



ACADEMIC HEALTH SCIENCE CENTRES

FULL STAGE APPLICATION

Note: The accompanying “*Academic Health Science Centres – Full Application Guidance*” contains essential guidance on the information you need to provide when completing this proforma.

Please adhere to the page limits stated within each box. Only information submitted up to this page limit can be assessed. Please do not alter the margins of this proforma.

Please note this form should be completed in font no smaller than 10-point Arial.

All fields must be completed.

Please insert your unique Reference Number into the Footer space provided.

1. DETAILS OF THE PROPOSED ACADEMIC HEALTH SCIENCE CENTRE (AHSC)

Name of the English NHS Provider/University Partnership:

Oxford Academic Health Science Centre (OxAHSC)

Name, email and telephone number of the Lead Contact for the proposed AHSC:

Note: *This will be the contact for all correspondence relating to this application.*

Professor Sir John Bell, Regius Professor of Medicine, University of Oxford: Regius@medsci.ox.ac.uk
ahsc@medsci.ox.ac.uk Tel: +44 1865 289 782

Please list the members of the partnership involved in the proposed AHSC, including names of NHS Provider(s) and university(ies) involved:

Oxford Brookes University (OBU)
Oxford Health NHS Foundation Trust (OH)
Oxford University Hospitals NHS Trust (OUH)
University of Oxford (UO)

2. ABSTRACT (250 words)

In plain English, present the specific aims, goals and objectives of the proposed AHSC.

OxAHSC proposes to bring together research, teaching and clinical care activities in the four partner organisations to address some of the greatest strategic challenges to health care systems here in the UK and globally. To achieve success the partners will need to apply innovative research ranging from molecular studies through population based research and research on health systems. Through the partnership it will be feasible to provide new solutions that can then be applied in clinical settings rapidly. Core to this programme will be 6 interconnected themes that will focus on strategic issues which the partners believe are central to sustaining a successful healthcare system. These are Big Data: Delivering the Digital Medicine Revolution; Building Novel NHS, University and Industry Relationships; Modulating the Immune Response for Patient Benefit; Managing the Epidemic of Chronic Disease; Emerging Infections and Antimicrobial Resistance; and Cognitive Health: Maintaining Cognitive Function in Health and Disease.

All these themes will involve all four partners and OxAHSC will bring the four institutions into strategic alignment around a set of programmes. OxAHSC will rely on the Oxford AHSN to link it to a wider regional health system and will be governed by a Board consisting of the four Chief Executives of the partners, chaired by the Regius Professor of Medicine. OxAHSC will build on and expand close working between the partners that currently exists on a bilateral level and will extend this to integrate teaching research and clinical care from all four partners.

3. STRATEGY (4 pages)

Please provide the strategy for how the alignment of strategic objectives will continue to improve health and healthcare delivery including:

- A restatement of the partnership's goals, vision and purpose;
- Specific overall short (1-2 years), medium (2-3 years) and long term (4-5 years) objectives for the AHSC;
- A summary of the partnership's top six specific themes or work programmes of focus and how they fit into the overall strategy and goals of the proposed AHSC;
- An outline of the expected specific deliverables of the AHSC over the 5 years of designation that could not be achieved through another type of partnership;
- How success of the proposed AHSC will be evaluated, including success against specified objectives and deliverables;
- Evidence that the partnership has a strong clinical informatics platform to underpin the delivery of the proposed AHSC objectives;
- How the partnership will further align NHS provider and university strategic objectives in order to harness and integrate world-class research, excellence in health education, and excellence in patient care over the 5 years of designation. How this will lead to improved health and healthcare delivery, including through increased translation of discoveries from basic science into benefits for patients.

The overarching vision for OxAHSC is that through integration the partnership will create the environment where the best research can be immediately translated, applied and evaluated for patient benefit.

The goals of OxAHSC include acceleration and realisation of patient benefit from research, by enabling smooth transition through the stages of the research lifecycle into clinical practice. To achieve these goals the partners have created an integrated research environment, physically and strategically embedding basic and translational research with clinical evaluation. Formal designation of OxAHSC will catalyse the efforts of the partners to increase the coordination of health and healthcare related activities throughout Oxford in delivering excellence in science, care and education with the potential for worldwide impact.

Objectives

- Short Term: The key objectives in the first two years will be to initiate work on the major theme projects, establish strategic objectives for the expanding clinical informatics programme both within OxAHSC and linked to the AHSN and contribute to regional discussions on economic growth. Within the first year,

discussions with Health Education Thames Valley will begin to consider the evolution of training programmes that align with the ambitions of OxAHSC.

- Medium term: The projects in the themes should be generating data by this stage of OxAHSC and we would expect that we will have exemplar projects in two chronic disease management programmes established, a set of collaborative programmes in digital health, mapping of major infections should be well underway and discussions should have led to progress in the antimicrobial resistance drug discovery field. An immunological monitoring lab will have been established, large scale analysis of health related data sets will be occurring and we will have initiated a further open innovation platform and created a set on incubating programmes in virtual biotech companies. Decisions of priorities based on data from all these programmes will be necessary.
- Long term: The clinical informatics platform across OxAHSC, linked to the AHSN, should be capable of supporting research and clinical care in at least 10 therapeutic areas. Linkage to digital health remote monitoring information should be feasible in at least 4 of these (COPD, heart failure, mental health, diabetes). Commissioning of digital medicine should have been initiated. Molecular microbiology service should be available for routine use and progress in identifying new chronic disease pathways should allow the implementation of such pathways in a commissioned care pathway. New courses for healthcare workers should have been established and funded. Capital development should have been initiated or completed on Big Data Institute, Targeted Cancer Centre, Bioescalator and Institute for Immunology and Translational Medicine.

A summary of the partnership's top six specific themes

Theme 1: Big Data: Delivering the Digital Medicine Revolution

Large datasets are increasingly available within the healthcare system and incorporate clinical records (EPR), laboratory tests, imaging, pathology, surveillance data, genomics and increasingly data obtained by digital monitoring. This theme will apply the unique skills within OxAHSC to collect and analyse this data to provide improved disease definitions, new diagnostics, clinical decision support, and improved approaches to clinical management.

Theme 2: Building Novel NHS, University and Industry Relationships

OxAHSC has an exceptional track record of interacting in novel ways with Industry. In the presence of a crisis in Pharma and Biotech, OxAHSC will expand and develop new paradigms for creating innovative new interventions and tools alongside commercial partners. These new models may contribute to reinvigorating the industry and ensuring Life Sciences remain a vibrant part of the UK economy.

Theme 3: Modulating Immune Response for Patient Benefit

Oxford's very considerable strengths in immunology and the established track record in discovering and developing both diagnostics and therapeutics will be used to align the partners around a set of programmes directed at redefining these disorders, identifying new and more powerful interventions directed at curing disease and establishing the capability to monitor a wide range of variables across the immune system that would allow the identification of disease subtypes and markers of therapeutic response.

Theme 4: Managing the Epidemic of Chronic Disease

The growing burden of chronic disease including diabetes, vascular disease, cancer, COPD, and mental illness demands new radical approaches to care that lead to better patient outcomes at lower cost. The partners all have a major interest in developing these new approaches to care, enabled by novel technological solutions and interdisciplinary support. This theme will explore and validate these approaches with the intention of establishing commissioned care pathways that are supported by strong evidence of both outcome and cost benefits.

Theme 5: Emerging Infections and Antimicrobial Resistance

Oxford partners have unparalleled capabilities in this field, with global reach and established surveillance capabilities recognized by the WHO, Public Health England and major charities such as the Gates Foundation. Because of its critical status for public health we will direct a programme that incorporates global surveillance and mapping as well as the development of molecular tools for tackling infections that can be applied in any setting (hospital, community, globally). This will be supported by our programme in animal health and our vaccine capabilities.

Theme 6: Cognitive Health: Maintaining Cognitive Function in Health and Disease

OxAHSC partners together have enormous scope to contribute to a better understanding of the major

neurodegenerative diseases, with strength in vascular dementia, Parkinson's Disease and with Simon Lovestone's recruitment, Alzheimer's Disease, This programme will prioritize discovery science and will create an environment optimized for clinical trials by creating memory clinic capabilities that allow early detection of patients and outcome measures that better reflect quality of life.

An outline of the expected specific deliverables of the AHSC over the 5 years of designation that could not be achieved through another type of partnership

Short-term deliverables (1-2 years)

- Establish single strategic oversight for electronic records integration
- Initiate new training programmes to support development of new healthcare workforce including chronic disease management and scientific staff to support large data analysis in hospitals
- Initiate development of Big Data Institute

Medium-term deliverables (2-3 years)

- Complete Targeted Cancer Centre with integrated Molecular Diagnostics and Imaging capacity
- Obtain NHS funding to support roll-out of digital medicine initiative
- Initiate construction of Bioescalator

Long-term deliverables (3-5 years)

- Complete programmatic objectives for 6 themes (see 2.0)
- Establish new Open Innovation Platform for 10+ pharma companies, new collaborations with 4 mid-size companies, create 15 SMEs
- Establish new pathways of care for 4 chronic diseases, integrating prevention, acute management and community based care, and utilising digital tools to empower patients and carers

How success of the proposed AHSC will be evaluated, including success against specified objectives and deliverables

- Progress in themes will be evaluated against specific milestones and metrics agreed by the OxAHSC Board
- Capital plans will be assessed against targets
- Clinical informatics will be assessed for evidence of record integration, data warehouses for disease areas associated with standardised datasets, availability of simple access to all records via patient identifier
- Increase in Life Sciences economic activity and evidence of an additional £500 million of Gross Value Added (GVA) In Oxfordshire over a five-year period

Evidence that the partnership has a strong clinical informatics platform to underpin the delivery of the proposed AHSC objectives

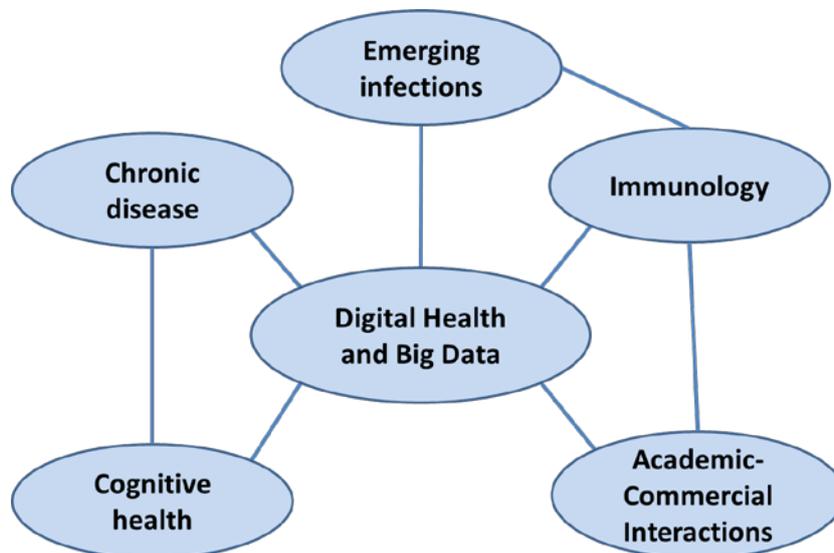
- OxAHSC has a major commitment to the development of robust systems of health informatics that will aid its research endeavours. As a platform, both OH and OUH have established electronic patient record systems that are progressively being rolled out across all services. Particularly strong data warehouses exist for infectious disease and microbiology where clinical and genomic data are available and where health records are linked between tertiary and primary care. In cancer, data warehousing has been expanded dramatically in the last year to accommodate phenotypic data as well as genomic profiling data of cancers. Diabetes is being developed as an exemplar of chronic disease management again intended to bridge across all care providers in a single integrated system.
- OH's electronic patient record is also advanced and OH/OUH True Colours system is particularly innovative in acquiring significant amounts of patient inputted data for the tracking and monitoring of the major psychoses, particularly bipolar disorder. This is now being taken further with both universities in their bid for an NIHR applied research grant to look at its application in other long term conditions including perinatal mental health.
- UO has benefited considerably from the strong interest in health records in the Computing Science Department led by Jim Davies, and has taken national leadership roles in developing health records for research purposes. OUH has taken the lead on the NIHR Health Informatics Collaborative (NHIC). This collaborative brings together the five hospital Trusts (also bidding for AHSC designation) hosting major comprehensive biomedical research centres in the South East to create common warehouses for clinical data. Data warehouses are currently being developed in acute coronary syndrome, ovarian cancer, renal transplantation, intensive care medicine and chronic viral infections (HepC, HepB and HIV).
- Oxford has many other substantial capabilities in healthcare related data. Its imaging groups, led by Steve Smith and Stephan Neubauer, are two of the leading groups globally in acquiring and developing the analytical tools for brain and heart imaging. The FMRIB group are part of the Human Connectome project and are also leading the acquisition of 100,000 brain MRI scans as part of the Biobank cohort. In

the field of genomics, Oxford has a strong position in collecting and managing clinical genomic data. Our epidemiologists have extensive experience utilising the large national sets of patient data available for follow up of large patient cohorts including the Health Episode Statistics (HES) database, cancer and death registries, and are closely involved in developing other large sets of data that will be accessible for follow up of patients in their cohorts.

- Central to many of these initiatives are the analytical capabilities being developed in the Big Data Institute. It is planned that the Institute will be completed in two years' time and will house 350 scientists from UO Departments of Computing Sciences, Statistics, Engineering and Medicine, focused predominantly on the characterisation of large datasets associated with patients being managed in the healthcare system. OxAHSC therefore, has a strong commitment and interest in the continued evolution of the NHS' unique health record capability and is determined to provide leadership in this crucial area of biomedical research.

How the partnership will further align NHS provider and university strategic objectives in order to harness and integrate world-class research, excellence in health education, and excellence in patient care over the 5 years of designation. How this will lead to improved health and healthcare delivery, including through increased translation of discoveries from basic science into benefits for patients.

- The six themes selected for priority in OxAHSC bring together expertise and established programmes of the four partners to improve the speed and effectiveness of these initiatives. In each theme, multiple partners are contributing in different ways to ensure that the trajectory between discovery and translation into routine practice is steep and rapid. The themes have been chosen because of their potential impact on patients and the NHS and have linked partners with expertise in discovery, translation, clinical care and teaching. The need for multi-partner participation is evident in every theme and most of the themes show interdependence with other themes, allowing partners to contribute directly or indirectly to most of the programmes.



- Each theme will allow partners to benefit from contributions across the partnership. This will require tight alignment of projects to ensure success. For example, the Big Data theme will require the strong analytical skills of UO, contributions to electronic patient records from both Trusts and contributions to training from OBU. All partners will need to contribute to programmes intended to facilitate economic growth, either from discovery efforts (UO/OBU) or through contributions to development (OUH/OH). Approaches to basic and translational research in Immunology will involve both Universities and both Trusts while in Chronic Disease, OBU will provide crucial training capability for a new type of healthcare worker and the Trusts will need to flex their care pathways to accommodate significant changes. For the Emerging Infections theme clinical input from the OUH will be crucial, alongside UO international surveillance programme and the need to train new types of public health workers (OBU). Cognitive health will need hospital and community support for patient access in acute (OUH) and chronic (OH) neurodegenerative disease. Again, training will be an essential component of altering the nature of care

for these patients (OBU).

4. GOVERNANCE AND LEADERSHIP (2 pages plus an Organogram)

Detail the governance and leadership arrangements for the proposed AHSC including:

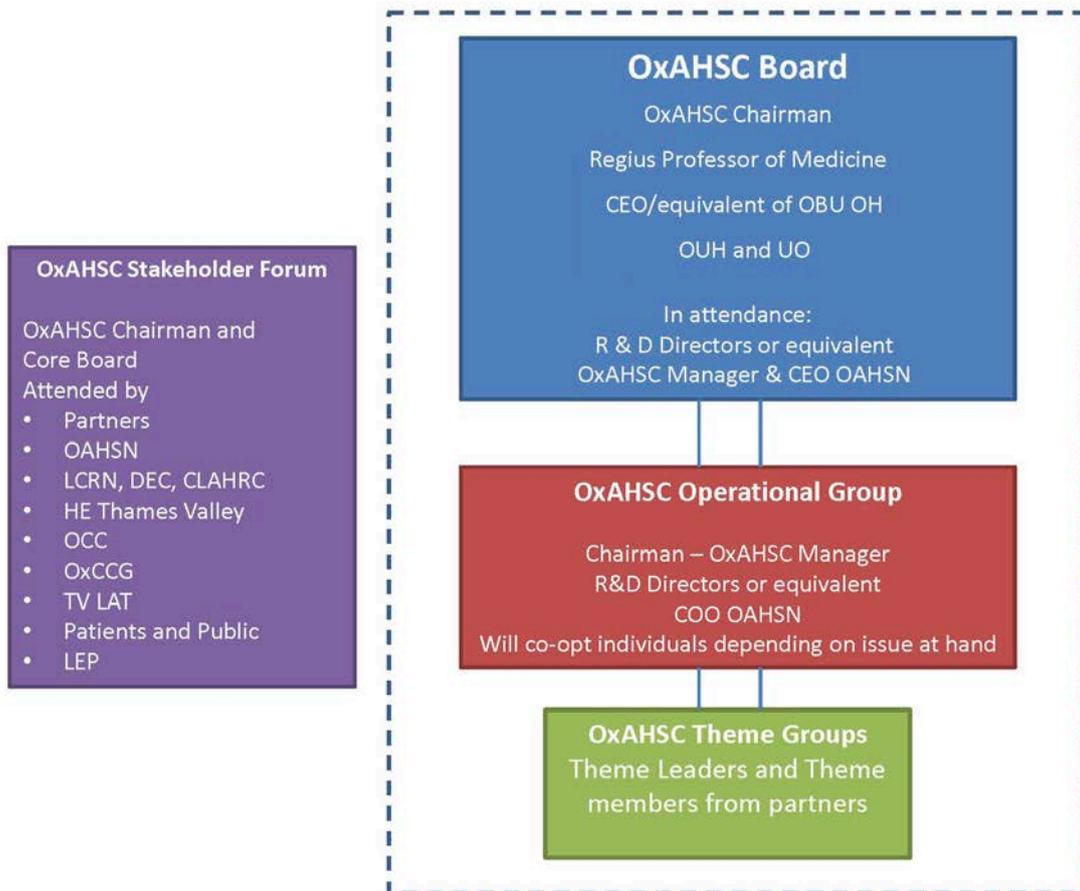
- Details of the organisational model and governance arrangements of the proposed AHSC. This should include an organogram outlining lines of accountability within the governance arrangements;
- Evidence of the functionality and effectiveness of the governance arrangements;
- Detail of the leadership of the proposed AHSC including key posts and post holders, illustrating how the posts will contribute to the delivery of the goals, visions and purpose of the proposed AHSC.

- The **governance structure** builds on existing strategic and operational bilateral partnerships between OxAHSC partners which had been put in place in the last two years. The strategic partnership between the UO and OUH, with the Strategic Partnership Board, is an example. The bilateral working agreement between OUH and OBU is another example reflecting the importance of these relationships in delivering common objectives. The governance of OxAHSC brings together these four partners as a means of recognising the four way partnership and the strengths and value that can be drawn from this without in any way impacting on the existing arrangements.
- **OxAHSC Board** will be chaired by Professor Sir John Bell, Regius Professor of Medicine, UO. The members are Mrs June Girvin, Pro Vice Chancellor and Dean, Faculty of Health and Life Sciences, OBU; Mr Stuart Bell CBE, Chief Executive, OH; Sir Jonathan Michael, Chief Executive, OUH; and Professor Alastair Buchan, Dean of the Medical School and Head of the Medical Sciences Division, UO. The composition will ensure a flexible and inclusive management structure to oversee the delivery of the themes and integration of high quality research, care and education as set out in the strategy agreed by the partners. A key function for the Board will be to ensure that any potential barriers to delivery are resolved quickly at the right level and that any resources required in support of the objectives can be identified without delay. The Board will meet at least bimonthly.
- Board membership means that no additional agreements are required between the partners as OxAHSC decisions can readily be cascaded through each partner in line with existing arrangements. The individual members' accountability remains within their own organisations. OxAHSC will develop a formal working agreement in support of its activities.
- Also in attendance will be the partners' R & D directors (or equivalent) and the Chief Executive of the Oxford AHSN reflecting the importance of partnership with the Network and its role in the translation and dissemination of research findings, innovations and improvements in health and education. The Board will assume responsibility for delivering the main objectives of the OxAHSC, including the six themes. Additional programmes of strategic importance will also be considered by the Board at the request of at least two partners.
- The Board will meet at least twice a year with stakeholders and others as the **OxAHSC Stakeholder Forum (SF)**; this group will receive updates on the strategy of OxAHSC, reports on progress with the Themes, specific updates in relation to, for example PPI and PPE, and on updates on steps being taken to further integrate research, education and patient care. Key Stakeholders include the Oxfordshire Clinical Commissioning Group, the Oxfordshire County Council (public health and social care), Oxford AHSN, the Thames Valley CLRN (Thames Valley and South Midlands CRN from 1.04.2014), Health Education Thames Valley, and Oxfordshire Local Enterprise Partnership and its partners including Oxfordshire County Council and Oxford City Council. Representatives from patient and public groups will also be invited to attend these meetings. The SF meetings will also be used as an opportunity to showcase the themes and other aspects of OxAHSC's work.
- Accountable to the OxAHSC Board will be the **Operational Group (OG)**. The partners will appoint an OxAHSC Manager to ensure coordination and delivery of work under the themes. The OxAHSC Manager will chair the OG consisting of the partners' R & D directors (or equivalent) and COO of Oxford AHSN. The OG will ensure that the delivery of the six themes is monitored, that the right resources are in place to meet the Themes' objectives and that any issues are raised with the Board for resolution. The Theme leaders will attend these meetings as required to report on progress and to highlight any issues to be resolved. The OG will also ensure that the full engagement of all partners is maintained during delivery of the themes and objectives.
- The **Theme groups** proposed for the OxAHSC will draw from existing activities across the partnership, and in particular the Biomedical Research Centre and Unit. The strength of this foundation is that OxAHSC will benefit from the thematic alignment and governance arrangements already used by the partners promoting delivery. The Theme Groups will in turn be accountable to the OG through the

OxAHSC Manager who is accountable to the Board through its Chairman. The Theme leaders will make sure that updates are provided on the activities of the themes in line with their aims and objectives (see theme forms) which in turn support the aims and objectives of OxAHSC.

- The effectiveness of the governance arrangements of the partnership will be measured through delivery of agreed themes and objectives as monitored by the CB and through reports considered through the individual partners' governance arrangements. A formal review of delivery will take place after one full year of designation for discussion at OxAHSC Board and by the partners' governing bodies. The review will take the form of an Annual Report and will highlight delivery of themes and their objectives, workforce development, developments in education and training, partner engagement, stakeholder engagement and the effectiveness of plans to develop both PPI and PPE.

OxAHSC Governance



5. THEMES/WORK PROGRAMMES (4 pages per theme)

Please use the Specific Theme Form to complete this section (*SpecificThemeForm_AHSC-2013-10004*). Please use a separate form for each of the six specific themes or work programmes.

Theme leads

6. INCLUSIVITY AND DIVERSITY (2 pages)

Please provide evidence of the proposed AHSC's commitment to equality and diversity including:

- How the partnership will realise the full potential of talent from across the whole workforce including promotion of equality and diversity;
- The partnership's strategy for meaningful patient and public involvement (PPI) in the delivery of the objectives of the proposed AHSC;
- The partnership's strategy for meaningful patient and public engagement (PPE).

How will the partnership realise the full potential of talent from across the whole workforce:

- The partnership will draw on existing expertise and structures wherever possible and work will be coordinated across the partners and with the other key organisations to draw on relevant skills and expertise. Events will also be arranged to support the Athena Swan programmes in both Universities.
- As one of its activities to realise its core value of equality, diversity and inclusion, OBU submitted an application for an Athena SWAN bronze Award in November 2012. This is fully supported and resourced by OBU's senior management team and will be the first in a number of applications to reflect the University's commitment to women in Science, Engineering and Technology. OBU also has a detailed action plan in place to cover all aspects of this and other aspects of equality and diversity. OBU's Vice Chancellor is co-chair of the Equality Challenge Unit, which works to further and support equality and diversity for staff and students in higher education across all four nations of the UK.
- UO's VC and the four Heads of Divisions launched a special fund; the Vice-Chancellor's Diversity Fund, is made up from both divisional and central contributions. One of the primary aims of the new fund is to address the under-representation of women in senior research and academic posts. Much good work is being done across the University to support the appointment and promotion of women, and the progress made in the sciences has been acknowledged with Athena SWAN Bronze Awards to seven departments and Silver Awards to a further four - a tally that puts Oxford second equal among universities nationally. There remains much more we can do, including extending work for Athena SWAN to all disciplines, and the creation of the new fund signifies the priority UO attaches to this work.
- UO made a number of applications during 2013. Bronze awards have already been made in the Departments of Primary Health Care Sciences, Biochemistry, Clinical Neurosciences, Engineering Science, Experimental Psychology and Chemistry.
- Joint working has already allowed the most appropriate partner to lead an activity with support from the other organisations, and shared understanding of approach has removed barriers, improving communications outcomes and allowing a quick response to opportunities. For example, targeted media activity to aid recruitment to the BRC Cognitive Health in Ageing project (involving all partners) ensured strong media coverage which increased the project's daily web hits from 11 to 2,400 and led to 300-plus potential participants coming forward, allowing the project to complete its recruitment.
- The partnership will draw on and extend existing initiatives for all staff groups, extending multidisciplinary and multiprofessional opportunities and ensuring equity of access to opportunities, for example, in developing research capability and capacity, working with the HE TV. As an example, OUH is a national leader in implementing Modernising Scientific Careers (MSC), a radical programme designed to harmonise and modernise training pathways across the NHS scientific workforce. The process of redesigning the scientific workforce in an appropriate, targeted but flexible way is underway to develop these knowledgeable and highly skilled individuals to their full potential. MSC career pathways are already producing highly trained, multi-disciplined clinical scientists and engineers across the Physical, Life and Physiological Sciences, able to contribute significantly to all OxAHSC themes. In particular, new Scientist Training Programmes in Genomics, Clinical Bioinformatics and Clinical Engineering will provide the scientists needed to support the Big Data theme. New schemes are being introduced to expedite research and innovation outcomes, including using scientist trainees at the end of their NHS training programme, and students at the end of their PhD programme, to undertake one/two year projects. This will maximise use of their acquired expertise before they join the substantive workforce, and provide a return on our investment in their training.
- Both OH and OUH are fully committed to the Equality Act 2010 and have objectives and plans in place to support and promote equality and diversity throughout their organisations.
- Events to promote inclusion of PhD students and ECR as well as senior colleagues will be held, for example, an OxAHSC Annual Research Meeting – using themes and cross cutting topics such as Women in Science, outreach and patient engagement. OxAHSC Stakeholder Forum will also provide

the opportunity to showcase the work of the themes.

- OxAHSC will work with the Oxford AHSN which will coordinate a strategic approach for both PPI and PPE across OxAHSC partners and key stakeholders within the local geography – the BRC and BRUs, The Thames Valley and South Midlands CRN, the CLAHRC and Health Education Thames Valley. This will ensure the widest range of resources can be drawn on for the benefit of all. The Oxford AHSN has a lead for patient and public involvement engagement and experience and will work with colleagues at OUH, OBU, UO and OH to develop and implement realistic strategies for the consideration of OxAHSC as part of the wider work. In addition, the skills and experience of the CRN, the CLAHRC and CCGs will be available to OxAHSC, and in turn it will be able to share the resources, skills and knowledge of its partners.
- OxAHSC will identify leads for patient and public understanding/outreach and for patient and public engagement. The intention will be to encourage all major research teams to have patient user groups – building on good practice of OBU Movement Science Research Group – adult and children’s user groups, and the BRC’s development of patient panels for Research Themes, e.g. Patient panel for the Infection Theme. This approach will also ensure that staff from all groups will be exposed to the methods for strong patient and public engagement and the importance of this not only in research but across all areas of activity. Family group for vaccines research (Andrew Pollard and Matthew Snape) are in place and Parkinson’s Disease has strong support locally and nationally for research under the functional neuroscience theme.
- Examples of activity already underway include: cross-Oxford AHSN PPI/E mapping exercise in progress; BRC Patients in Research website being developed across Oxford AHSN geography; currently in consultation/ collaboration with NIHR and INVOLVE; development of a shared PPI payment policy; developing shared metrics for PPI; individual research themes will describe specifically how patients and the public will be involved in the range of research activities across research cycle e.g. OxBRC Infection Theme – Creating research projects with patients for patients. In addition, local Priority Setting Partnerships (PSPs) are being established for identification of research uncertainties; these build on the existing BRC commitment to fund PSPs locally; this work will be supported by the appointment of two James Lind Alliance PSP Advisers in-house, the first such appointments in the country.
- The HEXI Education Group is coordinating work on PPI in medical education and OUH is developing a strategy in line with GMC requirement to involve patients in curriculum development through to examinations – using real patients, actors and patient experience video. The Group will be extending to involve OBU and hence a range of health education students. A researcher is to be appointed to develop the evidence base.
- Methods for PPE will include the use a multi-media approach including traditional media, digital media, social media and events. The approach will develop over time and initial work will result in feedback to contribute to improved communication, engagement and consultation. The experience of OH as an FT with a well-established membership and that of OUH in developing its membership will be drawn on to continue this work in a focused way.
- A crucial component of the Big Data, Chronic Disease and Cognitive Functions themes will be the empowerment of patients and their carers. Mobilising and engaging patients is likely to revolutionise chronic disease management and we intend to focus on technologies that enable patient and carers’ involvement.
- The partners will engage the wider public through mechanisms including Open Days, (cf BRC Open Day), Science Bazaars with Health Research Themes in developing patient and public engagement. An annual series of events will be considered – for example, a Health Research Week similar to the national science and engineering weeks where partners open their doors to the public in a range of events as well as local events organised by organisations including Science Oxford. OxAHSC’s Stakeholder Forum will provide the opportunity for the public and patients to engage directly in its activities and the meeting will provide opportunities for showcasing the work of OxAHSC and its partners together for the first time.
- OBU already has a number of outreach activities linking into the community which range from Baby Café, the Biotech Loan Scheme for local Schools, and events with Pegasus Theatre. OBU has appointed a Science Communication Research Fellow to support and develop this work. The experience of both OBU and UO in engaging with the public, and particularly young people, to raise awareness and interest across their activities, particularly in the life sciences, will also be drawn on.
- OxAHSC will develop a website to promote and share its activities and provide information for the wider public, particularly on its themes and priorities. It will be able to act as a landing page for partners’ sites and include a range of features of interest to the public wanting to find out more about how to become involved in research and research related activities. A wide range of features will be available through the website including podcasts to incorporate the theme leader and information from patients and

researchers in the areas being covered. Links will be provided to resources including Healthtalkonline, James Lind Alliance, INVOLVE, NIHR, the partners' websites, the OAHSN and the BRC.

7. CONTRIBUTION TO ECONOMIC GROWTH (2 pages)

Detail of the proposed AHSC's strategy and ambition for contributing to economic growth including:

- The track record of the partnership to contribute to economic growth and the economy, including through improved health outcomes and through collaborations with industry;
- The strategy for how the proposed AHSC will contribute further to economic growth and the economy together with plans to measure this contribution;
- The plans and strategy for identifying, managing and exploiting intellectual property, including the track record of patents filed and granted, the establishment of spin-out companies and income generated from the commercialisation of intellectual assets.

Partners in OxAHSC are crucially important contributors to the Economic Growth Agenda, both nationally, locally and regionally. UO, OUH, and OBU have contributed to an analysis of the high tech cluster undertaken over the past year by the economic consultancy, SQW. This report, to be announced by David Willetts on Oct. 3rd, described for the first time the size, scale and potential of the Oxon high tech cluster. Healthcare and biotech were one of four major technology sectors identified and, together, the Oxon cluster – although fractionally smaller than Cambridge in terms of numbers of employees and companies using a very conservative definition of “high tech” – is approximately the same size as Cambridge when publishing and automotive is included in the category. Crucially, however, Oxford sits at the Western end of the UK's largest high tech cluster - Thames Valley (TV), which incorporates a wide range of high tech R&D manufacturing and services capabilities. A key output of the SQW report was to identify contributions that the partners could make to further enhance economic growth and OxAHSC will play an active role in the evolution of the Economic Growth Strategy, both for Oxon and for the wider TV.

In the biotech sector, the partners already have a well-established position and the Oxon Cluster has more than 150 biotech companies, including some of the most successful biotech start-ups in the UK. They were responsible for more than half the new inward investment in biotech in the UK over the past year and include all the companies which struck major pharmaceutical deals in the last six months, including Immunocore, Adaptimmune, Oxford Cancer Biomarkers and Oxford Nanopore. Oxford can also point to a range of improved health outcomes from its research activities. In particular, the demonstration of efficacy and utility of most of the major therapeutic interventions in cardiovascular disease, as demonstrated by the CTSU's programme of large-scale trials over the past 20 years, has had an enormous impact on health outcomes and with this economic impact.

Creating further economic growth is a major objective of OxAHSC, as it is for Oxford AHSN and all partners. In life sciences, this is a significant challenge. The pharmaceutical company model is under serious threat and the two major UK based pharmaceutical companies are attempting to evolve their business model to ensure their continued success in the future. Both these and other pharmaceutical companies need to evolve their innovation model and all are looking outward to partners to help them discover and develop truly new efficacious medicines for conditions with a high disease burden. Given that many or most previous academic industry collaborations have been unsuccessful, we are actively considering new ways to engage the industry. This is the subject of a specific theme in the OxAHSC bid. Similarly, venture capital for the biotech sector has largely disappeared; even in California, 80% of the funds in this area have been unable to raise money, mostly due to the high risk associated with this form of innovation and the very long gestation period of most biotech companies.

We are reconsidering our approach to partnerships with the pharmaceutical sector. We have had considerable success with novel relationships with mid-sized pharmaceutical companies, UCB, Takeda, Gilead and NovoNordisk. These are amongst the most rapidly growing and most innovative companies in the sector, making interactions with the academic community relatively easy and successful. We have well-established relationships with the pharmaceutical industry through our large clinical trials in cardio/metabolic disease. The Clinical Trials Service Unit (CTSU) is one of the largest clinical trial programmes in academia and the Diabetes Trials Unit led by Rory Holman undertakes more large scale trials in diabetes than any other centre in Europe. We have a range of other specific relationships that are either broad strategic relationships (Merck and inflammatory disease) or focused specifically on collaborations to develop individual molecules (Novartis). The novel approaches to large scale clinical trials developed in the CTSU have been the focus of attention of many major pharmaceutical companies, all attempting to reduce the cost of their late-stage programmes. This approach, which focuses on

statistical approaches to managing data rather than CRO monitoring and which utilises essentially paperless trials has been transferred to a range of pharmaceutical companies, including Merck, GSK, Roche and Novartis.

The most innovative approach to engaging large pharma companies, however, has been through our Structural Genomics Consortium (SGC) open innovation platform. This platform relies on precompetitive research activity in fields where pharmaceutical companies cannot easily undertake the basic research needed to identify and characterise new targets and also develop small molecule probes that can be used for proof-of-concept testing. SGC has a collaboration of this kind with nine major pharmaceutical companies which have brought in \$80m research funding in the field of epigenetics. Other open innovation programmes are planned.

In the biotech sector, the challenges confronting all high tech clusters are also evident in Oxford. Companies are usually spun out far too early, gestation periods are too long and the risk is too high for venture capitalists to make significant returns. Despite this, several Oxford based biotech companies have made very substantial progress; for example, Immunocore and Adaptimmune have signed two major pharmaceutical deals in the last six months, worth over \$600 million in direct support and more than \$10 billion in Biodollars. Nevertheless, we are experimenting with other approaches to creating value in the biotech sector reducing the risk for risk capital investors and insuring the creation of more successful start-ups. These approaches include:

- Creating a low cost environment where single management teams may manage multiple single product companies simultaneously. We are attempting to create an environment where biotech companies can be physically adjacent to the large biomedical campus near all four partners in Headington. This has been very considerably facilitated by the development of estates owned both by UO and OUH.
- We are seeking out funds that support both activity in academia and the transition to commercial entities and have become the UK site for the Harrington Fund.
- The partners are participating in and developing plans to fund more activity in the universities and hospitals that allows programmes to go well beyond target discovery and into proof of concept studies, without creating a small company. We are working with Stanford on such a project evaluating utility of CD47 antibodies in cancer. SGC has a wide programme intending to do proof-of-concept studies in pre-competitive mode, and we are looking for other opportunities for funding of pre-competitive projects within universities before they are spun out. Creating a new model for biotech where the commercial activities begin after targets and molecules have been de-risked at proof-of-concept stage is very likely to create a highly successful industry if it can be achieved in even a limited number of cases.
- Having expertise available to ensure that academic groups properly develop their molecules is crucially important and UO is engaging a group of established ex-industry experts to provide both rigorous external assessment of programmes and also to provide advice on the appropriate development strategies.

We hope that these approaches will help transform the nature of the biotech sector in the UK, again creating viable commercial organisations capable of pursuing innovative science and, in some cases, eventually growing into mid-sized pharmaceutical companies.

A crucial component of our strategy for life sciences is consideration of how we can participate in new areas ripe for commercial development and position the UK powerfully in these new economic sectors. We already have several excellent examples. The first is in the field of health informatics where we have an important set of expertise in all partners in OxAHSC. This provides us with a unique opportunity to develop a new range of digital monitoring tools alongside informatics capabilities and software that will create new clinical decision support, novel diagnostics and new paradigms for healthcare delivery. This is a rich field where the UK is in a unique position internationally; the NHS' clinical records, alongside projects such as the 100,000 Genome Project which will bring genomics and clinical data together in single, anonymised databases for analysis, provides a remarkable opportunity for the UK to thrive in this area. What is needed is real expertise in informatics, statistics and algorithm generation through processes such as machine learning. It is our intention that the Big Data Institute will house much of this expertise and we have left space for the necessary capabilities and software development to insure the creation of new companies in this area. Two start-ups are being developed at the moment and we see this as an enormous engine for economic growth in the UK. If properly applied, it will be a major new focus for commercialisation over the next five years.

The hospitals provide ideal environments for the evaluation, particularly of medtech innovations, and this too will be a significant focus in the next five years. For example, we are developing a collaborative programme with Pronova which operates at the cutting edge of radiation oncology development with integrated machines capable of delivering both proton beam therapy and imaging simultaneously. These have the potential of dramatically altering the cost base of proton beam therapy. Pronova is moving its European headquarters to Oxford alongside significant R&D activities and a manufacturing base. The

attraction of Oxford is the local expertise in radiation oncology, the strong clinical presence in the OUH and the new Targeted Cancer Centre and the possibility of having R&D facilities immediately adjacent to this major hub for biomedical research.

The success of Oxford will be judged by its ability to increase both employment and productivity in its high tech cluster over the next five years. We have targeted an increase of £500 million GVA in the next five years to be added to UK GDP. We expect to continue to be amongst the leaders and start-up companies and would hope to lead the country in commercial income based on industrial collaborations.

A crucial element of this strategy is the protection and exploitation of intellectual property. Although UO has an outstanding record in creating spin-outs (#1 in the UK for spin-outs in 2010-2012 (PraxisUnico Spinouts UK Survey Annual Report 2013), there is still a need to modernise the approach. In keeping with the nature of the partnership, all four partners will maintain responsibility for IP protection. OxAHSC will coordinate its exploitation plans, utilising Theme 2 to develop not only more spin-outs and licenses, but also to create more successful companies.

The real success of the Oxford programme however, may also be judged in the context of the ability of Oxford to work more effectively with Imperial College in jointly developing the Thames Valley Cluster and then working with the other London based medical schools and Cambridge to genuinely create a South East Cluster that could compete with the major clusters globally in life sciences. This has been difficult to achieve in the past because of competition between the organisations, but we are beginning to develop much more effective interactions and this should be the overall goal of the programme.

8. STRATEGIC PARTNERSHIPS & WORKING WITH NIHR-FUNDED RESEARCH INFRASTRUCTURE (2 pages)

Detail of the proposed AHSC's strategy for building meaningful external partnerships including:

- The strategy for linking with NIHR-funded research infrastructure, e.g. Biomedical Research Centres or Units, CLAHRCs, Healthcare Technology Cooperatives, Diagnostic Evidence Cooperatives and Clinical Research Network;
- Other existing strategic partnerships, and the strategy to develop new partnerships, that will enhance the delivery of the proposed AHSC's objectives.

Collectively OxAHSC partners through their receipt of significant infrastructure funding from DH/NIHR and BIS/Research Councils can leverage academic, education and clinical resource at all stages of the innovation pathway to support the development of technologies to deliver benefit to NHS patients. At the core of this effort is the critical mass of research infrastructure created in partnership with the National Institute for Health Research (NIHR) which brings together all participants in research, promoting involvement and engagement of patients and public, iterating throughout the research pathway and life cycle to deliver priority driven and relevant healthcare solutions. These major investments include:

- The **NIHR Oxford Biomedical Research Centre (BRC)** based at OUH is a £95m programme is delivered in partnership with the UO, comprising fourteen research themes translating research into patient benefit. In addition, Oxford BRC collaborates with other BRC hosts and colleagues on both individual programmes and initiatives as mentioned below. **NIHR Oxford Musculoskeletal Biomedical Research Unit (BRU)**. The Oxford BRU is a world leading specialist research capability bringing together a partnership of the OUH's Nuffield Orthopaedic Centre with the UO's Nuffield Department of Orthopaedics and Musculoskeletal Sciences. **NIHR School for Primary Care Research**, the UO Department Of Primary Care hosts the office of the National Director of the NIHR School for Primary Care Research, co-ordinating eighty centres of excellence in primary care and providing a direct link between the Oxford CLAHRC and this national infrastructure. OH was designated host of a **NIHR Collaboration for Leadership in Applied Health Research and Care (CLARHC)** in the recent funding round. The CLAHRC is a collaboration that spans the Oxford AHSN region and includes UO, OUH, OBU, Oxford AHSN, Buckinghamshire County Council, Oxfordshire County Council, Oxfordshire Clinical Commissioning Group, Chiltern Clinical Commissioning Group, Aylesbury Vale Clinical Commissioning Group, Thames Valley Local Area Team and Health Education Thames Valley.
- OUH has for many years played an integral role in the Thames Valley region through hosting **NIHR Clinical Research Networks**, supporting NIHR portfolio studies; ensuring that appropriate resources are made available across the Thames Valley region. This requires a high degree of coordination and management between OUH, as the host, and other NHS Trusts across the Network, and with funding bodies from public or third sector. Moreover, OUH was recently selected to host the LCRN from April 2014. In addition to leading the coordination of the clinical research network, OUH in partnership with UO,

OH and OBU has played the lead role in the successful licensing of the **Oxford AHSN**, now working to bring together expertise and resource across the region to drive innovation and improvements in patient care, frontline services and health outcomes.

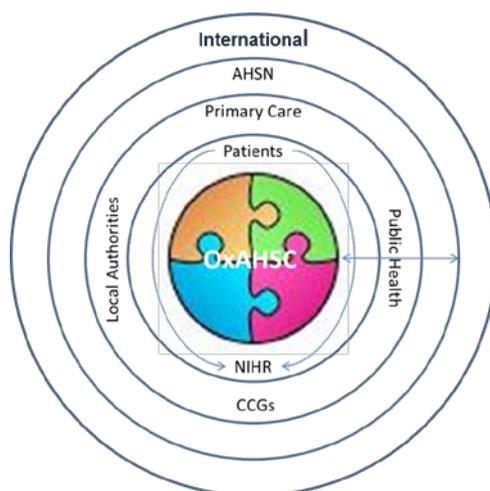
- The partners recognise that to achieve maximum benefit for patients it is essential to work in partnership across England and therefore have built and continue to build links with colleagues across the health research sector. These include initiatives such as the **NIHR Translational Research Partnerships (TRPs)** where OUH was selected to host Oxford's participation in both of the NIHR TRPs, in inflammatory joint disease and in inflammatory lung disease; **The NIHR Health Informatics Collaboration (NHIC)**, to collaborate over NHS data to improve translational research to benefit patient care; **NIHR Diagnostic Evidence Co-operatives (DECs)**. UO's Department of Primary Care and OH form one of four DECs bringing together a wide range of experts and specialists from across the NHS and industry. Oxford will focus on diagnostic tests which will bring the newest medical technology across a range of common diseases like diabetes, into primary care, including GP services.
- In addition to research and evaluation UO and UCL have leveraged their respective BRC resources to create the **Centre for the Advancement of Sustainable Medical Innovation (CASMI)** to develop new models for medical innovation, addressing issues that have led to current failures in the translation of basic bioscience into affordable and widely adopted new treatments.
- OxAHSC will combine the above activity with a broad base of research expertise and excellence supported by a variety of funders, including research institutes supported by all the major funders: MRC (Weatherall Institute for Molecular Medicine, Clinical Trials Service Unit), Wellcome Trust (Wellcome Trust Centre for Human Genetics), CRUK (Oxford Cancer Centre). Oxford City Council's economic growth strategy is built around the contribution of innovation to economic growth, and UO is working closely with the City to help them deliver this. The **City Deal** proposal is also focused on innovation. The bid has been drafted and approved by all of the city, county and district councils in Oxfordshire, the Local Enterprise Partnership (LEP) and the universities. The highest priority project is a new **BioEscalator** building designed to translate scientific advances into commercial healthcare products, and UO is working with the OUH and other regional and national partners to deliver this. There are already very strong links between UO and the Harwell site and the UO, UKAEA and STFC are creating a partnership board to reinforce and strengthen these links with one focus on advances in healthcare. The partners are working closely with the LEP to explore the possibility of a joint appointment to ensure the relationship is concretely embedded in collaborative working.
- The governance structure proposed in section 4 of this application will allow the partners to forge links with all aspects of the health sector across the Oxford AHSN region and where appropriate more broadly. Creation of such a network via the stakeholder forum and existing collaborations will promote not only dissemination of research evidence but also adoption and translation of novel technologies, techniques and approaches into practice.
- OUH, OBU and DenDRoN have formed a new research centre, **Oxford Huntington's Disease Research Centre (OxHDC)** which will cover genetics, movement, psychology, observational studies and clinical trials, working with staff, patients and their families.
- The partners in OxAHSC have a wealth of international partnerships which reflect the quality of the underpinning science and the ability of Oxford scientists to link widely to help facilitate the development of their programmes. In brief, these international collaborations by theme include:
 - *Theme 1 Big Data: Delivering the Digital Medicine Revolution.* This theme has a strong collaboration with Dan Roden and his team at Vanderbilt which has one of the most advanced electronic patient record systems in America. In addition, Stanford University has identified Big Data in Health as being a key strategic priority and have partnered with UO in a bilateral strategic relationship, both to raise money from philanthropic donors and also to jointly develop the tools necessary to make big data in this setting work. Each institution has now hosted one major international meeting on this subject and this will continue in the future on an annual basis. The Li Ka Shing Foundation is contributing to some of the funding of this joint programme. The Big Data initiative is also strongly supported by the commercial sector with collaborations with Microsoft and Oracle as well as collaborations with technology providers Illumina, Life Technology and Oxford Nanopore.
 - *Theme 2 Building Novel NHS, University and Industry Relations.* This programme has a wide range of interactions with the commercial sector incorporating both large, medium sized and small companies. Established collaborations exist with Lilly, GSK, Novartis, Roche, Gilead, Merck, Johnson & Johnson, Takeda, UCB, NovoNordisk and also with the Harrington Project which provides novel forms of risk capital into an academic setting. The programme also has established collaborations with Stanford evaluating new approaches to developing commercial products in Academia. The programme at the Structural Genomics Consortium has 184 academic collaborators, half of which are outside the UK
 - *Theme 3 Modulating Immune Response for Patient Benefit.* This programme has strong commercial

collaborations with Novartis and UCB and is also collaborating directly with Stanford for the development of immunomonitoring capabilities using their platform as a model.

○ *Theme 4 Addressing the Epidemic of Chronic Disease:* This programme has collaborative links with Proteus, a digital health provider from Palo Alto which provides a state-of-the-art patch for patient monitoring. It also has links through the George Institute to centres working on chronic disease control in China, India and Australia.

○ *Theme 5 Emerging Infections and Antimicrobial Resistance.* This programme links a set of institutions globally as part of its surveillance programme. These include collaborative programmes in Thailand, Vietnam, Shantou, China, Indonesia, Laos. In Beijing, we have a close collaboration with Professor George Gao, Research Director for China CDC. The ABRAID programme is funded by the Gates Foundation and also has a wide set of collaborative public health bodies in multiple different countries providing up-to-date surveillance data. The relationship with Pirbright is important to the theme. The antimicrobial resistance programme is developing links with at least one major pharmaceutical company.

○ *Theme 6 Cognitive Health: Maintaining Cognitive Function in Health and Disease:* This theme has a number of international links including imaging individuals at-risk of dementia (Mackay van Buchem – Leiden), cognitive ageing (Mackay Silke/Lux – Julich,), blood pressure and risk of vascular dementia (Rothwell Chalmers/Anderson – Sydney, Staessen – Leuven, O'Brien – Dublin); Cognitive Neurology and Alzheimer's Disease Centre (Nobre Mesulam – Chicago), intensive cognitive phenotyping (Nobre Darby – Melbourne), dementia care mapping (Fossey Chenoweth – Sydney,) Prof. Lovestone will bring existing collaborations which include IMI-EMIF – €56m European Medical Information Framework integrating records and cohorts and bio datasets for Biomarkers including in AD. 60 academic and industrial partners in Europe, co-coordinated by Prof. Lovestone.



9. WORKING WITH THE NHS ARCHITECTURE (2 pages)

Please describe the proposed AHSC's strategy for engaging with the wider NHS architecture including:

- The strategy for ensuring that:
 - the AHSC is fully nested within the relevant local AHSN;
 - that there is integrated working with the local AHSN, emphasising the complimentary roles of AHSCs and AHSNs;
 - there is appropriate co-working with other AHSNs nationally to deliver improved outcomes for patients and the NHS.
- How the proposed AHSC will engage with primary, secondary and tertiary care sectors, NHS commissioning organisations and social care providers to improve outcomes for patients;
- How the proposed AHSC will work with other AHSCs to improve outcomes for patients and the NHS.

- All partners in OxAHSC are partners of the OAHSN and the leaders have been involved in its development and successful licensing. The Network is hosted by OUH. OxAHSC will be fully embedded within the licensed OAHSN with strong cross representation and working. The four OxAHSC partner leads are also members of the OAHSN Management Board and the CE of the Network will be in attendance at OxAHSC Board.
- It is recognised that OxAHSC will have a key role within the Network reflecting the R & D, innovation, knowledge management strengths of both the partnership and the individual partners. Perhaps emphasise primary role of OxAHSC in taking basic science to the bedside and the OAHSN in supporting taking through clinical trials and dissemination across region and throughout England through other AHSNs. The Chief Executive of the Network will be in attendance at OxAHSC Board meetings, reflecting the importance of the wider NHS landscape and the role of the Network in supporting the translation and dissemination of, for example, research and developments in health care and education, across the Network.
- The CE of the Network will be leading its R & D Programme in recognition of the importance of this area of activity, the importance of developing a 'research active' network, and the strengths of OxAHSC partners. Similarly, the OAHSN will be able to inform OxAHSC of activities from across its geography which covers Bedfordshire, Berkshire, Buckinghamshire, Milton Keynes and Oxfordshire.
- OxAHSC will also develop collaborative relationships with neighbouring AHSNs, working both through the Oxford AHSN and building on existing links and partnerships: e.g. partnerships between the Medical Sciences Division and Imperial; the partnership of the five BRCs in England and the strong links through bodies such as the UK University Hospitals Association, the Shelford Group and GMEC. For example, the proposed diabetes theme for the SBRI Challenge now underway is being led jointly by the Oxford and South London AHSNs and the NHIC programme in informatics which links King's, Imperial, UCL, Cambridge and Oxford is led by Sir Jonathan Michael.
- The significant clinical, research and academic resource within OxAHSC, and the existing strong links with life sciences industry, will support all areas of the OAHSN's activities and ensure the widest possible reach and spread of outcomes, best practice and improvements. The Oxford AHSN will be working with NHS England in the development work on metrics for wealth creation, innovation and economic growth and again the resources within OxAHSC will support this.
- A number of the OAHSN's programmes and themes are led by staff working within OxAHSC's partners and many have national expertise and reputations in their fields. Examples include the diabetes clinical network, the pharmacy clinical network, patient and public involvement, engagement and experience. OAHSN has complimentary areas of work that will map on to the majority of the themes; for example, new models of collaboration links into the healthcare innovation and wealth creation programme.
- OxAHSC will be in a dialogue with OAHSN to ensure that, once evidence is generated for a new healthcare innovation and its cost effectiveness established, the adoption across the network will be rapid and complete. This requires excellent communication to ensure institutions have planned for new innovation effectively.
- It is recognised that there will be benefit in pooling resources between OxAHSC, its constituent partners and the Network and plans are in development for shared posts and shared plans in a number of key areas including the development of the informatics strategy, digital health and big data, and in innovation dissemination and wealth creation.
- OxAHSC will ensure continued engagement with commissioners, public health and the local authority, building on strong existing relationships. It is intended that these bodies within Oxfordshire will link with OxAHSC through a Stakeholder Forum as described in Section 4. A number of the themes will necessarily require active work with organisations from the wider NHS; for example chronic care – the theme will engage actively with community services, the voluntary sector, the County Council (public health and social care) and the Commissioners. Close collaboration will also be required to deliver on the cognitive health theme, already a focus for collaborative partnership across Oxfordshire.
- Partnerships with the City and County Councils and the Local Enterprise Partnership will support delivery of a key theme in relation to new models of collaboration; this theme builds on work already in place as described in Section 8.
- OxAHSC will work collaboratively with other AHSCs and will look to discuss areas of collaboration, again building on existing partnerships and relationships. For example, the five major centres in the SE have agreed a term sheet in rare disease with a major pharmaceutical partner.
- It is to be expected that a significant partnership of AHSCs and AHSNs in the South of England will be created and that this collaborative working will have a significant impact on the ability of individual health organisations, supported by academic and life sciences partners, to improve outcomes for patients and the NHS as a whole, and to contribute to wealth creation.

- The OxAHSC will play its part in leading this work, recognising its importance for the NHS and UK life sciences.

10. INTEGRATION OF RESEARCH, HEALTH EDUCATION AND PATIENT CARE (3 pages)

Detail of the proposed AHSC's strategy over the next five years for the furthering integration of research, health education and patient care including:

- Evidence that the partnership's ability to translate discoveries from basic science into excellent translational, clinical and applied research, and into benefits for patient health and improved health outcomes. Please provide 5 examples from over the past 5 years;
- A description of how the partnership will achieve further integration of research, health education and patient care over the next 5 years as an AHSC;
- How this increased integration will lead to improvement in research, health education and patient care;
- The partnership's vision and strategy for maximising the impact that multi-disciplinary and multi-professional working across the AHSC;
- Details of the partnership's close working with the Local Education and Training Board and how this will further the aims of the AHSC.

There are many specific examples of basic science research being progressed into translational and applied research, and ultimately into patient benefit, emerging from the Oxford. We have chosen five broad areas where there have been multiple examples of conversion of discoveries into healthcare benefit, as well as examples of the development of translational and applied research from basic science discoveries. They are: **Genomic medicine.** The strengths of genetics in Oxford are well recognised but, in recent years, UO as well as OUH and OH have made major efforts to translate basic genetic tools and information into real advances in patient care. These have been done in collaboration with Life Technology and Illumina and have led to a range of new tests based on genetic information and novel technologies that are now being applied widely in the NHS.

- The application of molecular genetics to develop a panel of markers for diagnosing sudden cardiac death (hypertrophic cardiomyopathy, long QT syndrome and dilated cardiomyopathy). This test was approved and introduced into the NHS five years ago and has now been further developed with the use of next generation sequencing on a wider panel of genes. Many of the variants on the panel were discovered by Professor Hugh Watkins' BHF programme in cardiomyopathy at UO.
- Life Technology, the TSB and the Oxford BRC have developed a 46 gene test for cancer which is now in routine use for patients with a range of cancers in the OUH. This test is the first of its kind to be developed and applied in the UK and will be followed soon with a 152 gene test based on the same methodology.
- The cranio-facial diagnostic programme, led by Professor Andrew Wilkie, routinely uses genetics to diagnose specific syndromes and has pioneered whole genome sequences for the purpose.
- Oxford has pioneered the use of next generation sequencing in molecular microbiology and has now developed the methodology for characterising the genome of *M. tuberculosis*, MRSA and *C. difficile*. The TB test is being rolled out across the NHS, by four major Public Health England laboratories creating a database for contact tracing and clinical epidemiology and diagnostics.
- Whole genome sequencing (WGS) is the likely platform for many future genetic tests. The BRC and the Wellcome Trust Centre for Human Genetics (WTCHG) in Oxford have pioneered the application of WGS in a wide range of patients including those with autoimmune diseases, cancer, rare Mendelian diseases and endocrine disorders. Over two years, this work will lead to the first description of the utility of WGS in many of these conditions as well as facilitating the development of the two analytical tools necessary for handling this type of data in a clinical practice.

Prenatal diagnosis. The development of tools for prenatal diagnosis is advancing rapidly. OBU, OUH and UO have all been involved in the development of important new tools to improve the accuracy and reduce the costs of these tests.

- Pioneering new immunoassays for inhibin A and B, developed by OBU, have contributed to a significant improvement in the accuracy of pre-natal screening for Downs Syndrome. Use of inhibin A in the 'Quad' and 'integrated' tests is widespread in the US (c.3million screened annually) and was recommended by the NHS in 2010, leading to a significant increase in the use of the assays (c.120,000 annually) in the UK. In the UK, the Quad test became the recommended standard of care for second trimester screening in 2010 and is now offered by all but 3 of over 160 NHS trusts. Denis Lo, from UO and Jim Wainscoat from

OxH filed the original patents describing foetal DNA in the plasma of pregnant mothers. This has led to the development of screening tests, particularly for Down's Syndrome, using next generation sequencing on maternal plasma. Applying this methodology for evaluating the presence of tumour DNA also looks viable and is being explored by the translational genomics programme of the BRC and the WTHG.

- Prenatal embryonic screening for potential IVF parents is a test described by Degan Wells and colleagues in the BRC Genomic Medicine Theme. The first child screened by this methodology was born recently. Next generation sequencing will improve the ability to detect chromosome abnormalities and identify the embryos with the best chances of producing a viable pregnancy. Potentially, this should lead to improved IVF success rates and a lower risk of miscarriage.
- Thalassaemia screening. The pioneering work of Profs. Sir David Weatherall, John Clegg and Higgs in defining many of the molecular variants responsible for β and α thalassaemia has been developed into a range of tests. The National Testing Laboratory in Oxford, led by Dr John Old, has demonstrated the significant impact of this fundamental science and its conversion into tests.

T-cell biology. This programme, established by Prof. Sir Andrew McMichael, has led to a range of translational and applied research projects that have also delivered a number of new diagnostics and therapeutics into the clinic. These include:

- The ELISPOT assay developed by Adrian Hill and Ajit Lalvani is now widely used in immunology. ELISPOT tests for the diagnosis of tuberculosis are commercially available based on this methodology.
- Profs McMichael and Bell, in collaboration with Prof. Mark Davis (Stanford), developed the use of tetramers as a way of measuring the number of antigen specific T cells in individuals with a range of viral infections and autoimmune diseases. These are commercially available and are used for plotting T-cell frequencies.
- Prof. Fiona Powrie was responsible for the discovery of many of the components of the IL23 receptor pathway leading to the production of TH17 cells and IL17. This is still a very active area of translational research, evaluating how antibodies specific for IL17 and perhaps also for IL23 may have important roles in the treatment of autoimmune disease.
- T-cell mediated vaccines. Progress in this area emerged from the basic science labs and has moved into translational research programmes. The Jenner Institute has a wide range of vaccine candidates based on prime/boost strategies to raise CTL numbers to protective levels and
- The exquisite specificity of T-cell antigen receptors for MHC peptide combinations makes them a potentially important new class of biological therapeutic. Immunocore and Adaptimmune are two companies spun out of the MRC Human Immunology Unit which has been working on this problem for ten years. Based on technology developed at OxO, and on clinical data from Phase 2a studies in cancer, Immunocore and Adaptimmune have secured a series of major pharmaceutical partnerships, making these companies two of the most successful in UK biotech.

The molecular basis for diabetes. Oxford leads the world in defining a range of new types of diabetes and developing tests for diagnosis for these conditions. These include:

- MODY diabetes. The original glucokinase variant that described the first form of MODY diabetes was described in Oxford by Andrew Hattersley and the late Robert Turner. Subsequently, Oxford has developed a protein biomarker that defines the presence of this variant that has been used in clinical testing as well as playing a role in characterising the genetic basis for other forms of MODY, all of which are in clinical use today.
- The role of the ATM locus in determining the response to metformin has been documented by Prof. Mark McCarthy and other Oxford scientists and has been converted into a test which predicts response to this drug.
- Prof. Fran Ashcroft and Prof. Andrew Hattersley have demonstrated that mutations in the sulfonylurea receptor can be responsible for neonatal diabetes. The important clinical application of this fundamental science is that patients with this form of neonatal diabetes can now be successfully treated with sulfonylureas where before they were subjected to insulin injection.

Malaria. Oxford-based scientists dominate the field of both basic and applied malaria research and account for five of the top ten cited scientists in this field globally. This work has contributed substantially to international WHO guidelines.

- Demonstration of the utility of artemisinin in malaria. These landmark trials demonstrated both efficacy and the need for combination therapy. The results of the trials have led to global indications for artemisinin in combination therapy (ACT) as the major arm for *P. falciparum* therapy.
- Malaria in pregnancy. The clinical impact of malaria in pregnant women was demonstrated by a series of studies from Oxford scientists in SE Asia. These were accompanied by studies demonstrating the benefits of therapy in this setting, now adopted as WHO guidelines.
- Malaria surveillance. The malaria atlas developed by our Kenya programme has provided the essential data for malaria eradication programmes as they have been developed in Africa for community study of

artemisinin suppositories. Artemisinin suppositories distributed to the community in Tanzania demonstrated the efficacy of early therapy using this intervention and this is now a widely used form of malaria control in Africa. Oxford now manages malaria surveillance for the WHO.

Increasing integration of research health education in patient care:

- OxAHSC partners will continue to progress a process of integration that began five years ago. UO and OUH have coordinated and managed their interactions between research, teaching and patient care through a Partnership Board chaired by OUH Chairman and the Vice Chancellor of UO. The creation of OxAHSC will add another dimension to this integration, bringing together the two other partners, OBU and OH, into a structure where key strategic decisions can be discussed and agreed by the Chief Executives of the four partners.
- Functionally, again the partners have developed methods of working that bring the capabilities in research, teaching and patient care closely together. The BRC has been catalytic in providing the OUH with very significant assets in translational research, often integrated with patient care. Similarly, OH hosted CLAHRC and the BRC programme in dementia will have a significant impact on integration of applied research and of the dementia of Cognitive Health Theme.
- An excellent example of integration between the partners is the work on the single neuroscience theme bridging OUH, OH, and UO. Breaking down the barriers between these artificial clinical specialties of psychiatry and neurology has brought the healthcare providers much closer together. Similarly, the programme in chronic disease brings together all parties and has a profound impact on the way we approach teaching and clinical care. OBU is a crucial partner in the creation of an appropriate workforce to implement many of these changes in care pathways. Both these programmes will further develop the integration of research and clinical care.
- OBU has established a Centre for Rehabilitation that evaluates factors affecting optimal human performance in health and disease. It is multidisciplinary with clinical links with the Oxford Centre for Functional Imaging of the Brain (OUH/UO) and Department of Clinical Neurology, UO and the Nuffield Orthopaedic Centre (OUH). The Movement Science Group in the Centre shows how patients can be involved in research strategy and design. The MSG Steering Group includes 'research users', and patients who have suffered from the chronic, long-term neurological conditions that form the focus of the research studies.
- The integration of teaching with research and clinical care will be enhanced by OxAHSC. The requirement for both professional training and training new types of healthcare workers are likely to emerge. These will be linked through the partners to training programmes and courses and through the Stakeholder Group to Health Education Thames Valley. Combining this with the established linkage with the UO Clinical Academic Graduate School (OUCAGS) will ensure broad impact of research results and training. OUCAGS, OBU and BRC are working together to support increases in research capacity and capability across the healthcare professions.
- Integration can also be promoted by co-location and the partners are embarking on a significant set of new developments that will bring their interest together, in particular their research areas. Of note are the collaborations to develop a Targeted Cancer Centre and the Bioescalator jointly between OUH and UO. OUH and OH will have a significant role to play in the new Big Data Institute, also on the Old Road Campus, and OUH and UO are jointly fundraising for the new Centre for Immunology and Experimental Medicine, again to be located on the Old Road Campus.

Maximising the impact of multidisciplinary and multiprofessional working

- It is clear that future healthcare innovation and delivery will require greater cross-disciplinary working at every level. In the research setting, it is our firm belief that this is a major driver for innovation and hence we are incorporating scientists from a wide number of different backgrounds in our overall programme. In the arena of patient care, as we change the nature of healthcare workers, this too will need to bring in new disciplines. The approach to modernising scientific careers will incorporate significant changes for the training of clinical scientists in the hospitals. Healthcare workers managing chronic disease will need to be capable of addressing the multiple co-morbidities ranging from mental health disturbances all the way through diabetes and vascular disease effectively. This integration will require a significant change in the teaching of healthcare workers and healthcare professionals clearly prioritised as part of the work of OxAHSC. Links to the Oxford AHSN will ensure that widespread adoption is tied to engagement with the innovation agenda across all disciplines.

Details of the partnership's close working with the Local Education and Training Board and how this will further the aims of the AHSC.

The Partnership has established strong and close working relationships with Health Education Thames Valley

and three of OxAHSC leads (OUH, OH and OBU) are members of its Board. June Girvin (OBU) chairs the Education Expert Reference Group.

11. FINANCIAL PERFORMANCE (1 page)

Please describe the current and prospective financial performance of the partnership's constituent NHS provider and university organisations.

High Level 5-year financial forecasts						NOTES
	2013/14	2014/15	2015/16	2016/17	2017/18	
OBU						
Income	100.9	101.6	106.1	108.6		2017/18 not available
Expenditure						
Faculties	41.2	41.5	41.9	42.3		
Directorates	41.9	42.1	42.0	42.2		
Non devolved	15.8	13.9	14.3	13.2		
Net balance	2.0	4.0	7.8	10.8		
	2013/14	2014/15	2015/16	2016/17	2017/18	
OH						Plans in place to mitigate risks incl. delivery of CIPs, out of area treatments, CQUINs, activity management
Income	285.3	282.0	278.0	274.1	270.3	
Expenditure	(269.2)	(264.2)	(260.3)	(256.3)	(252.3)	
Normalised EBITDA	16.0	17.8	17.8	17.8	18.0	
EBITDA % margin	5.6%	6.3%	6.4%	6.5%	6.7%	
Normalised net Surplus/(Deficit)	5.5%	5.3%	5.4%	5.4%	5.7%	
Monitor FRR	3	4	4	4	4	
	2013/14	2014/15	2015/16	2016/17	2017/18	
OUH						
Income	840.6	822.1	815.7	817.0	819.8	
Operating expenses	(767.1)	(748.8)	(743.5)	(744.6)	(745.5)	
EBITDA	73.4	73.3	72.2	72.4	74.3	
EBITDA % margin	8.7%	8.9%	8.9%	8.9%	9.1%	
Depreciation and finance charges	(65.1)	(64.9)	(63.9)	(64.2)	(66.1)	
Retained surplus	8.4	8.3	8.2	8.2	8.2	
Adjustments	2.5	2.5	2.4	2.3	2.2	
Breakeven duty surplus	10.8	10.9	10.6	10.5	10.4	
Adjusted surplus %	1.3%	1.3%	1.3%	1.3%	1.3%	
TDA FRR	3	3	3	4	4	
	2013/14	2014/15	2015/16	2016/17	2017/18	
UO						
Income						
Grants incl. HEFCE	185.0	177.4	171.8	171.1	172.0	
Student fees	203.0	225.9	240.2	248.2	254.9	
External research income	465.8	480.0	475.9	463.2	469.0	
Investment income	52.0	57.6	57.2	58.3	64.1	
Other income	182.1	186.9	191.8	196.0	200.3	
Total income	1087.9	1127.8	1136.8	1136.7	1160.4	
Expenditure						
Pay	538.4	562.9	569.0	577.6	591.7	
Non pay	522.0	533.1	530.5	526.3	534.9	
Total expenditure	1060.4	1096.0	1099.5	1103.8	1126.6	
Surplus	27.5	31.9	37.3	32.9	33.7	

12. ADDITIONAL COMMENTS (1 page)

Please use this section to address directly any feedback provided by the Panel on your application at the shortlisting stage, including any highlighted issues with quality of patient care such as adverse Monitor or CQC ratings.

Strength and appropriateness of governance arrangements. Since 2009, OxAHSC partners have worked to create an integrated and coordinated health research environment in Oxford, recognising that this was essential to achieve the common goal of translating excellent research into application in healthcare. This led to the creation of formal organisation level agreements, for example:

The formation of OUH from the Oxford Radcliffe Hospitals and Nuffield Orthopaedic Centre was coincident with implementation of the Joint Working Agreement between UO and OUH. This has enabled alignment of clinical and academic departments and therapeutic groupings, and active engagement of clinical academics in clinical leadership. The Joint Research Office provides aligned research facilitation and governance across the partnership. The Directors of R&D and Education are joint OUH-UoO appointments. Similarly, OBU and OUH have Joint Working Agreement in place to support their collaborative approach aimed at improving patient care and experience and improving experiences for students, supported by scholarly activity and service improvement initiatives.

The partners recognised the need to include a wider stakeholder group and therefore the Oxford Academic Health Consortium (OAHC) was launched in Feb 2012 comprising the OxAHSC partners, clinical commissioners, social care and public health. In addition, all OxAHSC partners are partners in Oxford Academic Health Science Network (OAHSN). Each partner is actively engaged in leading specific programmes within the OAHSN, including best care and clinical networks, R&D, and healthcare innovation and wealth creation, and cross-cutting themes, including informatics and medical technologies, patient and public engagement and knowledge management. The above governance structures are allied to more local management structures such as the NIHR Oxford BRC and BRU steering committees, ensuring close co-ordination of research and practice.

As set out in section 4, the OxAHSC governance structure builds on the above arrangements which will promote rapid initiation of OxAHSC activities.

Clinical Outcome Data (OUH)	
SHMI 2012	95.6 (overall) and 74.49 (elective) "deemed statistically significantly lower than the benchmark using 95% confidence intervals. Plotting the SHMI over a 3 year period demonstrated an overall linear decline. OUH is one of eight trusts in the Shelford Group that has a statistically significantly lower than expected SHMI for the time period analysed.
ICNARC (Intensive Care National Audit and Research)	SMRs 0.7-0.8, indicating 20-30% fewer in hospital deaths than average
National cardiac arrest Audit (part of ICNARC)	29% survival to discharge about national benchmark
MINAP	Within 90 minutes of arrival at Heart Attack Centre: 93.5% Year on year improvement of 7% in proportion of patients treated within 150 minutes call for help (national average 92.2%)
Paediatric Diabetes (NPDA)	3 rd lowest level in country for HbA1c test: percentage of patients with HbA1c levels in the targets range increased increase (31.9% cf national average 15.7%)
C.difficile (OUH) numbers	92 (2012/2013) 103 (2011/2012) Reduction of 10%
C.difficile (OUH) rates per 100,000 bed days	19.81 National average 21.9 (11/12)
Subarachnoid haemorrhage	Superior in patients Rx with coiling; 7% less likely to die if coiled (NNT = 14); 23% less likely to be dependent on carers (NNT = 4.3)
VTE risk assessment rates 12/13	92.43% (Target 90%)

13. DECLARATIONS AND SIGNATURES

By signing the declarations the named individual is agreeing that they are authorised to do so on behalf of their organisation.

Please print this page, have it authorised and return it by post by 7 October 2013 to the address stated at the bottom of this form.*

The applying English NHS Provider/University Partnership fully endorses the application for an Academic Health Science Centre award and assert that appropriate support will be provided to the AHSC should the application for designation be successful.

English NHS Provider/University Partnership: Oxford Academic Health Science Centre

Name, job title, address, email and telephone number of the lead contact for the proposed AHSC:

Professor Sir John Bell, Regius Professor of Medicine, University of Oxford, The Richard Doll Building, Old Road Campus, Headington, Oxford : Regius@medsci.ox.ac.uk; ahsc@medsci.ox.ac.uk Tel: +44 1865 289 782



Signature

Date: 30 September 2013

(Lead contact for the proposed AHSC)

If you have questions about the completion of this form please e-mail Sonja Tesanovic at sonja.tesanovic@nihr-ccf.org.uk.

This form must be submitted by **1:00pm on 30 September 2013**. The 'wet-ink' Declaration and Signatures section of the application form should be received by NIHR CCF on **7 October 2013**, and sent to:

Dr Sonja Tesanovic
NIHR Central Commissioning Facility
Grange House
15 Church Street
Twickenham
TW1 3NL



ACADEMIC HEALTH SCIENCE CENTRES SPECIFIC THEME / WORK PROGRAMME

Note: The accompanying “*Academic Health Science Centres – Full Application Guidance*” contains essential guidance on the information you need to provide when completing this proforma.

Please use this form to provide details on one of the six specific Themes / Work Programmes of focus for the proposed AHSC.

Please use a separate form for each of the Theme / Work Programme. Please complete no more than four pages for each theme; only information submitted up to this page limit can be assessed.

Please note this should be completed in a font no smaller than 10-point Arial.

Please insert your unique Reference Number into the Footer space provided.

1. DETAILS OF THE PROPOSED ACADEMIC HEALTH SCIENCE CENTRE (AHSC)

Name of the English NHS Provider/University Partnership:
Oxford Academic Health Science Centre (OxAHSC)

2. THEME / WORK PROGRAMME

2.1 Name of the theme/work programme.

Theme 1: Big Data: Delivering the Digital Medicine Revolution

2.2 Aims and objective of the theme/work programme.

- The short to medium-term aims are to establish a platform for ‘Big Data’ that integrates large existing databases such as patient cohort data, electronic patient records, surveillance data, digitised data from pathology slides, radiology and genomics. Analysis of such diverse datasets will transform the way diseases are defined, lead to development of new diagnostics and targeted medicines, and ultimately help identify strategies for more efficient healthcare delivery.
- The long-term objective is to enable the delivery of personalised treatment and/or disease management plans based on the aggregation and probabilistic analysis of multiple types of data collected at various times during the individual’s lifetime.

2.3 Description of how the proposed theme or work programme will contribute to the aims of the AHSC.

- Medicine has been slow both to develop the tools necessary to capture digitally the data acquired during the multiple interactions of a population with healthcare services and to analyse the large datasets (from self-monitoring data to CT scans, pathology slides to discharge summaries) generated as a result of these interactions. The analysis of these data will allow us to better characterise patient populations, leading to much more precise disease definition, identifying individuals who do or do not respond to particular therapies, determining which high-risk patient populations are more likely to benefit from more intensive surveillance and enabling a more targeted application of healthcare resources based on a detailed understanding of outcomes in large patient populations.
- Large-scale inefficiencies in healthcare systems are driven by a failure to recognise where resources should be applied for maximum benefit. In part, this relates to the imprecise way diseases have been defined; however, it is also the result of a lack of information on patient populations which require intensive support. In addition, there is a lack of tools for allowing patients to take control of their own disease management in the chronic phase. Many of OxAHSC’s themes are directed at this general problem (chronic disease, cognitive health, immunological modulation, emerging infections). In all cases, large datasets will be available to enable us to characterise disease more precisely and tools will be

developed to allow timely access of information by healthcare professionals, patients and their caregivers, leading to better shared decision making. All these approaches will require the extraction of the most clinically useful evidence from large, diverse datasets.

- OxAHSC is strongly positioned to take advantage of this opportunity. A key aim of OxAHSC is to accelerate the realisation of patient benefit from research, and the topic of Big Data in healthcare has emerged in a number of existing research activities (genomics, high-throughput biology, mega-cohorts, multi-modal imaging and machine learning). Bringing these together within a single theme will be crucial to the success of the whole OxAHSC programme. A new type of multi-disciplinary scientific team will be assembled, capable of developing the tools necessary to extract and display clinically-useful information from the petabytes of primary, secondary and social care data. Using these tools to capture, aggregate, link and analyse these large datasets, we will be able to define and characterise disease more accurately, leading to an era of precision medicine. By sharing healthcare information more widely, we will also improve care delivery in the healthcare system in our region, empowering patients and carers in chronic disease monitoring and management.

2.4 Description of how the proposed theme or work programme will contribute to the further integration of research, health education and/or patient care and how this will lead to improvements in patient care.

All the elements are in place in Oxford for the integration of a number of research programmes which have the acquisition of very large datasets at their core and have recently begun to focus on Big Data analytics:

Genomics and High Throughput Biology (Donnelly, McVean, McCarthy, Flint)

The most dramatic disruption of medical research by digital transformation has occurred in experimental laboratory science. Starting with the revolution in genetic technologies and now encompassing a range of other approaches, high-throughput biology has become the dominant theme across laboratory-based experimental science. In genomics and genetics, next-generation sequencing has led to the ability to generate large sets of structured data. Very large genomic studies, such as the NHS 100,000 Genome Project, potentially allow genetic variation between individuals to be linked to differences in susceptibility to human disease, in turn providing vital clues to the pathophysiology of disease processes and to potential new therapies. Other exploratory systems including proteomics, epigenetics and RNAseq have also been developing rapidly, allowing large datasets to be generated using a variety of experimental tools; these too will have a profound impact on our ability to characterise many aspects of human disease biology.

Mega Cohorts, Controlled Studies of Phenotype and Disease (Collins, Beral, Peto)

The epidemiology programme in Oxford has focused on accumulating large datasets for risk factor characterisation and for defining therapeutically responsive patient populations. Professor Sir Rory Collins has been instrumental in establishing the UK Biobank, a cohort of 500,000 individuals in whom a combination of environmental exposure data, physiological data including lung function, blood pressure, bone marrow density, ECG and metabolic data, have been collected on recruitment. In this cohort, very high volumes of imaging data have also been acquired (100,000 individuals with brain, heart and whole body scans) and similarly for genomic data (700,000 SNP chip applied across the entire cohort). This is a unique resource, largely because of its scale and its linkage to national NHS electronic records which are now being interrogated for the follow-up of sub-sets of this patient population. UO also hosts the Kadoorie Study, an equivalent 500,000 individual cohort based in China where similar data and genomic information are being collected, and the Million Women Study with 1.3 million women recruited through the NHS Breast Cancer Screening programme. The ability to assemble these digital assets, collect and curate the relevant data, and then analyse these extremely large datasets provides a model for Big Data analytics within OxAHSC.

Big Imaging Data: Applications of Clinical Imaging Research (Smith, Neubauer)

Oxford is home to several world-leading clinical research and basic science imaging facilities, focusing on brain and cardiovascular imaging. In addition to the hospital imaging facilities, Oxford has taken a global lead in assembling large sequencing datasets. Over the last few years, the imaging field has recognised the opportunity to follow the example of large-scale population genomics efforts, and complement those with similarly large-scale non-invasive imaging-phenotyping studies. Cohorts such as UK Biobank provide powerful opportunities to gather imaging data in a clinical context. Biobank's imaging enhancement, led out of Oxford and sponsored by MRC and the Wellcome Trust, will be the largest imaging phenotype study to date. It is planned to perform MR imaging on 100,000 members of the original cohort, or 16 times the size of the MESA cohort in the US, for multi-modal neuroimaging and cardiac MRI, amongst other measures. Such large numbers are required for nested case-control studies, which will prospectively identify the phenotypical predictors of major clinical events. Oxford imagers will co-lead the brain and cardiovascular imaging components of UK Biobank.

Next-Generation Electronic Health Records (Davies, Landray, Lovestone)

Electronic patient records represent an opportunity to obtain detailed clinical phenotypic and response data for entire populations using existing infrastructure, with the advantage of clinical input and oversight. The

OxAHSC partners are linking data from primary, secondary, and social care to produce an integrated summary care record. Primary care data are linked in partnership with Healthcare Gateway Ltd, providers of the Medical Interoperability Gateway; these data are used, for example, to check medication for in-patients and emergency admissions. 75% of Oxfordshire practices are already engaged, with the remainder expected to join during the next year. The Oxford AHSN will work to extend this linkage across the region. The challenge now is to increase quality and depth to the point where data are of sufficient quality for clinical trials, to allow observations made of different patients in different settings to be compared, and deep enough to facilitate translational research and service improvement, with detailed information on co-morbidities, risk factors, compliance, outcomes, and quality of life. This challenge requires a combination of automation (using semantic technologies and model-driven engineering) and engagement, with patients contributing to and actively reviewing their integrated health records. New algorithms, techniques, and architectures are needed to cope with the number of variables, the volume of data, and the computational complexity of the proposed analyses. UO's Computer Science Department has an impressive track record of achievement in all three areas.

Digital Patient Monitoring: A new wave of Big Data (Tarassenko, Watkinson, MacMahon, Rahimi)

Another key driver for the Big Data revolution is the increased availability of highly granular, longitudinal patient monitoring information. Professor Lionel Tarassenko, from the Institute of Biomedical Engineering on the Old Road Campus, has a long-standing track record in the acquisition and analysis of such large datasets. The principles used by his group to develop data fusion algorithms for monitoring jet engines (such as the Trent 900 on the A380 aircraft) have also been applied in hospital settings ranging from high-risk surgery to critical care and the Emergency Department. Large datasets of vital signs routinely collected during a patient's hospital stay have been analysed systematically to design early warning algorithms for the reliable detection of physiological deterioration on general wards. These approaches are now being deployed more widely in the community by utilising self-monitoring data in patients with a variety of chronic diseases. For example, UO, OH and the OUH have recently established a collaboration with Proteus Digital Health, a leader in digital medicine based in California, and are evaluating the use of a wearable patch which can passively record normal physiological variables (pulse rate, respiratory rate, motion and body angle) and also monitor medication adherence, utilising FDA-approved and CE-marked micro-chips implanted in drug tablets. These digital self-monitoring data are being integrated into the EPR via the Oxfordshire Care Summary. Research access to these types of data has the power to transform our understanding of disease processes for conditions such as heart failure, COPD and diabetes as well as mental health disorders. This approach may also represent the first step in a significant paradigm change in healthcare, as the information will be readily available in real time to patients as well as their carers, leading both to patient empowerment through increased understanding and to improved disease management by carers.

Integration of Big Data research: a multi-disciplinary challenge

UO has significant capabilities in Big Data for health, with world-leading programmes in statistical genetics (Donnelly, McVean), mathematics (Grindrod), and engineering (Tarassenko). A substantial programme in health informatics has been established, with significant engagement from computer science (Davies). The programme has delivered new infrastructure in infectious diseases, cancer research, and mental health, in partnership with both OH and the OUH, and is working with other academic health science partners to establish comparable data standards in key therapeutic areas.

All the institutions in OxAHSC are investing heavily in this area of Big Data and digital medicine. The two hospitals have substantially increased their efforts to create data warehouses of patient information to provide appropriate phenotypic information; OBU has strong programmes for training healthcare workers who will be capable of meeting the Big Data challenges in a healthcare setting (see below). UO is creating the Big Data Institute (BDI) entirely focused on Big Data in healthcare. The Institute, to be built on the Old Road campus, will bring together 350-400 scientists from UO, OH and OUH in an integrated effort to tackle the problems of the acquisition, handling and analysis of large complex datasets. Crucial to the success of the BDI will be the ability to utilise all the available multi-disciplinary skill sets alongside those who understand the precise critical problems being resolved, hence the adjacencies to the other biomedical scientists from clinical and epidemiological backgrounds will be crucial. The BDI will also house significant expertise in software development, enabling the algorithms and discoveries made in the Institute to be converted into usable and commercially viable projects.

Health education

We believe that Big Data analytics will have considerable impact on the future of medicine and, as a result, we intend to modify and develop our teaching and training programmes to provide students with the necessary capabilities in this domain. For some years, quantitative skills have been de-emphasised in medical training. Although this has not happened at Oxford, we propose to step up our training in quantitative skills for University medical students. We also plan to recruit more doctors with a background in quantitative subjects to empower the clinical workforce of the future with leaders in this area.

A crucial component of the Big Data agenda will be to equip all healthcare workers in the future with much more quantitative skills so that they can be involved in the use of evidence generated by these integrative, analytical approaches in an intelligent and effective way. This will mean the provision of more training in quantitative methods as part of the training of healthcare workers such as nursing staff. OBU is centrally involved in the training of a range of healthcare workers, many of whom will increasingly need these skills. OBU students will be trained to understand the methodology of digital management tools and they will be taught to deliver, and manage the outputs of, these tools, particularly for monitoring patients with chronic diseases in the community. Given its strengths in IT training and statistics, OBU is ideally positioned to develop the training which will allow new types of healthcare workers to emerge, capable of managing these important types of data for the well-being of their patients. Similarly, OUH's Modernising Scientific Careers programme for NHS scientific staff will also be crucial in developing staff with expertise in statistical genetics and large-scale data analysis to deliver the digital medicine agenda.

Improvements in patient care

Evidence of the beneficial impact on patient care of Big Data analytics is already available from programmes already operating in Oxford:

- The Stroke Prevention Unit led by Peter Rothwell manages a cohort of 92,000 people within Oxfordshire primary care, focusing on the risk of acute vascular events. By utilising these computerised patient records, including clinical evaluations and imaging, the group has been able to identify a series of markers predicting high risk of subsequent strokes. This strategy has been implemented as part of the National Stroke Strategy and is estimated to have prevented 10,000 strokes per year, saving the NHS £200 million in acute care costs.
- The Stroke Prevention Unit, through its Big Data analyses, has also identified remarkable and unpredicted benefits of aspirin, previously unrecognised. They have demonstrated that low-dose aspirin reduces the incidence and mortality of colorectal cancer as well as other cancers of the gastrointestinal tract with up to 40% reduction in incidence.
- Big Data analysis aggregating large scale genetic data from over 150,000 research subjects with Type - 2 diabetes, led by Professor Mark McCarthy, has provided the most complete description of the genetic basis of any major disease to date. This has led to the identification of genetic differences that influence individual responses to medicines (ATM variants and metformin), new targets for drug discovery, and an inventory of the molecular content related to the function of human pancreatic islet cells.
- Analysis of major epidemiological samples and conduct of large-scale clinical trials have provided clear evidence of cardiovascular risk factors and the interventions necessary to reduce them, including statins, aspirin and blood pressure lowering agents. Meta-analysis of trials of more than 200,000 women with breast cancer has given the first clear evidence of the impact of a range of therapeutic interventions with high confidence intervals (Peto).
- Large-scale SNP analysis as part of the Wellcome Case Control Consortium, led by Peter Donnelly, has contributed to the characterisation of genetic variants strongly associated with disease pathogenesis. 2000 of these variants are now recognised, many of them emerging from the large scale genetic analysis done at the Wellcome Centre for Human Genetics.
- Combined analysis of genomic data on 2000 malaria parasites and epidemiological data has identified a small region in Western Cambodia where drug resistant malaria invariably emerges. This strain of the parasite has variations in the *mut* locus making it prone to increased mutations when put under selection pressure. Global malaria eradication strategies will now look completely different with this insight.
- Large-scale studies of digitally-acquired physiological variables in acutely ill patients in hospital have provided an evidence-based track-and-trigger system for identifying patients at high risk of deterioration (Tarassenko and Watkinson). This required the development of a data fusion methodology which can be applied to a range of clinical variables, including lab results and imaging data.

The Big Data theme in OxAHSC will build on these early successes and deliver further improvements in patient care. For example, unplanned admissions to ICU will be reduced as a result of the integration of physiological, biochemical and radiological data to identify deterioration early. Large-scale data analysis will continue to inform the interventions necessary to reduce cardiovascular risk factors, and help to identify the genetic differences that influence individual responses to medicines. Ultimately, the integration of genetic and molecular data with phenotypic data will allow the creation of a personalised risk profile, as well as a disease management plan (and when appropriate, a treatment plan) for individual patients.

2.5 Description of how the theme/work programme will involve and enhance multi-disciplinary and multi-professional working.

The multi-disciplinary nature of the digital health theme means that conventional boundaries between engineers, statisticians, mathematicians and computer science experts, and clinical epidemiologists,

medical imagers, pathologists and a wide range of healthcare providers need to be broken down for the revolution in healthcare to occur. OxAHSC is already well along the path to ensuring that this happens. The emerging digital tools will be routinely used, not just by healthcare workers, but also by the most important contributors to healthcare management – the patients and their associated carers. This will represent a fundamental shift in the workforce and in the management of disease, which will be enabled by the generation of powerful evidence for optimised disease management pathways, refined definitions of disease and more stratified approaches to medicine generated by the analytical capabilities underpinning this theme. Not only will there be multiple participants in the Big Data programme, it will ultimately impact all those working in healthcare; scientific and healthcare workers from a broad set of backgrounds will need to embrace the changes delivered by this programme.

2.6 Description of leadership and key individual and organisational contributors with responsibility for delivering the theme/work programme.

This theme will be led by Professor Lionel Tarassenko, a leader in digital health monitoring. He will be supported by the leadership team of the Big Data Institute in Oxford which includes Professors Peter Donnelly, Gil McVean, Rory Collins and Dominic Kwiatkowski and Mr Mike McEnaney, OH Finance & Information Director. Professor Jim Davies will provide leadership in the Computer Science and Electronic Patient Record domains.



ACADEMIC HEALTH SCIENCE CENTRES SPECIFIC THEME / WORK PROGRAMME

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Please use this form to provide details on one of the six specific Themes / Work Programmes of focus for the proposed AHSC.

Please use a separate form for each of the Theme / Work Programme. Please complete no more than four pages for each theme; only information submitted up to this page limit can be assessed.

Please note this should be completed in a font no smaller than 10-point Arial.

Please insert your unique Reference Number into the Footer space provided.

1. DETAILS OF THE PROPOSED ACADEMIC HEALTH SCIENCE CENTRE (AHSC)

Name of the English NHS Provider/University Partnership:
The Oxford Academic Health Science Centre (OxAHSC)

2. THEME / WORK PROGRAMME

2.1 Name of the theme/work programme.

Theme 2: Building Novel NHS, University and Industry Relationships

2.2 Aims and objective of the theme/work programme.

In the UK, multi-national pharmaceutical companies are downsizing, and only a very small number of biotechs are being created. In the past decade this has resulted in the loss of several thousand high skilled jobs and reduced inward investment. Globally, the number of innovative medicines being produced is very small, and the cost of these is becoming unaffordable. With ageing societies and diseases of modern living, the demand for “site targeted”, disease modifying therapies, is on the increase. The causes for this failure, are scientific (poor understanding of human disease and therefore poor identification of novel targets, poorly predictive preclinical assays, non-optimal biomarkers and patient stratification methodologies) and organisational (too much duplicative activity on failed targets, limited resources even in the largest of enterprises, limited access to patient material, limited multi-disciplinary research). There is no doubt that the discovery of innovative new medicines is expensive, high risk and long term, and is becoming increasingly difficult and unaffordable for any one organisation. Within the OxAHSC, we believe the answer is to bring together the immense strengths of all stakeholders through new types of relations. By fostering these, we aim to create a much more collaborative and efficient translational environment. The three key players are the NHS, the University and several types of industry. Their respective strengths are:

- **NHS:** clinical research including exceptional opportunities for innovative Phase I / IIa / Experimental Medicine / clinical Proof of Concept (POC) studies, a unique access to stratified patient cohorts and databases, and opportunities for close working relationships with patient groups
- **Universities:** excellence in fundamental research in Biomedical, Medical, Physical and Social Sciences, and a large talent pool for innovation and enterprise. They also play a critical role in teaching and training of scientists and scientific entrepreneurs in subjects ranging from Biomedical Science (UO, OBU), Biology (UO, OBU), Medicine (UO), Medical Sciences (OBU) to Biotechnology and Biotechnology with Business (OBU).
- **Industry:** comprising a) **Medtech** with expertise in new devices and diagnostics b) large

pharmaceutical companies with proven capabilities in high throughput screening, lead optimisation, large Phase IIb / III clinical studies, regulatory filing and marketing c) **biotech** with appetites for slightly more risky projects than may be undertaken in pharma and d) **contract research organisations (CRO)** which are increasingly performing lead optimisation, toxicology, ADME and pharmaceutical development activities for many academic and private enterprises.

Our objective in the short term is to pool these strengths, reduce the barriers to collaboration, generate better targets for drug discovery, create long-term collaborative relationships, and drive innovation and entrepreneurship in order to:

- More efficiently translate our fundamental research, for the benefit of patients
- Facilitate the creation of commercial value for our private partners
- Attract inward investment into the region and UK
- Create many more high skilled health sector jobs, associated with unique opportunities for education and training
- Create more sustainable biotechs, developing new approaches for bridging the Valley of Death and ideally creating one or more mid-size pharm companies.

2.3 Description of how the proposed theme or work programme will contribute to the aims of the AHSC.

Already within Oxford, several researchers in UO, OBU and the NHS have built some quite unique industrial networks, and important relations with patient groups and VC organisations. Our aim is to build on these through a five pronged strategy:

- Build on our leadership in **Open innovation**
- Exploit fully the new **Target Discovery Institute**
- **Mature “new biotechs”** within the OxAHSC to major value inflection points, prior to securing VC or other private funds
- Facilitate interactions between the medical and physical science divisions within UO, with OBU and with colleagues supporting patients in the NHS, and entrepreneurs, to create many more **novel medtech and life science applications**: in e.g. diagnostics, site targeted delivery, promote healthy living, new sensors, regenerative biology, mobile devices and importantly “health informatics”
- Establish a **“BioEscalator”** to maximally exploit the output of our open innovation projects, more cost effectively use the infrastructures, resources, and expertise within the universities and the NHS, and to optimally harness the local entrepreneurial talent pool.

We have described below the deficits in the current environment, how each of these strategies will remedy such issues, our intended outputs and operational plans, and where appropriate some recent achievements:

a) Open innovation

There is currently much discussion about reducing barriers to collaboration, pooling resources, increasing innovation and reducing duplicative efforts, through open innovation. There is however probably no other group in the UK that demonstrates this quite like the Structural Genomics Consortium (SGC). Based in the Nuffield Department of Clinical Medicine, this group is working closely with eight large pharmaceutical companies (GSK, Pfizer, Novartis, Lilly, Boehringer Ingelheim, Janssen, Abbvie and Takeda), and has access to their medicinal chemistry expertise, screening capabilities, infrastructure and resources (each donating \$8M over 4 years). Together the consortium is generating new tools for drug discovery (human proteins, assays, structures, inhibitors and antibodies). The SGC is producing nearly 10% of all novel human protein structures per annum, and is now a leader in epigenetics chemical biology. All reagents are made freely available to the global biomedical community (academia, pharma, biotech, CRO), and all data or “know how” is published immediately. The group are collaborating with nearly 200 of the best academic labs in the world to evaluate these novel reagents in disease relevant assays, to establish new targets for drug discovery. These freely available, novel reagents are catalysing a broad and deep exploration of target biology (something financially impossible within any one private organisation), are enabling the initiation or acceleration of proprietary programmes, and the creation of new biotechs. For example, a new biotech is currently being formed, using an epigenetic inhibitor generated by the SGC and GSK. UO’s technology transfer group (ISIS) have already identified a lead investor and several others are showing keen interest. This unique group of open innovation researchers are now being approached by patient organisations and CROs, to further exploit the SGC outputs, by creating disease specific drug discovery pipelines, and more advanced tools for drug discovery.

Spurred on by the success of this open endeavour, we are promoting clinical POC as the “new pre-competitive boundary”. This is because currently many groups and companies work on the same few pioneer targets, “in parallel and in secret”, only to find that >90% fail in clinical POC studies. We propose to generate freely available clinical candidates for such pioneer targets, and then use the expertise and

resources of the OxAHSC to clinically validate such targets (in patients!). Industry may then choose to generate proprietary molecules for such de-risked targets. This project will reduce the current wastage of resources, and the needless exposure of patients to molecules destined for failure. A programme in cancer is already underway with Cancer Research UK, and two major initiatives are being organised with the Canadian Institute for Health Research and several pharmas in neuro-psychiatry, and with the Helmsley Trust in Inflammatory Bowel Disease.

Within OxAHSC we are also discussing other major “open” programmes to facilitate pioneer drug discovery for Alzheimer’s Disease, rare diseases and anti-microbial resistance.

b) Target Discovery Institute

A major limitation in commercial drug discovery has been the failure to properly understand the potential role of individual targets in biological processes, before drug discovery programmes are launched. There are numerous examples where new programmes have been launched based on single prominent publications, which have subsequently turned out to be incorrect. It is clear that an extensive evaluation of targets to understand exactly how they operate in pathways, and how and when, they may be relevant in disease processes, is a critical step. In commercial settings, this fundamental research is often not feasible. To address this gap, within the OxAHSC, we have built a new Target Discovery Institute (Professor Peter Ratcliffe). This new facility has capabilities to undertake large amounts of high-throughput science, including small molecule screening and development, siRNA screens, proteomics and genomics, and is focused around a number of therapeutic areas with the intent of thoroughly evaluating a set of pioneer drug targets. Such “better understood targets” will then be advanced with our colleagues in industry. This Institute represents a new concept for academic institutions, and is a bold, but important experiment in demonstrating how academia can work with industry to de-risk and advance pioneer targets.

c) Mature “new biotechs”

It is clear that many biotechs have been spun out of universities far too early: at a point where they have reduced value, but require several private funding rounds before they achieve major value inflection points (clinical POC). Of course each funding cycle dilutes the returns to the founders and the local ecosystem. Furthermore, due to constrained and short term exit focused funding, the progression paths are often sub-optimal, and therefore usually result in failure. The current modus operandi is also extremely inefficient, because large and expensive management teams often support only one asset, and are usually not located in scientific, technical, innovation, clinical expertise or patient research focussed hubs (universities and hospitals). Within the OxAHSC we aim to mature new biotechs to major value inflection points, using the infrastructure, expertise and resources of the Universities and the NHS (BRC, BRU and seven Clinical Research Facilities). OxAHSC has also been chosen as a strategic partner for the Harrington Project, a philanthropic programme to discover and develop novel therapies by working with the Universities, local hospitals and an “Industrial Board”. This partnership will use single management teams to drive a portfolio of projects.

This visionary model is already being pursued, in collaboration with entrepreneurs at Stanford. For example, we are working with Irv Weissman to do a Phase I study with a CD47 antibody, within the Oxford Haematology BRC, using public funds. Other projects currently in discussion, include a novel oral insulin molecule, and a number of novel target-disease linkages from the SGC. OxAHSC with its stakeholder network is therefore uniquely placed to produce a step change in the creation of more valuable and sustainable biotechs in the UK.

d) Novel medtech and life science applications

Medtech and **diagnostics** do not suffer the long lag times of therapeutics development. However, such projects often lack early clinical input and ready access to patients. Within OxAHSC and the Oxford AHSN, we have established a programme to provide such clinical, scientific and technological advice, and patient access. For example the university and local cancer hospital researchers are working with ProNova, to build new proton beam radiation oncology platforms which will allow integrated imaging, and reduce the number of radiotherapy sessions and treatment costs. ProNova has already agreed to commit substantial resources to undertake these clinical studies within the OxAHSC, and thereby leverage the local, world leading capabilities in radiation oncology.

We envisage **health informatics and software development** as important growth areas in the next fifteen years: analysis of large datasets will lead to new diagnostics, biomarkers, methodologies for patient

stratification, disease insights, and computer based “clinical decision support devices”. These scientific and technical advances are destined to transform health care delivery, and accelerate the goal of individualised medicines and treatment regimes. We intend, as part of our Big Data Initiative (Theme 1), to pursue aggressively the algorithm and software development components necessary to create multiple companies in this area. Given the assets provided by the NHS in terms of large sets of patient data and the capability to analyse the single payer system with fifty million individuals, in a longitudinal fashion, it is very likely that the UK will be a leader in this area. We envisage that OxAHSC will drive this leadership.

e) BioEscalator

OxAHSC has already created important adjacencies between the University and the local hospitals. An important component of our vision is to create similar adjacencies with selected industrial partners. By building a “BioEscalator” in the midst of the local hospitals, and biomedical and bioengineering research campus (Old Road Research Campus), OBU (Headington Campus) and housing key industrial partners, we will optimally exploit OxAHSC infrastructures, expertise, resources and outputs. Such close, daily interactions will facilitate “adjacent innovation”. This proposal has been put to the Government as part of the Oxford City Deal. This facility will also house some of our open innovation projects, and will be an “open” meeting place for local academics and entrepreneurs. Our aim is to use this vehicle for catalysing the translation of our basic science, in order to produce therapeutic benefit for patients and economic benefit for the NHS.

2.4 Description of how the proposed theme or work programme will contribute to the further integration of research, health education and/or patient care and how this will lead to improvements in patient care.

The essence of this theme is to breakdown disciplinary and organisational boundaries, to pool the strengths of all stakeholders and to construct more sustainable relations, in order to create integrated patient focused programmes and outputs. Such efforts will more rapidly progress patient need driven academic innovations, into evaluation in local hospitals, and to implementation and adoption in the wider NHS. A critical aspect of our vision is the Industrial Board composed of clinicians, industrial scientists, funders and entrepreneurs with track records in translation and commerce. This Board will provide the cohesion of relevant stakeholders, and a sharp milestone based focus on the clinical or commercial output.

An additional element to this theme will be creative approaches to teaching, nurturing and supporting, entrepreneurs and managers, by making full use of our academic, NHS and industrial partners. This will require important input and access to the resources of the Saïd Business School at UO. We also aim to capitalise on the Entrepreneurship Development programmes at OBU and our partnership with Stanford on the Stanford/Oxford Biodesign Programme. The latter aims to foster entrepreneurs in software development and medtech.

2.5 Description of how the theme/work programme will involve and enhance multi-disciplinary and multi-professional working.

We believe that significant patient and healthcare focussed innovations are to be derived from bringing together medical, physical and social scientists. We aim to further build on these by creating partnerships between academic, industrial and NHS groups, and by pooling or accessing the infrastructures and resources of patient organisations and funding entities. Our aim is for this new paradigm, to be significantly more efficient than the current paradigm. Success will be in the form of new therapeutics, new tools for clinical investigation and diagnosis, new private organisations, new vehicles for training, new jobs, and more investment from outside the UK.

2.6 Description of leadership and key individual and organisational contributors with responsibility for delivering the theme/work programme.

This theme will be led by Professor Chas Bountra, Director of the Structural Genomics Consortium, and Interim Director of the Oxford BioEscalator. He will be supported by a team that includes Professor Peter Ratcliffe (Founder of the Target Discovery Institute), Professor Keith Channon (Director of NIHR BRC), Dr Mark Payton (biotech entrepreneur), Dr Kevin Johnson (entrepreneur and VC), Professor Fell, OBU, Stuart Bell CBE (CEO, OH), Dr Glenn Wells (OUH), Dr Nick Edwards (angel investor and AHSN) and Dr Paul Durrands (COO, AHSN)



ACADEMIC HEALTH SCIENCE CENTRES

SPECIFIC THEME / WORK PROGRAMME

1. DETAILS OF THE PROPOSED ACADEMIC HEALTH SCIENCE CENTRE (AHSC)

Name of the English NHS Provider/University Partnership:
The Oxford Academic Health Science Centre (OxAHSC)

2. THEME / WORK PROGRAMME

2.1 Name of the theme/work programme.

Theme 3: Modulating Immune Responses for Patient Benefit

2.2 Aims and objective of the theme/work programme.

Immune and inflammatory responses are crucial determinants of human health. These responses are pivotal in defence against pathogens but when misdirected can lead to a range of autoimmune and inflammatory diseases that are responsible for a substantial disease burden. Indeed, it is increasingly recognised that aberrant inflammatory responses underlie a wide range of diseases including acute vascular disease, obesity, diabetes and Alzheimer's disease. On the other hand, the striking recent results from the use of checkpoint modulators of immunity in the treatment of cancer illustrate the power of manipulating the immune system to control malignant disease. OxAHSC will build on its partners internationally renowned track records in basic science, clinical research and pathways to clinical care to apply a multi-disciplinary approach that will innovate the diagnosis, monitoring and treatment of immune mediated diseases moving from the accepted management of these debilitating conditions to the cure that patients seek.

The theme has the following key aims:

- Application of a state of the art immune phenotyping platform to aid diagnosis, monitoring and treatment of disease.
- Identification, development and testing of novel therapeutic targets for treatment of chronic inflammatory diseases
- Redefinition of disease based on molecular pathogenesis and application of this with clinically and genetically defined patient cohorts for stratified medicine approaches.
- Harnessing the immune response to accelerate the development of novel vaccines for infectious disease and anti-tumour immunity.
- Applying a novel science-led interdisciplinary and multi-professional approach to innovate clinical care pathways in inflammatory diseases.

2.3 Description of how the proposed theme or work programme will contribute to the aims of the AHSC.

Work in this theme will fulfil key criteria of OxAHSC as it applies cutting edge basic science in immunology and inflammation to provide new diagnostics and therapies for immune-mediated diseases. The theme provides an innovative approach to translational medicine through the integration of a multidisciplinary basic science programme in close proximity to clinical research and clinical care. Major advances to flow from this programme will be identification of key pathways of molecular pathogenesis and understanding of their relevance in distinct chronic inflammatory diseases including inflammatory joint, skin, respiratory and

intestinal and liver diseases. Detailed understanding of fundamental aspects of immune activation, negative regulatory checkpoints and inflammatory pathways will be applied to development of novel therapeutic targets that can be rigorously assessed in experimental medicine studies. This programme will redefine diagnosis and treatment of chronic inflammatory diseases not based solely on clinical phenotype but on the integration of underlying molecular pathogenesis, genetic make-up and clinical phenotype. Closely allied with industrial partners, this theme will capitalise on the strengths of OxAHSC partners through multi-disciplinary and multi-professional working to effect real change not only in therapeutic strategies but in pathways of patient care.

2.4 Description of how the proposed theme or work programme will contribute to the further integration of research, health education and/or patient care and how this will lead to improvements in patient care.

The theme builds on Oxford's outstanding basic science programmes in infection and immunity together with demonstrable capabilities in human immunology and translational medicine. All together this effort will bring together Institutes and Units comprising nearly 1000 clinical and basic research scientists engaged in human immunology and inflammation providing unique critical mass in this field.

A key asset of this programme lies in the fact that our world leading Institutes and Units are intimately linked with clinical research programmes providing unparalleled opportunity for translation of basic science into improvements in human health.

The MRC Human Immunology Unit (HIU) led for many years by Sir Andrew McMichael and now directed by Professor Vincenzo Cerundolo, was crucial in mapping out the role of cellular immune responses in antiviral immunity and establishing a better understanding of the role of T-cell receptors and MHC molecules in disease. This fundamental knowledge has been applied to the treatment of autoimmune disease, cancer, influenza and HIV.

Sir William Dunn School of Pathology. The immunology programme in the Dunn School has and continues to contribute fundamental insights into immunobiology including the function of leukocyte surface molecules (Barclay), macrophage biology (Gordon) and therapeutic tolerance (Waldmann).

Translational Gastroenterology Unit. This Unit, led by Professor Fiona Powrie, has integrated the large clinical programme in inflammatory bowel disease, led by Dr Simon Travis of OUH, with the outstanding immunology programme led by Powrie, Simmons and others. This is a unique combination of clinical expertise, translational medicine and fundamental immunology that has already made substantial breakthroughs in identifying new targets for drug development and evaluating a range of novel therapeutic interventions in collaboration with industry.

Kennedy Institute for Rheumatology (KIR). The recent migration of the KIR to Oxford adds another powerful domain to OxAHSC's immunology and inflammation programme. Focused on immune and inflammatory factors responsible for rheumatoid arthritis and other forms of inflammatory arthritis, this programme – now tightly linked to the Nuffield Orthopaedic Centre within OUH provides core fundamental immunology research based in a new Institute intended to house 250 research scientists with a powerful clinical axis at the NOC supported by a new translational research facility and an NIHR Biomedical Research Unit. The Institute has already begun to attract significant international figures such as Professor Michael Dustin from NYU, and will be a key hub for immunological research nationally and internationally.

The Jenner Institute and the Translational Vaccinology Centre. Oxford has supported the development of a strong translational programme in vaccine development over the past 15 years and has created the strongest academic programme in vaccine discovery and development in the world. The Jenner accommodates over 100 scientists and is developing novel vaccine candidates in diseases such as malaria, TB, HIV, influenza and Dengue. This programme bridges basic cellular immunology and translational vaccine development based around a range of novel challenge models. The Jenner works closely with the Translational Vaccinology Group led by Professor Andrew Pollard who has unique capabilities in early clinical testing of commercial vaccines and who has established Oxford as a major centre in the UK for testing and evaluating immune responses generated by new vaccines

The Medawar Institute for Pathogen Research. This Institute, led by Professor Rodney Phillips is focused on the immunology and epidemiology of chronic viral infections such as HIV and HepC and B. Scientists in this Institute were first to describe the phenomenon of viral escape from the immune response and current work involves development and clinical testing of novel vaccines for HepC (Klenerman and Barnes).

Respiratory Medicine. The recent recruitment of Professor Ian Pavord to lead Respiratory Medicine in Oxford provides an opportunity to add a strong aspect Type 2 immunity to the programme. Professor Pavord has a long-standing interest in inflammatory diseases of the lung, particularly asthma, and has been pivotal in establishing the clinical utility of targeting eosinophils in allergic lung disease.

Solid organ transplantation OUH has a major transplantation programme that incorporates kidney, islet cell, pancreas and small bowel. It is supported by a strong transplant immunology programme led by Prof. Kathryn Wood in the Nuffield Department of Surgery.

Enabling Technologies. Because of its strengths in immunology, Oxford has also developed a range of

enabling tools that have advanced the field including a major Structural Biology group (Stuart and Jones) and a strong immunogenetics programme that has utilised the skills in the Wellcome Trust Centre for Human Genetics to make important contributions to our understanding of the genetics of autoimmune disease.

Beyond basic science discoveries, the legacy of scientists in this programme is also evident in the clinic. The most important therapeutic intervention in autoinflammatory diseases, the TNF antibodies were discovered by Professor Marc Feldmann, currently Director of the Kennedy Institute, and Professor Tiny Maini. Similarly, Professor McMichael's antibody, Raptiva, and Professor Waldmann's antibody, alemtuzumab, represent clinically validated therapeutic interventions that were discovered and partly developed by these scientists. Of the new generation of scientists in the immunology programme, Professor Simon Davis in the Human Immunology Unit was amongst the first to produce anti-PD1 antibodies, now shown to be highly efficacious in the treatment of a range of different cancers.

Delivering our Aims: An integrated programme

We will build on our proven capacity in basic and clinical science outlined above to deliver innovative multi-disciplinary approaches that represent a paradigm shift in the translation of basic science, through clinical research into patient care as follows:

Quantitative immune phenotyping. Current management of immune-mediated diseases is hindered by a lack of tools for accurate diagnosis, prognosis, stratification and monitoring. We will apply advances from our basic and translational immunology programmes to utilise high throughput platforms including state of the art imaging, multi-parameter flow cytometry and mass spectrometry, proteomic and transcriptomic platforms for quantitative measurement of the immune response. These platforms will allow assessment of thousands of parameters facilitating a systems approach to characterisation of complex immune processes. This multi-disciplinary approach will be co-ordinated through the NIHR BRC Translational Immunology lab housed in OUH and the Translational Research Facility at the NOC. Recent exemplars include the identification of an immune signatures associated with transplantation tolerance (Professor Wood and colleagues) and development of a high throughput assay for autophagy that has been applied to IBD, cancer and neurodegenerative disease (Dr Katja Simon).

Identification, testing and development of novel therapeutic targets. Advances in our understanding of the cellular and molecular basis of inflammatory pathways in the KIR and TGU have identified a wealth of new therapeutic targets including major IBD susceptibility pathways IL-23R (Powrie), NOD2 and autophagy (Simmons) and epigenetic modification (Opperman). The integration of basic science and target discovery provides new pathways for the development and testing of potential targets using novel human tissue assays, defined chemical probes (SGC) and high throughput cellular assays using gene-overexpression and knock down approaches (TDI). Proximity to defined patient cohorts in a range of inflammatory diseases (skin, joint, gut, liver, kidney and lung) will allow proof of concept immune modulation in experimental medicine studies accelerating the flow of new treatments to the clinic.

Redefining disease based on molecular pathogenesis. Research in Oxford and elsewhere has shown that common pathologic mechanisms underlie diverse inflammatory diseases. Examples include barrier surfaces defects in atopic skin disease and IBD, the IL-23R/Type 17 response in psoriasis, alkylating spondylitis and IBD and autophagy in haematological disorders, neurodegeneration and IBD. The pharmaceutical industry model of drug development away from patient cohorts has failed to recognise heterogeneity within diseases often resulting in drugs that are efficacious for some failing to meet primary endpoints. By applying understanding of the molecular pathogenesis of disease in clinically and genetically defined patient cohorts, we will develop tailored therapies for defined patient subsets. This programme benefits from the new multidisciplinary accredited Clinical Trials Unit embracing clinical trials in inflammatory (rheumatic, gastrointestinal, hepatic and respiratory), musculoskeletal and oncological diseases. The stratified medicine initiative (STOP-HCV) is a UK wide consortium, led from Oxford (Barnes and Klenerman), that will use patient stratification to optimise treatment of patients with HCV. The consortium combines clinical and scientific expertise, in partnership with industry, supported by NIHR infrastructure. It will develop novel genetic sequencing methodologies, integrated with immune and other biomarker parameters to define patient subgroups. Large scale clinical studies of novel anti-viral agents are being used to probe the biology underpinning patient response heterogeneity. In other studies Professor Peter Taylor and colleagues have developed power Doppler ultrasound for quantitative vascular imaging of inflammatory joint disease. This will be tested as a stratification marker for response to biologic therapies.

Harnessing the immune response to accelerate the development of novel vaccines for infectious disease and anti-tumour immunity. Building on the expertise in development and testing of vaccines at the Jenner Institute and fundamental human immunology in the HIU this programme will combine targeting of negative regulatory pathways (Cerundolo) with novel vaccines and adjuvants (Hill, Pollard, McShane) to promote protective immunity in infectious and malignant disease.

New clinical care pathways through a science-led interdisciplinary and multi-professional approach

Novel interdisciplinary interactions between clinical, academic and ancillary specialists (nurse practitioners, dieticians) through the unique expertise of OxAHSC partners will be applied to the development of patient-based monitoring, data collection (Big Data Institute) and management of chronic inflammatory diseases. Early identification of patients is key to successful treatment strategies and enhanced links between primary, secondary and tertiary care will allow agreed pathways for referral of patients with suspicious or red flag symptoms. Alongside physical disability and pain, chronic inflammatory diseases are often complicated by low mood and self-esteem. Collaboration between psychiatry and rheumatology and gastroenterology (Taylor, Sharp, Hammond, Harmer, Geddes, Travis) will develop a personalised tool for the quantitative assessment of patient wellbeing and establish the role of a range of pro-inflammatory cytokines in the modulation of well-being.

Capital Investments. There has been considerable investment in infrastructure to support this theme including the Kennedy Institute building, the NOC Translational Research facility and the Wolfson funded Centre for Cellular Imaging in the WIMM. In addition support from philanthropic donations will be sought for a new Institute of Immunology and Translational Medicine which will act as a flagship for OxAHSC co-locating basic science, translational medicine and clinical care for gastrointestinal and liver diseases and associated cancers in a purpose built facility on the Old Road Campus.

With the research capacity and infrastructure described above supporting this theme and generating tangible outputs in the form of novel technologies and treatment paradigms, there is a very high likelihood of changing not only the variety of therapeutic options available to the health service but also the patient care pathway. This will in turn impact on healthcare education and training and OxAHSC partners are ideally placed to lead this agenda and change.

2.5 Description of how the theme/work programme will involve and enhance multi-disciplinary and multi-professional working.

The seamless integration of basic science and translational medicine will generate new pathways to care including a new type of clinical trainee who can apply a multidisciplinary approach to the diagnosis and treatment of disease. Multi-professional education in chronic disease will bring together nurse practitioners, pharmacists and dieticians for a holistic approach to patient care involving patients themselves and integrated primary, secondary and tertiary care. The programme of work in this theme represents a true collaboration between individuals from a variety of disciplines and skill sets providing crucial added value to the effort to translate basic science to the clinic.

2.6 Description of leadership and key individual and organisational contributors with responsibility for delivering the theme/work programme.

The theme will be led by Professor Fiona Powrie (UO) and supported by Professor Alison Simmons (UO), Dr Simon Travis (OUH), Professor Sir Marc Feldman (UO), Liz Westcott (OBU)

If you have questions about the completion of this form please e-mail Sonja Tesanovic at sonja.tesanovic@nih-ccf.org.uk.

This form, together with other requested attachments must be submitted by **1:00pm on 30 September 2013**.



ACADEMIC HEALTH SCIENCE CENTRES SPECIFIC THEME / WORK PROGRAMME

Note: The accompanying “*Academic Health Science Centres – Full Application Guidance*” contains essential guidance on the information you need to provide when completing this proforma.

Please use this form to provide details on one of the six specific Themes / Work Programmes of focus for the proposed AHSC.

Please use a separate form for each of the Theme / Work Programme. Please complete no more than four pages for each theme; only information submitted up to this page limit can be assessed.

Please note this should be completed in a font no smaller than 10-point Arial.

Please insert your unique Reference Number into the Footer space provided.

1. DETAILS OF THE PROPOSED ACADEMIC HEALTH SCIENCE CENTRE (AHSC)

Name of the English NHS Provider/University Partnership:
The Oxford Academic Health Science Centre (OxAHSC)

2. THEME / WORK PROGRAMME

2.1 Name of the theme/work programme.

Theme 4: Managing the Epidemic of Chronic Disease

2.2 Aims and objective of the theme/work programme.

Chronic diseases now consume about two-thirds of all healthcare resources in established markets, and a rapidly increasing proportion of resources in developing and emerging markets. The rising burden of chronic cardiovascular, neoplastic, metabolic, respiratory, musculoskeletal and psychiatric conditions reflects a range of factors, paramount among which is the rapid ageing of populations and the logarithmic increase in the number of people reaching middle and older age, when chronic conditions are most likely to strike. In addition, the development and implementation of effective therapies for the acute treatment and secondary prevention of common chronic conditions such as coronary heart disease and stroke, has increased the size of the population surviving such diseases but still requiring long-term care. To date, the response to this challenge has chiefly been to increase healthcare supply in proportion to need, and this has become a key driver of the growing proportion of GDP spent on healthcare. Since this rising burden shows no sign of abating, the trend threatens the sustainability of health systems worldwide. Innovation is therefore urgently required to find more sustainable ways in which to increase the capacity of healthcare systems to deliver services to all those in need. Specifically, solutions are required that will deliver healthcare at lower cost and of higher quality. OxAHSC has therefore identified innovation in chronic disease management as one of its major themes.

OxAHSC will undertake several targeted programmes designed to contribute to the development of integrated models for chronic disease management. This approach transcends traditional boundaries between primary, secondary, tertiary and social care, focusing on outcomes for patients that reflect the net contribution all these sectors. Integrated care must be patient-centred and value-driven, as well as cohesive. Although much has been said about the need for integrated care pathways, most attempts to implement such strategies at scale have failed, largely because sustained change in the behaviour of organisations is rarely achieved through the simple introduction of a single new process or technology within a long-established system. Robust solutions will require much more comprehensive strategies designed to facilitate end-to-end reform of the system and its processes. We believe that such changes are

possible, particularly with the broader application of facilitative technologies that provide a range of tools by which to improve the accuracy of diagnosis and the specificity of treatment, as well as increase the efficiency and safety of healthcare. The development of such models of care requires research that focuses on the broader system of healthcare as well as its component parts. To deliver this, OxAHSC will take a multi-pronged approach requiring the full engagement of all academic partners as well as associated components of the healthcare system. The major elements of this programme include:

1. Redefining diseases to deliver safer, more effective healthcare. The main classifications of chronic disease (cardiovascular, neoplastic, metabolic, respiratory, musculoskeletal and psychiatric), reflect diagnostic criteria based on clinical phenotypes originally described more than 100 years ago. While in some areas there has been improvements in the specificity of disease categorisation (e.g. breast cancer), in others (e.g. chronic back pain) there has been little if any. Without question, the failure to refine diagnostic categories and identify biologically discrete diseases within broad clinical groupings has blunted the apparent therapeutic capacity of many treatments, ultimately reducing their cost effectiveness and limiting their impact. Hence, a key component of the OxAHSC strategy is to continue our efforts to understand the mechanistic heterogeneity of chronic diseases and develop a taxonomy that reflects the specific disease mechanisms that may be sensitive to specific therapeutic strategies, rather than the broad clinical phenotype. Such a redefinition of disease will have two major implications. First, it will help define individuals who more likely to develop the complications and exacerbations of chronic diseases. This will ultimately lead to a more personalised approach to therapeutic management that will deliver greater impact of drug therapies and reduced risk of adverse effects. Second, it will help to change the natural course of chronic diseases turning some into curable conditions through the development and implementation of new targeted interventions: as has been achieved, for example, with gastric ulcers and certain types of cardiac arrhythmia. The redefinition of the major chronic diseases is now progressing apace. In some pharmaceutical companies, as many as 70% of drugs under development are targeted to patient subpopulations based on specific genetic or phenotypic markers. In cancer, a better understanding of the driver mutations in tumours has already created a remarkable change in the way drugs are discovered, developed and applied to patient populations. Such fragmentation of disease categories is also occurring in other areas such as respiratory disease, in which our new Professor of Respiratory Medicine, Ian Pavord, has identified a major subset of asthma driven by eosinophils with a TH2 response that has directly facilitated the discovery of a range of new therapeutic agents that could not otherwise have been developed in the absence of such disease stratification (CRTH2 inhibitors and IL13 inhibitors). Diabetes turns out to be a more challenging problem, in large part because of the wide range of disease subtypes that this diagnostic category subsumes. We already know that rare forms of diabetes, of which there are more than twenty, can be precisely defined, have different natural histories and different responses to existing therapies. But what we need to know is how to stratify the bulk of those currently defined as having type-2 diabetes to better understand who will develop micro- or macro-vascular complications, and who will experience the greatest benefits and lowest risks of treatment. Our new Professor of Statistics and Epidemiology, Mark Woodward, oversees a large research program on phenotypic and genetic predictors of outcome in type-2 diabetes and has shown that the effectiveness of both glucose lowering and blood pressure lowering treatments vary substantially in subgroups so-defined. OxAHSC views disease redefinition as a central component of any strategy to manage chronic disease effectively and efficiently and is committed to facilitating this across a broad range of conditions. Initially, new targets will include chronic obstructive airways disease (COPD) and congestive heart failure (CHF).

2. Effective interventions for primary and secondary disease prevention. Given the human and financial toll exacted by acute manifestations of chronic disease, it is essential that healthcare systems prioritise the provision of effective preventive services to individuals at high risk. OxAHSC has a well-established record of both quantifying the potential impact of modifiable risk factors and evaluating the actual effects in large-scale trials. The Clinical Trials Services Unit (Peto and Collins), for example, has contributed, arguably more than any group worldwide, to the body of evidence that has allowed preventive strategies to reduce the deaths from coronary heart disease by half over the past fifteen years. Their work on cholesterol lowering and antiplatelet therapy has transformed clinical practice worldwide. Stroke prevention is another area where partners in OxAHSC have had a major impact. In a large cohort of stroke patients identified through electronic records in Oxfordshire, Peter Rothwell was able to identify the profound importance of minor cerebrovascular events as predictors of major cerebrovascular events. He then showed that treating these patients aggressively with a combination of preventive measures substantially reduced the risk of fatal or disabling outcomes. This example of effective secondary prevention has had profound consequences for clinical practice in the UK and elsewhere. Similarly work conducted by The George Institute for Global Health has shown that prolonged reductions in blood pressure reduce the risk of recurrent stroke among patients with cerebrovascular disease, irrespective of initial levels of pressure. Additionally, the George has recently shown that by beginning blood pressure lowering in the acute phase of cerebral haemorrhage, severe disability can be avoided. Prevention of stroke and its complications is clearly an area where OxAHSC can continue to be a global leader. OxAHSC will expand the range of projects concerned with effective primary and secondary prevention of chronic disease. New

targets for such efforts will include diabetes, COPD and CHF.

3. Improving the management of acute complications of chronic disease. While OxAHSC ranks the prevention of chronic disease as its greatest priority, it also remains committed to research designed to improve the management of acute complications of the same diseases, since these will continue to be a major source of premature disability, life-long disability and healthcare expenditure for some time to come. To this end, a major goal must be to ensure that hospitals implement evidence-based clinical pathways to ensure optimal outcome for patients presenting with acute complications of chronic conditions. The OUH has implemented such pathways across a range of conditions including acute coronary syndrome, with very strong door to balloon times exceeding the national average and excellent survival data. Similarly, the Acute Stroke Service established by Professor Alastair Buchan was one of the first of its kind in the UK and continues to deliver effective acute stroke management with attendant reductions in mortality and morbidity. OxAHSC plans to undertake research that will assess strategies for the implementation of similar programs in district general hospitals. It will also undertake research to evaluate the impact of implementing clinical pathways in other important but neglected areas, such as the management of acute heart failure and non-specific acute syndromes as atypical chest pain and unexplained breathlessness. A key element of OxAHSC strategy will be to continue to refine acute management strategies based on the best clinical research, utilising assets such as the unique Acute Vascular Imaging Research Unit positioned next to the emergency department.

4. Community-based approaches to integrated healthcare. A key challenge in the management of many chronic conditions is how to manage patients effectively in the community without repeated visits to tertiary referral centres. The solution to this will require several complementary strategies including components directed at workforce re-engineering and others to the implementation of digital technologies designed to improved healthcare management in the community. OxAHSC views such developments as a major objective of its research programmes over the next five years. Success in this endeavour will, however, require substantial changes in the way the local health economy operates. We are fortunate in that OH is responsible for the community hospital network in Oxfordshire and OUH has already begun to establish community outreach programmes for chronic disease. A sustainable and comprehensive community healthcare system requires a new type of workforce supported by clinical decision support tools that enable the management of multiple different diseases given the frequency of co-morbidities among those with chronic diseases. It will also require full engagement with primary care community hospitals and tertiary referral centres to allow the joint management of patients to occur seamlessly. None of this is possible without an integrated electronic patient record, but much progress has been made towards that, with around 75% of GP practices now agreeing to have a common accessible Oxfordshire Care Summary of patient records. OxAHSC plans a series of controlled studies of the introduction of innovative community models of disease management across a range of priority areas including diabetes, COPD and CHD.

5. Managing comorbidity among patients with chronic disease. A key challenge in managing conditions associated with ageing is the co-morbidity that is effectively routine among those with chronic disease. This requires both multidisciplinary and multispecialty input. An example is the psychiatric comorbidity that occurs in a quarter of patients with chronic medical conditions: failure to manage this comorbidity results in worse patient outcomes, increased cost of medical care and poor patient experience. Integrated medical and psychiatric care must, therefore, be a key component of any chronic disease management strategy. Similarly, the co-existence of diabetes and vascular disease, the interaction between heart failure and obstructive airways disease demonstrate and the primarily vascular complications of hip fracture demonstrate how consideration of coexistent chronic disorders is crucial for successful clinical management. The Oxford CLAHRC, recently approved by the NIHR and involving all partners, has a major theme evaluating better ways of managing co-morbidity with particular focus on mental health. This will allow us to develop a focus on co-morbidity as part of the broader OxAHSC strategy for managing chronic disease.

6. Digital monitoring of patients with chronic disease. As a part of our digital health theme, we will be evaluating digital methods designed to allow the monitoring of patients outside hospital. In the management of chronic disease, we will focus on the monitoring of key physiological variables that may indicate relapse (e.g. heart-rate and respiratory rate in CHF patients) or non-compliance with treatment. It is now possible to monitor a wide range of vital signs and parameters wirelessly and provide feedback to both clinicians and patients, as demonstrated by early results from studies led by Dr Kazem Rahimi and Professor Lionel Tarassenko. Working with technical partners such as Proteus, we have plans to assess the impact of patch-based technologies to detect early signs of clinical deterioration and initiate early therapeutic intervention. Linkage of output from these technologies to the clinical decision support systems we are building for use in both hospital and community settings should further improve the quality of care provided and the clinical outcomes achieved. The feedback that these systems provide to patients themselves is also a potentially important factor that should facilitate improvements in self care. Digital monitoring also has the potential to improve patients' quality of life and reduce healthcare costs by enabling patients to remain in their homes, rather than being admitted hospital for monitoring. Thus, the integration of

the chronic disease theme and our digital health theme is an important part of OxAHSC strategy.

2.3 Description of how the proposed theme or work programme will contribute to the aims of the AHSC.

Innovation leading to improved preventive and therapeutic strategies for common serious conditions is a key aim of the OxAHSC bid. This chronic disease theme will exemplify this. Given the increasing burden of chronic disease and the failure of almost all healthcare systems to adjust care pathways to cope with the burden, developing innovative cost-efficient approaches to managing these patient populations to produce better outcomes at lower costs is not merely an option - it is an imperative in modern healthcare. For this reason we have sought to highlight this as a major component of the bid. Several of the other themes will help inform the strategies that we will formulate and evaluate in this theme. For example, the big data theme will almost certainly generate evidence about the management of chronic disease in the UK that will become the focus of new projects designed to improve weaknesses or emulate strengths. Similarly, the work on digital health will also complement the present theme through the development and evaluation of new state-of-the-art technologies that might be incorporated in chronic disease pathways of care. This combination of disease-focused and technology-themes offers great potential to ensure that innovation is informed by needs and not supply alone. Conversely, it offers great potential for the development of non-obvious but potentially highly-effective strategies for disease control through insights provided from outside the traditional professional skills applied to chronic disease management. Collectively, this will enable OxAHSC to generate and evaluate truly innovative solutions for the management of both the chronic and acute manifestations of those conditions responsible for the greatest proportion of disease burden and healthcare expenditure in the UK. The results have the potential to transform the way the healthcare system works – with the real possibility of securing affordable improvements in outcomes in the near term (i.e. within just a few years).

2.4 Description of how the proposed theme or work programme will contribute to the further integration of research, health education and/or patient care and how this will lead to improvements in patient care.

Pivotal to the management of the global epidemics of chronic disease will be the establishment of a new healthcare workforce that, supported by innovative digital technologies, will deliver affordable high-quality preventive and therapeutic care within communities. This workforce will be empowered to provide personalised care across therapeutic areas and to manage concurrently the multiple co-morbidities that so often exist. This workforce will also monitor the health of patients with chronic conditions, and identify those at an early stage of deterioration such that they receive rapid and effective management in a secondary or tertiary care facility. This is a key objective of OxAHSC chronic disease theme, and OBU, through its Department of Clinical Health Care, is developing a training programme for this new workforce. There will also be a need for new approaches to the training of doctors and medical students in the long-term management of chronic diseases, which will continue to represent a major component of their workload for the foreseeable future. The integration of such training with research on the control of chronic diseases is firmly part of the objectives of OxAHSC.

OxAHSC is at the cutting edge of the development of new tools for chronic disease monitoring and treatment, and the combined resources of two Trusts and two universities linked to a powerful primary care network provides an ideal environment in which to introduce and evaluate new potentially transformative approaches to patient care. With this goal, our programme will pursue the following strategies:

- The use of large linked clinical datasets for the development and validation of highly discriminative risk prediction tools, with the aim of early detection of those developing chronic disease and well those at highest risk of their acute manifestations. We will initially focus on three major clinical conditions: Diabetes, CHD and COPD.
- The establishment of an integrated IT framework that will allow electronic patient records to be commonly utilised for the management of chronic conditions across primary, secondary and tertiary care. This electronic platform will include real-time risk prediction algorithms for selected common chronic conditions onto which electronic clinical decision support for evidence-based management of such patients will be mounted.
- The development of community-level cohorts of patients in whom repeat measures of health status will be obtained using innovative user-friendly digital tools applied in the home environment. The granular longitudinal data obtained will then be used to refine the prevailing static risk prediction tools (using state-of-the-art Bayesian data analytics and machine learning techniques).
- The design and conduct of complex intervention trials testing the hypothesis that IT-supported management for chronic conditions improves clinical outcomes at low cost. The intervention will use components developed from previous work (risk prediction algorithms, clinical decision tools, home monitoring technologies, and integrated IT for retrieval of relevant information and communication of results to different stakeholders). In addition, a specially trained remote management team will be employed to support the delivery of such care.

- The development of a research programme that aims to evaluate novel approaches to cancer care. Including methods for early detection of cancer and experimental studies of new or existing therapies for prevention and early treatment.

2.5 Description of how the theme/work programme will involve and enhance multi-disciplinary and multi-professional working.

The fundamental changes in the approach to healthcare that we propose, will by definition create opportunities for enhanced integration of care between existing health professionals, new types of healthcare providers and patients. Integrated care pathways will bring together expertise in disease prevention and treatment, through a community-based health management system linked by a common integrated IT system focusing on the needs of both patients and providers. Such a broad coalition of stakeholders represents a very different scenario from what which currently characterises our healthcare system. The success of this endeavour will require input from a range of disciplines including medicine, engineering, statistics and management. Acquisition of data by digital monitoring and patient input will require interpretation and analysis using advanced statistical techniques. The common IT system will need technical support, as well as engineering design. The care required to manage patients in the community as well as in hospital will require the engagement of both primary care and tertiary care medical staff, as well as a range of other healthcare providers. Entirely new types of healthcare workers specifically trained in the use of new digital technologies for the monitoring and management of patients with chronic diseases will be an important part of the solution. Crucially, the frequency of co-morbidities among those with chronic disease necessitates partnership between specialities, services and consumer groups to ensure balance, as well as excellence, in the care of this large and important clinical population.

2.6 Description of leadership and key individual and organisational contributors with responsibility for delivering the theme/work programme.

Professor Stephen MacMahon supported by Professors Richard Hobbs and Lionel Tarassenko (UO), and Dr Kazem Rahimi (UO), Liz Westcott (OBU) Prof Ian Pavord (UO) Mr Pete McGrane (OH)

If you have questions about the completion of this form please e-mail Sonja Tesanovic at sonja.tesanovic@nih-ccf.org.uk.

This form, together with other requested attachments must be submitted by **1:00pm on 30 September 2013**.



ACADEMIC HEALTH SCIENCE CENTRES SPECIFIC THEME / WORK PROGRAMME

Note: The accompanying “*Academic Health Science Centres – Full Application Guidance*” contains essential guidance on the information you need to provide when completing this proforma.

Please use this form to provide details on one of the six specific Themes / Work Programmes of focus for the proposed AHSC.

Please use a separate form for each of the Theme / Work Programme. Please complete no more than four pages for each theme; only information submitted up to this page limit can be assessed.

Please note this should be completed in a font no smaller than 10-point Arial.

Please insert your unique Reference Number into the Footer space provided.

1. DETAILS OF THE PROPOSED ACADEMIC HEALTH SCIENCE CENTRE (AHSC)

Name of the English NHS Provider/University Partnership:
The Oxford Academic Health Science Centre (OxAHSC)

2. THEME / WORK PROGRAMME

2.1 Name of the theme/work programme.

Theme 5: Emerging Infections and Antimicrobial Resistance

2.2 Aims and objective of the theme/work programme.

The successful development of both vaccines and antibiotics has had a major impact on many of the major infections afflicting mankind. Despite this, infectious diseases still represent a major threat to human health. In an era of globalisation and extensive travel, emerging infections now represent the leading public health threat in both developed and developing countries. This theme is intended to utilise the unique assets and global reach of the Oxford Infectious Disease Programme to develop surveillance capabilities for the major infectious disease threats, integrate these programmes with clinical research better describing the clinical syndromes associated with new emerging infections, and to couple these to our capabilities in genomics to characterise more precisely the pathogens responsible for outbreaks of disease. Additionally this programme seeks to establish a public sector programme to generate novel antimicrobial agents.

2.3 Description of how the proposed theme or work programme will contribute to the aims of the AHSC.

Emerging infectious diseases (EIDs) and antimicrobial resistance are a serious domestic and cross-border threat to human health, social and economic stability, and are a major challenge for the NHS, with the economic costs of infectious diseases in England estimated at £30 billion per year. The most profound current risks to human health in the UK relate to the emergence of highly infectious respiratory viruses: the Cabinet Office National Risk Register (2012) considers pandemic influenza to be the highest priority and most significant civil emergency risk facing the UK. With increasing international travel, the frequency of emerging infectious threats to England is likely to increase. Recent examples include avian influenza A subtype H7N9 in China and the Middle East Respiratory Syndrome Coronavirus (MERS-CoV), where nosocomial transmission is implicated in 26% of cases. The consequences of EIDs can be profound in both health and economic terms. The 1918 influenza pandemic is estimated to have killed 2.6 million people in Europe and the economic consequences of SARS have been estimated at US\$3-10 million per case. If antimicrobial resistant organisms are considered as emerging infections, then the threat is even greater; with the importance to England of antimicrobial resistance clearly laid out in the Chief Medical Officer's Annual Report of 2011.

Identifying and characterising new infectious threats at source (White, Snow, Horby)

Our experience with avian influenza reflects the important role played by Oxford scientists based in regions, such as Asia, which are hot-spots for emerging infections. The Oxford/Wellcome Unit in Vietnam, led by Professor Jeremy Farrar, was among the first to describe the clinical syndrome, high mortality and response to antivirals of H5N1 influenza. Similarly, our collaborators Professors George Gao and Hongjie Yu, Deputy-Directors of China CDC, have provided the most detailed clinical and epidemiological data on H7N9 influenza. The UO Centre for Tropical Medicine is a partner in the European Platform for Emerging and Re-emerging Infectious Disease Entities (EMPERIE), is the coordinating centre for the International Severe Acute Respiratory & Emerging Infection Consortium (ISARIC), the Southeast Asia Infectious Diseases Clinical Research Network (SEAICRN); and is coordinating three work packages of the new large-scale EU FP7 programme on European preparedness against epidemics. The University has developed through its Tropical Network a set of research and surveillance programmes across South Asia including and many sites established as a result of the H5N1 avian influenza epizootic that emerged in 2004 and they remain crucial for the monitoring and detection of pathogens and emerging epidemics. Within the UK, Oxford is working with Public Health England on the clinical research response to MERS-CoV and will coordinate the pan-European development of harmonised clinical case definitions, guidelines and protocols for large multi-site clinical studies in response to severe ID outbreak. Professor Chris Butler has recently joined Oxford from the University of Cardiff and will provide leadership in conducting prospective studies of emerging infections in primary care. These clinical networks are complemented by research platforms, such as the UO Oxford Genomics Centre, studying host-pathogen genomic interactions, and UO Structural Biology, studying the structure and host cell interactions of emerging and Category three pathogens. Oxford is therefore ideally positioned to deliver tangible improvements in systems and methods to detect and characterise EIDs in England and Internationally and provide the data needed to reduce uncertainty and to inform clinical decision-making. This work will deliver:

- The core capacity, infrastructure, and systems for an urgent clinical research response to EIDs across primary (OH) and secondary care (OUH).
- Systematic and standardised data on the clinical presentation, progression, treatment effects, and outcomes of EIDs, and information on the host and pathogen determinants of virulence.
- Systematically collected and characterised biological samples from patients with EIDs, for pathogen identification and the development and validation of diagnostic assays.
- Strengthened clinical outbreak research capabilities through the delivery of training to clinicians.

Creating evidence based maps for 174 global pathogens (Hay)

An important component of this programme is the advances in surveillance methodology led by Professor Simon Hay. The Atlas of Baseline Risk Assessment for Infectious Disease (ABRAID) is a unique surveillance programme led from Oxford and funded by the Gates Foundation. Less than 5% of clinically important infectious diseases have been mapped reliably and this presents a significant obstacle to any evaluation of the feasibility of new interventions for these diseases as well as to operational public health decision-making, including the geographical underpinning for quantification of disease burden, and assessment of risk in England. At the individual patient level, clinical decision-making for patient with imported fevers is hampered by ignorance of the contemporary geographic distribution of infectious diseases.

Developments in the field of Big Data, machine learning and online collaboration, coupled with expert oversight, will generate a comprehensive and routinely-updating global atlas of 174 infectious diseases of clinical importance within five years and ABRAID will be unique in the scope of diseases reliably mapped at global levels. The infrastructure to harness novel data sources is central to innovation in global health. Implementation is proposed through the following interlinked aims: 1) Use specialist-led machine learning (ML) and crowdsourcing (CS) to generate definitive extent distributions for all infectious diseases, and calibrate these for known reporting biases. 2) Create a cloud-based digital archive of environmental data relevant to infectious disease mapping globally. 3) Use geospatial techniques to infer from these three information sources the geographic distribution of risk for all infectious diseases. 4) Use a disease map "geo-wiki" for evaluation of the infectious disease maps. 6) Use these validation results to automatically update and iteratively improve the maps in a continuous feedback loop. This programme will provide:

- The information necessary to evaluate the feasibility and to target development for vaccines, other interventions, and treatments;
- A completely new strand of information with which to calibrate population at risk and global burden of disease assessments; and
- Improvements in patient diagnostic and treatment algorithms as a result of better-characterised risks of imported infections and of the range of clinical phenotypes associated with particular infections.

Genomic transformation of clinical microbiology (Crook, Peto)

UO and OUH have developed increasingly sophisticated tools for obtaining data to allow more accurate disease surveillance of a range of infectious pathogens. Generating a pathogen genome sequence is now cheap, making it cost effective for the identification and investigation of disease outbreaks, both in the

community and the hospital. This has been shown in a wide range of pathogens, both viral and bacterial, including influenza, *S. aureus*, *C. difficile*, *M. tuberculosis*, *S. pneumoniae* and *V. cholerae*. These advances have led large national infectious diseases reference centres to adapt this technology for routine work. In addition to tracking the spread of disease, the same pathogen sequence can also provide the entire information needed for species identification, antibiotic resistance determination and detection of specific virulence factors. This has the potential to capture, in one step, all the information provided by the complex and slower conventional hospital microbiology laboratory, which is used for individual patient management and pathogen surveillance.

Current NHS-funded research projects in OUH's BRC are developing these techniques for routine clinical service. It is clear that, over the coming decade, whole pathogen sequencing will progressively replace current hospital microbiology laboratory processes. Scientists in OUH (Crook and Peto) are at the cutting edge of this genomic revolution and were amongst the first to apply whole genome sequencing (WGS) methodology to aid with clinical diagnosis and management of patients within the NHS. Oxford has worked in partnership with Public Health England to develop the Modernising Medical Microbiology programme and has linked whole genome sequencing with electronic health data in Oxfordshire, Brighton, Birmingham and Leeds. The development and application of WGS and data mining techniques to microbial databases will yield unprecedented opportunities as follows:

- Improved patient management through unambiguous species identification and its antimicrobial resistance profile. Simultaneously, the pathogen can be related phylogenetically to all previous examples of this pathogen in a countrywide database, from which transmission networks can be inferred and interrupted;
- Rapid infection threat detection could become routine, and in some instances nearly instantaneous. Phylogenetic analysis of genomically defined transmission networks in conjunction with linked epidemiological data, will allow early detection of new outbreaks of existing pathogens both locally and nationally to allow intervention to stop outbreaks. In addition, early Phylogenetic analysis of genomically defined transmission networks in conjunction with linked epidemiological data, will allow early detection of new outbreaks of existing pathogens both locally and nationally to allow intervention to stop outbreaks.
- Rapid discovery of new pathogen-specific genes that encode particular novel and threatening phenotypes. Key examples would be the emergence of new resistances that cause life-threatening breakthrough infections, despite apparent optimal antimicrobial treatment.

Understanding and controlling animal reservoirs (Fazakerley, Hill UO)

The crucial role of animal reservoirs provides another opportunity for Oxford and its collaborators to provide leadership in this field. Pirbright, the national facility for animal pathogens, has been transformed in recent years with state-of-the-art category 3 and 4 facilities capable of handling and managing pathogens in a wide range of host species. Pirbright and UO have agreed to build on existing collaborations to evolve a strong integrated programme. The Institute of Animal Health at Pirbright created a vaccine programme targeting both animal and human pathogens while based at Compton. This programme, badged the Jenner Institute, has subsequently moved to Oxford and retains a shared programme with animal vaccines tested at Pirbright and human vaccines in Oxford. Pirbright scientists are engaged in a wide range of other collaborations with UO and OBU virologists and structural biologists studying a range of animal infections. A recent example of their success is the production of a heat stable Foot-and-Mouth vaccine based on a capsid protein created by mutational strategies based on structural data and experiments undertaken by Pirbright scientists alongside Professor David Stuart from Oxford using the DIAMOND synchrotron. OBU also has collaborative vaccine programmes with Pirbright, broadening the relationship across OxAHSC. This breadth of established relationships has led to a strategic collaboration between Pirbright and Oxford to characterise and potentially intervene at the level of animal reservoirs.

The Oxford Vaccine Programme

This provides another component of the programme designed to counter pandemic threats. The Jenner Institute, led by Professor Adrian Hill, has a wide range of programmes bridging basic immunology and vaccine early development. These include vaccine candidates for malaria (chosen by the Gates Foundation as the leading candidate after RTSS, TB, Dengue fever, influenza and HIV). Taking advantage of the expertise in cellular immunology, these programmes are achieving high levels of antigen specific CTLs against specific antigens from all these pathogens. This programme is allied with the Pirbright Virology group and is also committed to developing animal vaccines for a range of pathogens in wild or domestic animal populations. Additionally Professor Andrew Pollard runs a clinical testing programme for human vaccines which allowed a swine flu vaccine to be rapidly tested in humans before roll-out during the swine flu epidemic of 2010.

Treating antimicrobial resistant pathogens

The emergence of widespread resistance amongst common bacterial pathogens also presents a serious threat to human health. Serious resistant strains of multidrug resistant tuberculosis, *E. faecium*, ESBL-*E. coli* have already emerged globally and are only treatable with poorly effective and toxic drugs, with clear risks that other pathogens will also develop high-level resistance (e.g. *S. aureus*, Pneumococcus). This

leaves open a serious risk for patients and healthcare systems. In the presence of untreatable resistant pathogens, some elective surgery would cease, and the infective complications from immunosuppressive treatment and chemotherapy would render organ transplantation and cancer chemotherapy unacceptably dangerous. The development of new drugs is a considerable challenge as obstacles exist at almost every stage. New drug targets have been much more difficult to identify than predicted. In addition the assessment of new antibiotics has been hampered by current regulatory frameworks, which hinder patient recruitment into clinical studies. Finally, there is a market failure in that healthcare systems tend to restrict the use of new antibiotics to 'reserve drug' status threatening the likelihood of commercial success.

The importance of developing new antibiotics is clear and has been stated by the Chief Medical Officer and was affirmed at the recent G8 meeting. However, the necessary progress in this area is unlikely to emerge from the pharmaceutical companies and the most likely solution will emerge from publicly funded efforts to identify new antibiotics. In response to these challenges, OxAHSC will develop a PPP utilising the expertise provided by academic and clinical microbiologists aligned with the drug discovery capabilities in Chemistry, the Nuffield Department of Medicine and the Structural Genomics Consortium. Discussions are in place to collaborate with industry. Modification of the regulatory environment to facilitate fast track licensing will be addressed in collaboration with CASMI.

2.4 Description of how the proposed theme or work programme will contribute to the further integration of research, health education and/or patient care and how this will lead to improvements in patient care.

The integration of strong public health into OxAHSC is strategically important. One of Oxford's greatest strength in public health lies in the field of infectious diseases, particularly if they relate to emerging infections that could lead to substantial morbidity and mortality in the UK. In addition, the Oxford programme is interested in developing the tools that will make infectious disease surveillance and interventions more effective as set out above. Our programmes in vaccine discovery and development and our reach into animal reservoirs of human pathogens are both crucial components of the overall strategy. These programmes represent some of the most translational in OxAHSC as they require fundamental knowledge of the pathogens and their epidemiology which can be rapidly applied to surveillance and monitoring, to clinical investigation to describe the clinical syndromes associated with their infections and to the development of new tools that can rapidly be implemented in clinical microbiology or in the field to better monitor these disorders. Genomics will be to dramatically reduce cost while, at the same time, improve the accuracy of diagnoses and the speed at which pathogens can be characterised and interventions provided. Intelligence about major new infectious diseases will also have a profound impact on patients allowing the healthcare system to adjust in order to manage emerging infections as they spread through populations.

Programme of research

- The Disease Surveillance programme based in SE Asia and Europe will provide one of the most effective sources of data to identify and subsequently track emerging infections. This programme is coupled to significant capacity for emerging pathogen identification and significant clinical expertise to understand and characterise the relevant clinical syndromes. The programme is also capable of developing rapid diagnostics, mostly sequence based, of emerging pathogens.
- Complete infectious disease mapping of 174 major global pathogens assembled from a range of big data sources and updated frequently to track and monitor 50 infectious diseases. This is to be housed in the Big Data Institute but will have outreach to a range of data sources globally through ABRAID.
- Animal pathogens and animal reservoirs of human pathogens will be studied to control emerging epidemics. Virology and Vaccine development are key components of this strategy for controlling animal reservoirs of new human pathogens in collaboration with the Pirbright.
- Develop tools to modernise genomic microbiology. This programme will focus on genomic testing for hospital acquired infections, major community acquired infections such as *M. tuberculosis*, *C. difficile* and pathogens such as HCV and HPV. Led by OUH/BRC scientists in Oxford (Crook and Peto) and enabled by the statistical genetics expertise in the Wellcome Trust Centre for Human Genetics, this programme will further develop a *M. tuberculosis* sequencing strategy and database and roll this out nationally for use in contact tracing and epidemic control.
- Vaccine discovery and development bridging new vaccine design, the evaluation of new antigens and testing in humans with experimental challenge models where possible will provide a responsive system for the development of prophylactic vaccines against infectious threats.
- OxAHSC will explore a public sector drug discovery programme for antimicrobials in collaboration with one or more major pharmaceutical companies and incorporating the strong structural biology and medicinal chemistry capabilities of OxAHSC scientists as well as the expertise of CASMI to attempt to reengineer the regulatory environment and market place to support such a public sector endeavour.

Education Programme

- OxAHSC is well placed to ensure that the medical, nursing and allied health professional workforce have

the appropriate training and knowledge in emerging infectious disease and the important role of surveillance and vaccination as described in this programme. UO and OBU provide modules and MSc courses in Global Health, Infection Prevention and Immunology/Virology. These courses are made available online to reach healthcare workers worldwide. We will build on these to provide a range of modules and CPD courses to ensure continual updating of a wide range of healthcare professionals.

2.5 Description of how the theme/work programme will involve and enhance multi-disciplinary and multi-professional working.

This theme has many examples of multi-professional and multidisciplinary activities and workforce. It incorporates clinical epidemiologists, microbiologists, geneticists, clinical investigators, computational biologists, veterinary virologist and immunologists. The antimicrobial resistance programme will also rely heavily on the skills of chemists and those involved in considering regulatory policy. The surveillance strategy relies heavily on information obtained in a variety of settings globally and the infectious disease mapping programme led by Simon Hay is heavily dependent on IT and computing capabilities as well as big data analyses.

2.6 Description of leadership and key individual and organisational contributors with responsibility for delivering the theme/work programme.

The theme will be led by Dr Peter Horby who will be supported by Professors Simon Hay, Tim Peto and Derrick Crook (UO/OUH) and Linda King (OBU). The Pirbright linkage will be led by Professor John Fazackerly, and the vaccine programme will be led by Professors Adrian Hill and Andrew Pollard.



ACADEMIC HEALTH SCIENCE CENTRES

SPECIFIC THEME / WORK PROGRAMME

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Please use this form to provide details on one of the six specific Themes / Work Programmes of focus for the proposed AHSC.

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Please note this should be completed in a font no smaller than 10-point Arial.

Please insert your unique Reference Number into the Footer space provided.

1. DETAILS OF THE PROPOSED ACADEMIC HEALTH SCIENCE CENTRE (AHSC)

Name of the English NHS Provider/University Partnership:
Oxford Academic Health Science Centre (OxAHSC)

2. THEME / WORK PROGRAMME

2.1 Name of the theme/work programme.

Theme 6: Cognitive Health: Maintaining Cognitive Function in Health and Disease

2.2 Aims and objective of the theme/work programme.

Of all the major chronic diseases, those that disrupt cognitive function – particularly the neurodegenerative disorders such as dementia – will have increasingly significant implications for the NHS and wider society in the near future. The growing burden of these disorders associated with demographic shifts will not only create profound pressures on healthcare systems throughout developed economies, but they will also have a very substantial financial impact on many other aspects of society, particularly social care.

Our aims are to delay the onset, to reduce the incidence of disease, to prevent progression and to improve wellbeing - these aims are interdependent but need different approaches and methods. Our objectives are to understand how to prevent dementia, which is, of course, complex. For example, although Alzheimer's disease is a widely used clinical description, in reality its precise pathophysiology is far from clear and it, like Parkinson's disease, is likely to have multiple distinct pathogenic mechanisms. The underpinning aetiology of a majority of patients with Alzheimer's disease may involve distinct mechanisms not yet properly explored. Research, including drug discovery and development in dementia, has been substantially impaired by the lack of precise mechanistic definitions. OxAHSC is well placed for this work and will take full advantage our broad clinical and scientific approaches to dementia, spanning the partner organisations, with outstanding existing programmes in vascular dementia, Parkinson's Disease and cognitive health.

To achieve our objectives, we will deploy Oxford's strength in a wide range of therapeutic areas will be used to enhance our understanding of neurodegeneration. As just one example, inflammation may undoubtedly

has a role in Alzheimer's disease (AD); many susceptibility genes are inflammatory mediators, compounds effecting the inflammatory system alter risk of dementia and the AD brain carries a considerable inflammatory burden. We will bring the considerable academic and translational strength of inflammation science at Oxford, such as that at the newly established Kennedy Institute headed by Sir Marc Feldmann UO, to dementia studies and also to our study of delirium where inflammatory factors are clearly at play.

In addition, the programme will not be limited to Alzheimer's disease; it will also focus on more immediately tractable areas. Up to 30% of patients with dementia suffer from cerebrovascular disease and, although this has received less attention than the amyloid associated disorders of cognition, it is possible that interventions in this set of disorders will be more tractable, both to prevention and intervention strategies. We are confident that our programme on vascular cognitive impairment and post TIA/stroke dementia, headed by Peter Rothwell (OUH/UO), and focusing on pragmatic interventions to improve primary and secondary prevention, with particular emphasis on better phenotyping and more effective use of existing preventive strategies, will produce results in the next two years that will translate immediately into clinical practice.

We will also aim to maintain cognitive health through a programme led by Professor Kia Nobre (UO/OUH) by evaluating behavioural interventions to enhance neuronal plasticity via cognitive and physical training and will be further developed as public health interventions via the Oxford CLAHRC. Our aim is to integrate and coordinate these programmes where there is added value. OxAHSC will address some of the key issues that are important in retaining good levels of cognitive function into later life by bringing together the power of its intensively phenotyped local and national cohorts, basic discovery neuroscience and genetics, with the innovative big data, target discovery and digital health programmes to create an integrated system bringing together research, clinical services and education and training.

Our long-term goal is to identify disease processes in the preclinical phase and to develop disease modification therapies for secondary prevention; through OxAHSC theme we shall establish the conditions needed for the prevention of these devastating and costly disorders. OxAHSC will build on several existing cross-partner initiatives that include:

Oxford Cognitive Health: Advances in imaging, genetics, cell biology and cognitive neuroscience have now reached a stage where cognitive and mental disorders have become tractable. Their complexity makes interdisciplinary collaboration between clinicians, cognitive neuroscientists, geneticists and others essential and there has been rapid recent integration across the partners to Oxford create links between research, clinical services and in undergraduate and postgraduate education to take advantage of these developments and deliver benefits for patients. The strength of Oxford's innovation in neuroscience has been recognised by major strategic investment from Wellcome Trust (SCNi (Foster); FMRIB (Smith); Non-Human Primates (Rushworth); Wolfson Foundation (Centre for Prevention of Stroke and Dementia; Rothwell). Momentum and ambition in the area of dementia in particular was increased with the renewal of the Oxford NIHR BRC which includes a Vascular Dementia theme (Rothwell) and a programme on Cognitive Health (Nobre). The **NIHR Oxford Cognitive Health Clinical Research Facility** (Geddes) provides specialised facilities to support clinical experimental cognitive health research in four sites across OU, OUH and OH. **Prof Simon Lovestone**, who leads the NIHR Translational Research Collaboration in Dementia, will move to Oxford in 2014 to lead the work defining disease processes by investigation of biomarkers and extensive phenotyping in cohorts and drug discovery via academic/industrial collaboration. The **NIHR Oxford Cognitive Health Clinical Research Facility** (Geddes) provides specialised facilities to support clinical experimental cognitive health research in four sites across OU, OUH and OH. Applied health research and implementation is well represented in the Oxford CLAHRC and NIHR Programme Grants for Applied Health Research (Fossey).

Oxford Dementia and Ageing Research (OxDARE) Coordination of dementia research in Oxford was increased further with the creation of Oxford Dementia and Ageing Research (OxDARE), which brings together the world-class science in cell and stem cell biology, genomics including single cell genomics (MRC Functional Genomics Unit, StemBANCC, Oxford Parkinson's Disease Centre) neuroimaging (FMRIB, Oxford Centre for Human Brain Activity, Neurobiology of Ageing Group) cognitive neuroscience (Cognitive Neuropsychology Centre, Brain and Cognition Laboratory, Plasticity group) and epidemiology (Whitehall II, OxVasc, MRC/TRC Deep and Frequent Phenotyping Initiative), psychiatry, clinical neurology.

Oxford Parkinson's Disease Centre (Wade-Martins, Hu) acts as an exemplar of the collaborative translational neuroscience in OxAHSC. The OPDC Discovery cohort is on track to recruit 1500 unselected, well characterised early PD cases, 300 age-matched control and 300 'at-risk' subjects for PD in the Thames Valley over five years. Patients and at-risk subjects are assessed at baseline and longitudinally every 18 months in an integrated program of genetic analysis, biomarker discovery and the development of neuronal culture models from iPS cells. DNA is collected at baseline and serum every 18 months in all participants, along with measures of motor, cognitive and psychiatric function. A sub-set of patients undergo brain MR imaging, CSF collection and skin biopsy for fibroblast culture for iPS cell generation. This cohort offers an

ideal platform to investigate mechanisms of cognitive impairment in a population at ultra-high risk of dementia. Based on standard neuropsychological assessment, 30-40% of the cohort fall in the 'Mild Cognitive Impairment' range within the first three years of diagnosis.

Oxford Vascular Study (OxVasc, Rothwell) also exemplifies our approach. OxVasc is a population-based study of all vascular events in nearly 100,000 residents of Oxfordshire, which has recruited over 8000 patients to date. Established in 2002, it is the only such study in the world that does not exclude older age groups (30% of recruits are over 80). Patients with acute vascular events are recruited daily and have regular follow-up for 10 years, providing clinical data and a biobank, including brain and vascular imaging. Over 3,000 patients with TIA/stroke and 500 controls have cognitive function assessed during follow-up, which will underpin our work on vascular dementia and related syndromes (fatigue, gait impairment, depression, delirium). This programme, has provided some of the most important insights into clinical markers that define risk of disease progression and have been widely adopted into NICE and NHS guidelines for the management of stroke patients.

2.3 Description of how the proposed theme or work programme will contribute to the aims of the AHSC.

OxAHSC focuses on transformational advance in our understanding and preventing and treating disorders that cause the greatest burden for human society. Cognitive decline – especially age-related cognitive decline and dementia – constitute some of the most pressing health challenges and, in many cases, their incidence and prevalence is increased by advances in other areas of health and society. OxAHSC will bring together existing strengths in discovery neuroscience, genetics, and health services research with the promise of big data approaches and deliver fundamental advances in ways of protecting cognitive function and preventing dementia for the Oxford AHSN population and beyond. OxAHSC will develop new diagnostic procedures and treatments in novel partnerships with industry – improving both the health and wealth of the population. The coordination of research, clinical service provision and education across the OxAHSC partners will generate immediate benefits for patients and the local population, with more fundamental advances within five years.

2.4 Description of how the proposed theme or work programme will contribute to the further integration of research, health education and/or patient care and how this will lead to improvements in patient care.

In 2012, in recognition of the importance of dementia and cognitive decline, and the promise of the integrative effort in this area, the Oxford Academic Health Consortium chose the coordination and integration of research with clinical and social services for people with dementia as its first strategic priority. Considerable progress has been made – and this has enabled us to identify key areas of scientific strengths and innovative opportunities for delivering patient benefits. Major advance from the current position will, however, require a further step-change in our science and clinical application: the theme will provide this by driving further and deeper integration and acceleration of both scientific discovery and translation into benefits for patients by providing the strong strategic leadership required to enable the coordination required across the partners. We will build further links with OBU and UO, the NHS (including AHSN partners and clinical networks), local authorities, the national scientific resources at Harwell and industry (pharmaceutical and life sciences). The theme work programme will include:

- **Realise the potential of big data and digital medicine in cognitive health and dementia.** Harnessing the power of combining existing Oxford cohorts (OxVasc, UKPD, etc), linking through to national (e.g. NIHR CRIS-D led by Simon Lovestone and UK BioBank/Kadoorie cohorts) and international resources (e.g. European Medical Information Framework) with electronic medical records - through stratification and genomics, pervasive computing and devices for better risk identification, interventions and records-embedded decision aids; use remote monitoring of home BP to determine how best to improve consistency of control and reduce risk of recurrent stroke and dementia.
- **Characterise a wide range of novel biomarkers in cohorts of patients** to allow better definition of patient populations based on underpinning mechanisms to improve the likelihood of delivering new treatments, including identification and validation of treatment targets for both drug and non-drug interventions for maintaining cognitive function. For example cognitive and physical training has been translated into clinical intervention (BRC) and is now (CLAHRC) being implemented and evaluated at a population level in the NHS Health Checks in Buckinghamshire. In Parkinson's Disease we lead an ambitious programme with two biotech SMEs to develop biomarkers for early detection; bringing innovation in industry together with excellence in academia.
- **Develop strategies for maintaining cognitive health and preventing dementia** after transient ischaemic attack and stroke by better diagnosis, more reliable prognostication, and more effective use of existing preventive treatments. This will include developing a clinical risk score to reliably predict long-term risk of dementia after TIA/stroke in order to target preventive treatment, plan clinical support and identify high-risk individuals for inclusion in randomised trials; study long-term cognitive and vascular

prognosis of transient neurological attacks; cohort study and randomised trials of the effects of exercise on post-stroke cognitive decline and dementia; prognostic value of central arterial stiffness, middle cerebral artery flow and autonomic control of BP for risk of recurrent stroke, cognitive decline and vascular dementia; utility of functional brain imaging (perfusion; connectivity; white matter integrity; blood-brain barrier function) in predicting risk of cognitive decline after TIA/stroke.

- **Introduce extensive routine clinical phenotyping** (including MRI, neurocognitive tests with Birmingham Cognitive Screen-Lite (BCoS Lite Humphreys) with routine follow-up via Proteus chip (activity, sleep and adherence) and True Colours (carer mood, wellbeing, quality of life). True Colours, is a system developed by OH for integrating patient-supplied data with clinical records. It is being widely used by patients with mental and physical long-term conditions who are prompted daily or weekly to respond to a range of questionnaires.
- **Generate and validate more sensitive intermediate outcome measures** and methodologies for early phase treatment development and experimental medicine.
- **Develop and evaluate an integrated memory clinic assessment service**, including imaging with advanced and automated analysis, routine yet precise cognitive testing including through computerised tests linked to the electronic medical records and molecular diagnostics including established CSF and innovative blood markers for early diagnosis, stratification and prediction of progression. This information would expedite the establishment of appropriate care pathways and provision of therapy (or invitation to participate in a trial) that has been targeted for the patients' specific risk status.
- **Integrate BRC-driven developments in clinical informatics** - including an integrated electronic medical record with the NIHR funded D-CRIS programme and BRC clinical informatics working group to deliver an integrated dataset meeting NHS needs for clinical data, data from carers on function and resource utilisation and research needs for deep and frequent phenotyping with biomarkers and detailed neuropsychological assessment.
- **Research-based improvements in service delivery** including a CLAHRC-based evaluation and implementation of the DH-funded partnership project to improve dementia environments across 18 care homes, 7 community hospital wards and a ward at OUH; and Enhanced Care Home Outreach project which provides an integrated physical and mental assessment to reduce assessments/transitions and admission.

OxAHSC will provide immediate clinical benefits from the greater integration and coordination of services across multiple providers within the NHS, local authorities and other agencies plus the benefits of improved clinical informatics, improved physical infrastructure afforded by the embedded research facilities and increased access to diagnostic services (e.g. through MRI on the Warneford site). Scientific advance will be made available rapidly through early phase trials and experimental medicine. Engagement with the broader Oxford AHSN Dementia Clinical Network will increase involvement in research and implementation of research findings across the wider area and increase the integration between primary and secondary health services and social care. The AHSN DCN Board includes representatives from the main Trusts providing dementia services, commissioners and extensive patient and caregiver engagement, including a planned cohort of 2000 caregivers who will regularly input outcome data using the True Colours system. OxAHSC will facilitate the implementation of research in partnership with the Oxford CLAHRC. Recruitment into research studies in dementia is already impressive – with over 50% of Thames Valley DeNDRoN's 1664 currently live participants being from the OxAHSC area.

2.5 Description of how the theme/work programme will involve and enhance multi-disciplinary and multi-professional working.

The emerging epidemic of dementia requires specific expertise for those working in all aspects of the NHS clinical service as well as those involved in social care. The training programme will benefit from the multidisciplinary nature of the Oxford Cognitive Health programme and will focus on providing training for healthcare workers to allow them to assess and maintain people at home. We will create a Centre for Cognitive Health, based around the existing integrated memory clinics, including psychiatrists, neurologists, geratologists, memory clinic nurses, and neuropsychologists with close integration with acute and community services. The Centre will provide one-stop assessment clinics, access to imaging and a single point of access triage service. The Centre will provide training links across OxAHSC partners and across the wider AHSN Dementia Clinical Network and will include evaluated initiatives such as a dementia simulation course to improve education of nursing students, build on the existing workshops run by OBU's Faculty of Health and Life Sciences on 'Understanding the Person with Dementia' for staff at OUH and the Prime Minister's Dementia Challenge cohort of 50 Dementia Champions in physical health care settings. The Centre will introduce a community based cognitive tests service to create a cohort of people with prodromal dementia. Variability in diagnostic practice will be reduced through a programme of (a) regular webinars (e.g. for assessment of scans) and (b) video recorded interviews, remote assessment and central discussion and adjudication as a way of enhancing reliability of the diagnosis of mild cognitive impairment.

Developing innovative educational activity at the interfaces between the research and clinical pathways will enhance educational value across multidisciplinary groups: basic research, translational research, clinical research and clinical service. We will offer basic neuroscience PhDs students and post-doctoral researcher half-day seminars and hands-on contact with people suffering from dementia, the opportunity to watch an MRI scan, week long summer internships in a nursing home. We will develop a module in translational / experimental medicine to the Neuroscience MSc students. A seminar series will be developed bringing small-trials/experimental medicine researchers with the large scale international trials methodologists in Oxford. We will develop module in neurodegenerative diseases to MSc in Global Health. To increase research uptake across the clinical services, in collaboration with the Oxford Local Clinical Research Network we will support enable research and develop outreach training / CPD opportunities to clinical staff of all professional groups. We will develop a twinning-scheme, where there is an exchange between Trusts for a limited time of training. E.g. neurology-psychiatry; psychiatry-geratology; exchange general nurses-mental nurses. These cross-over individuals would act as seeds of expertise within their usual working environment and as multipliers of expertise, crucial for co-morbidity in medical wards, physical disease in psychogeriatric assessment wards. The Oxford Wellcome training scheme extended Wellcome Clinician PhD Programme now includes a stream on Mental and Cognitive Health, and specifically provides doctoral training across neuroscience for clinical psychologists, psychiatrists and neurologists. The theme will use this unique resource to train a new generation of clinical researchers in cutting edge science.

2.6 Description of leadership and key individual and organisational contributors with responsibility for delivering the theme/work programme.

Theme Lead: Prof. John Geddes, Director of Research for OH and Director of Oxford NIHR Clinical Research Facility OUH. With Dr Brian Murray (Clinical Director, OH); Prof. Kia Nobre (Director of Oxford BRC Cognitive Health Theme, OUH) Prof. Peter Rothwell (OU, OUH); Prof. Simon Lovestone (OU, Director, NIHR TRC-D); Dr Rupert McShane (AHSN Dementia Lead and DeNDRoN); Dr Ann Bradshaw, OBU; Dr Sarah Pendlebury (Dementia Lead OUH), Prof. Kevin Talbot (OU), Dr Jane Fossey (OH)

If you have questions about the completion of this form please e-mail Sonja Tesanovic at sonja.tesanovic@nhr-ccf.org.uk.

This form, together with other requested attachments must be submitted by **1:00pm on 30 September 2013**.