future funding needs should be identified simultaneously via coordinated applications, and funding may be awarded only if applications demonstrate collaboration (through the network) in terms of common standards, performance criteria and an overall coordinated strategy so that collection is effective in addressing priority research areas.

ABBREVIATIONS

ABBA	AZ BioBank Application
ABPI	Association of British Pharmaceutical Industry
AZ	AstraZeneca
BBMRI	Biobanking and BioMedical Resources Research Infrastructure
BBN	Brain Banks Network
BETA	Bureau d'Economie Théorique et Appliquée
BIOSSES	Biological Samples Enabling Solutions
BIS	Department for Business Innovation and Skills
BIVDA	British In Vitro Diagnostics Association
CaBIG	Cancer Biomedical Informatics Grid
CCB	Confederation of Cancer Biobanks
CEO	Chief Executive Officer
CIGMR	Centre for Integrated Genomics and Research
CRO	Clinical Research Organisation
DoH	Department of Health
EGA	European Genome-phenome Archive
ELIXIR	Electronic Library Exchange for Information Resources
EM	Experimental Medicine
ESA	Ecological Society of America
ESFRI	European Strategy Forum for Research Infrastructures
ESRC	Economic and Social Research Council
EU	European Union
FfCI	Framework for Capital Investment
FFPE	Formalin-Fixed, Paraffin-Embedded
FP7	Framework Programme 7
HBS	Human Biological Samples
HEFCE	Higher Education Funding Council for England
HTA	Human Tissue Authority
HTRP	Human Tissue Research Project
HUGO	Human Genome Organisation
IMI	Innovative Medicines Initiative
IP	Intellectual Property
LIMS	Laboratory Information Management System
MAHSC	Manchester Academic Health Science Centre
MND	Motor Neurone Disease
MRC	Medical Research Council
N8	N8 Research Partnership
NAPC	Nottingham Arthritis Pain Centre

NHS	National Health Service
NHSB	Nottingham Health Sciences Biobank
NICE	National Institute for Health and Clinical Excellence
NIH	National Institute for Health
NSF	National Science Foundation
OBBR	Office of Biorepositories and Biospecimen Research
OECD	Organisation for Economic Cooperation and Development
PI	Principal Investigator
R&D	Research and Development
RCPATH	Royal College of Pathologists
RCUK	Research Councils UK
RFI	Research , Development and Innovation
REF	Research Excellence Framework
RI	Research Infrastructure
R&I	Research and Innovation
RTI	Research Tissue Bank
SME	Small and Medium Sized Enterprises
SMIP	Stratified Medicines Innovation Platform
STRATUM	Strategic Tissue Repository Alliances Through Unified Methods
TSB	Technology Strategy Board
U-BIOPRED	Unbiased BIOMarkers in PREDiction of respiratory disease outcomes
UCL	University College London
UDBN	UK DNA Banking Network
UKBBN	UK Brain Banks Network
UKCTOCS	UK Collaborative Trial of Ovarian Cancer Study
USO	University Spin Out

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