

**Impact template (REF3a)**

**Institution: Oxford University**

**Unit of Assessment: UoA1 Clinical Medicine**

**a. Context**

The research in UoA1 has impact across the entire field of medicine, from molecule to man, from bench to bedside, locally, regionally, and internationally, including:

- Discoveries in basic research that have opened new fields of discovery and therapeutics.
- Tests for diseases and genetic disorders, including prenatal diagnostics.
- Drugs to transform the quality of life of patients, which are worth billions of pounds per year.
- Vaccines to prevent the spread of infectious diseases affecting millions of people.
- Effective treatments for some of the most deadly and widespread human diseases.
- Industrial partnerships and commercialisation of clinical technology.
- Influence on world health policy and guidelines, and informing of key decision-makers.

The track record in UoA1 is based on the philosophy that the greatest advances in human healthcare will come through strength in molecular biology and clinical medicine. This has been a guiding principle for the development of the medical school over the last 3-4 decades. Its development of impact is underpinned by:

- Strength in basic and clinical research.
- Multidisciplinary and collaborative approach to research.
- Infrastructure directed towards translation.
- Close ties with the NHS.
- Global perspective, including world-leading overseas units.
- Innovative partnerships with industry.

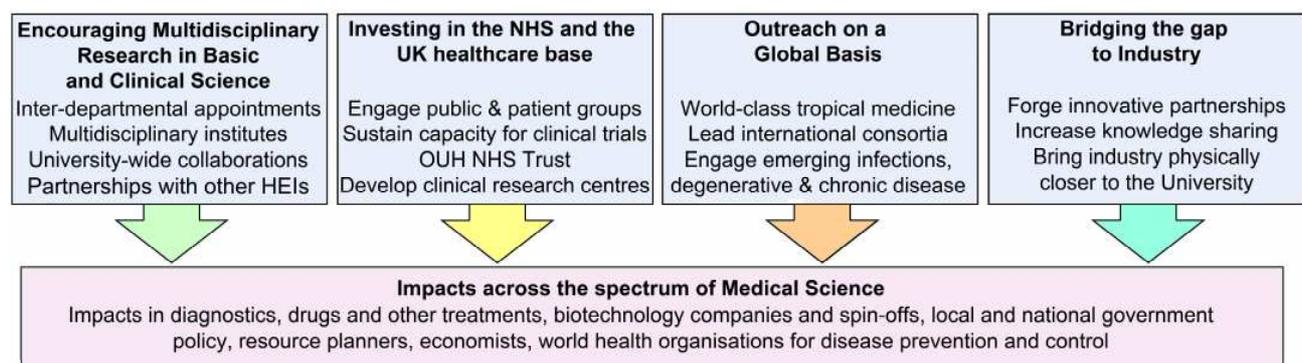
Themes of UoA1 research address the prevention of disease, treatment of chronic and degenerative diseases, cancer, children’s health, women’s health, surgery, vascular disease, inflammation, infection and immunity, nutrition, and tropical medicine.

The beneficiaries of UoA1 research include:

- Individual patients and carers.
- Clinicians, doctors and healthcare workers.
- National and international healthcare organisations and policy makers (NHS, NIH, NICE, WHO, FDA).
- Biotechnology companies, spin-offs, commercial start-ups, and pharmaceutical companies.
- Local and national governments, resource planners, economists; and world health organisations for disease prevention and control.

UoA1 staff are active in the development of policy at national and international levels, through chairships of committees and membership of governmental and non-governmental advisory bodies.

**b. Approach to impact**



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The Approach to Impact in UoA1 follows a pathway, which:

- Encourages basic and clinical researchers from a wide range of specialties to work together to address key issues in healthcare provision.
- Invests in the NHS and UK healthcare base.
- Supports outreach beyond the University and worldwide.
- Develops innovative working practices to bridge the gap between the University and its industrial partners.

The University, Medical Sciences Division and UoA1 Departments actively promote impact through the work of committees dedicated to infrastructure, planning and resource allocation, and financial support for collaborative initiatives.

**1. Promoting impact through basic and clinical research**

UoA1 encourages the generation of impact first by sponsoring multidisciplinary research, which brings together staff in basic and clinical sciences to address major problems affecting healthcare. It achieves this through cross-departmental and inter-institutional appointments; the deliberate sponsorship of research groups that cut across conventional scientific areas, using tools from mathematics, genetics, imaging, structural biology, physics, chemistry and other areas; and the development of its specialised institutes, linking clinical and basic scientists.

**1.1 Multidisciplinary initiatives leading to impact**

Collaborations between clinical and basic scientists continue to generate new impact within UoA1:

- *Cancer Drugs Targeting Oxygen-dependent Pathways.* Collaboration between renal physician (Ratcliffe) and chemist (Schofield) resulted in the discovery in Oxford of the fundamental mechanism by which cells sense oxygen. This has led to discoveries in the field of cancer biology and >£100M investment by the pharmaceutical industry in drug discovery programmes.
- *Non-invasive Cardiovascular Imaging.* Collaboration between physicists (Robson, Schneider) and clinicians (Neubauer, Choudhury) from the Acute Vascular Imaging Centre has led to world-leading progress in the field of MR spectroscopy, clinical high field (7T) and the use of hyperpolarised systems, and commercial development by Siemens.
- *Stable, Safe Vaccines.* Collaboration between virologists at the Pirbright Institute and structural biologists in Oxford and the Diamond Light Source, the UK national synchrotron facility, has resulted in manufacture of the first heat-stable RNA-deficient hand-foot-and-mouth disease virus (Stuart). The application of this technology across virus strains has the potential to transform vaccine delivery worldwide.
- *Transplant Organ Preservation.* Collaboration between transplant surgeons (Friend, Ploeg) and scientists in the Institute of Biomedical Engineering on the medical school campus (Coussios, UoA15) has led to the creation of a machine capable of organ perfusion at room temperature. This technology will increase the number of viable organs for transplantation and reduce the inflammatory response that occurs due to tissue damage.

**1.2 University-wide programmes to create impact**

The University also supports multidisciplinary research on an institutional scale under the Oxford Martin School, which brings together more than 40 laboratories from 17 University departments to address broad themes in healthcare, from the development of technology to the ethical and social aspects of medicine. For example:

- *The Institute for Emerging Infections* is a multidisciplinary team of biologists, mathematicians and clinicians (from UoA1 and 5) who study recently emerged infections and use the knowledge gained to anticipate challenges posed by novel emergent infections in the 21<sup>st</sup> Century. It has advised international bodies on a broad range of emerging infectious diseases including SARS, influenza, and Creutzfeldt-Jakob disease.
- *The Institute for Vaccine Design* links groups in six departments that aim to prevent disease by immunisation, by improving vaccine design and the ethical framework and regulatory and societal questions raised by new approaches to vaccination. The Jenner Institute's discovery of a way to stabilise dry vaccines for use in tropical countries using trehalose and sucrose sugars is one example this work, which is being commercialised with Cambridge Biostability Ltd and Nova Bio-Pharma Technologies.

## **2. Improving healthcare provision in the UK**

Over the impact period of 2008-2013, UoA1 has worked with the public, patient groups, and the NHS to build world-leading infrastructure, increase public engagement, accelerate new treatments, and improve access to clinical expertise in the healthcare system in the UK.

### **2.1 Engaging with the public and patient groups**

UoA1 engages with the public and patient groups in its research and communicates its findings through presentations and social media.

- Research is communicated through the press office and by interview, writing and public meetings, as well as engagement and outreach activities in the local community. During the REF2014 period, UoA1 researchers have given over 50 public seminars and talks each year, and published more than 70 blogs, podcasts and lectures with greater than 500,000 downloads.
- Major clinical trials have public representation, and local and national patient groups and charities are consulted in research planning and programme development.
- National normal and patient Biobank collections hosted by UoA1 are critical resources for discovery, as well as testing new hypotheses and potential treatments leading to impact.

### **2.2 Providing world-leading capacity in clinical trials**

Oxford has the largest clinical trials capacity in the UK, underpinned by one of only two University-run GMP Clinical Biomanufacturing Facilities in the country.

- This world-leading position in clinical trials and epidemiology is exemplified by the work of the Clinical Trial Services Unit (CTSUs, Collins UoA2), Diabetes Trial Unit (Holman) and Clinical Trials Research Unit (Altman).
- The United Kingdom Prospective Diabetes Study (UKPDS) recruited 5,102 newly diagnosed type 2 diabetic patients from 23 national clinics across the UK and has led to policy changes, which resulted in improved clinical treatments, improved quality of life and health for patients, and eventually a reduction in the economic burden of diabetes for the NHS.

### **2.3 Building closer ties with the NHS**

Accelerating local developments in the NHS, the formation of the Oxford University Hospitals NHS Trust (OUHT) in 2011 brought the NHS and University together in a joint Partnership Board. The University and NHS also administer the £112M Oxford NIHR Biomedical Research Centre, which is being used to accelerate a wide range of joint clinical research and support Clinical Research Centres and Clinical Research Networks in cancer, stroke and diabetes. Examples of collaborations with the clinical trials centres include:

- *The Gray Institute*, which has pioneered the development and trial of new modalities of radiotherapy including image-guided and intensity-modulated radiotherapy. It has provided support to the specialty more generally within the UK, contributing to resurgence and reinvigoration of radiation oncology nationwide.
- *In Medical Oncology* Oxford has become a pioneer in early phase or Phase I trials of new cancer drugs, notably in melanoma and prostate cancer.
- *The Acute Vascular Imaging Centre* has pioneered the development of non-invasive vascular imaging in acute heart attack (UoA1) and stroke (UoA4).

## **3. Influencing healthcare on a global scale**

By placing top researchers overseas, UoA1 achieves groundbreaking research and clinical impact on a local and global scale; the trials units linked to our Tropical Medicine Units are pre-eminent in their fields. Researchers in these groups achieve impact by working within the communities affected by emerging infections and tropical diseases, and via active outreach to organisations that can implement widespread change, including governments, the World Health Organisation and the World Bank.

### **3.1 Investing in world-class tropical medicine**

The Mahidol-Oxford Research Unit (MORU) in Thailand (White, Day) and its sister units at Kilifi in Kenya (Marsh) and Ho Chi Minh City in Vietnam (Farrar; Thwaites from Oct 2013) are currently conducting more than 20 clinical trials in over 15 countries.

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- By undertaking much needed, high quality, targeted research in the field, and on the clinical frontline, research from UoA1 has directly led to changes in clinical management where there has otherwise been little guidance.
- The combination of resources in Oxford and overseas, coupled with its highly devolved structure, has enabled UoA1 to respond rapidly and effectively to global challenges, including emergencies.

**3.2 Leading international consortia**

UoA1's ability to promote international research networks and respond to major challenges to world health is shown in its leadership of impactful international consortia, for example:

- World Wide Antimalarial Resistance Network (WWARN).
- African Quinine versus Artesunate in severe Malaria Trial (AQUAMAT).
- CODFIN (Counterfeit Drug Forensic Investigation Network).
- Melioidosis Clinical Trials Study Group.
- Southeast Asia Infectious Disease Clinical Research Network (SEAICRN).
- South-South Network for Antimicrobial Pharmacology.
- Wellcome Trust-Institut Pasteur Collaboration into tropical and neglected diseases.

**4. Developing innovative industrial partnerships and activity**

Over the period 2008-2013, UoA1 has sought to bring basic research and industrial partners closer physically and to increase the exchange of knowledge. It supports this activity through the Medical Sciences Division Office of Business Development and Planning (Allen). It is notable in having pioneered several new working practices to achieve these aims.

**4.1 Knowledge sharing and industrial partnerships**

The Structural Genomics Consortium (SGC), founded in 2003, illustrates the change in the relationship between UoA1 and its industrial partners; its success has provided a model for future activity.

- The primary goal of the SGC is to enable drug discovery through the creation of new knowledge, tools and chemical starting points, which it then makes freely available to the world without restriction on use.
- This "open access drug discovery" model aims to bridge the gap between academia and industry.
- Its first probe (JQ1: an nM inhibitor of the BET family of bromodomains) has been shown to reduce proliferation and increase apoptosis in cells derived from a human intractable cancer (NUT midline carcinoma) and is in a Phase I clinical trial.

**4.2 Thames Valley High Technology Cluster**

This group contains 170 small- to medium-sized businesses in the biotechnology sectors.

- A joint partnership committee, chaired by the Regius Professor of Medicine, is responsible for planning strategy.
- A Centre for the Advancement of Sustainable Medical Innovation (CASMI, with UCL), addresses general issues relating to the innovation gap and translation by industry, including the nature of research and legislative hurdles.

**4.3 Supporting technology transfer**

- The University has a generous scheme to reward commercial activity and allowances for consultancy work.
- Isis Innovation Ltd is a wholly owned subsidiary of the University, which is responsible for technology transfer and intellectual property management.  
During the REF2014 period, Isis handled 665 invention disclosures and 413 patent applications for the Medical School, with a total of 199 patents granted and 4 new spinouts generated by UoA1 staff in the period 2008-2013.

**Impact template (REF3a)****c. Strategy and Plans**

The Strategic Plan for Impact in UoA1 **strengthens the current pathway** and **addresses limiting steps**.

**1. Promoting impact through basic and clinical research**

The inability of the pharmaceutical industry and University sector to convert more core research to impact stems from several problems:

- Poor or inaccurate target identification.
- Too early a focus on specific disease indications.
- Unwillingness or inability to explore the biological characteristics around these targets.
- A failure to identify patients where these characteristics are most relevant to disease, for which we need both a better molecular classification of patients and disease, and increased capacity to handle large quantities of data.

Finally, at a global industrial level:

- Too early an entry into the environment of commercial competition, which drives multiple independent attempts to pursue ineffective targets with little or no opportunity to share negative experiences. UoA1 has three strategic initiatives to address these problems.

**1.1 Extend the pre-commercial and collaborative phase of drug development**

UoA1 will adapt the highly successful multidisciplinary research model introduced by the SGC in the £23.8M Target Discovery Institute (TDI), which was opened in 2013, and will:

- Bring together academic groups in the biomedical and physical sciences with technological platforms in genomic medicine and pharmaceutical partners including UCB, Takeda, Boehringer Ingelheim, Janssen and Abbott.
- Provide clinical material in an environment that extends the 'pre-competitive' phase of drug development to share risks, defray expenses, and maximise output.
- Identify the tractable biochemical pathways for drug development, extend the 'pre-competitive' phase of drug development through the generation of freely available chemical probes, and accelerate the commercial exploitation of clinically validated targets.

**1.2 Invest in molecular pathology and imaging**

UoA1 will increase its capacity to classify disease using molecular biology and pathology by:

- Continuing to invest in the Wellcome Trust Centre for Human Genetics.
- Providing new funds to develop pathology services across the spectrum of human disease through the Oxford NIHR/BRC Translational Pathology Programme.
- Bringing comprehensive molecular genetic and cellular phenotyping to the clinical interface, for example: by investing in mass cytometry at the Botnar Centre and Kennedy Institute, in order to characterise abnormal patterns of autoimmune disease; and by using proteomics in the TDI and in collaboration with our partners in UoA5, to classify cancer phenotypes and pathways.

**1.3 Increase the knowledge and data sharing of large datasets**

The first million genomes, likely to be completed by 2017, will require 500,000 terabytes of storage; other experimental systems, such as proteomics, RNAseq, epigenetics, siRNA screens, structural biology, flow cytometry and imaging, will all add to this data explosion. These resources present an unrivalled opportunity to advance healthcare, and combining these datasets represents a huge opportunity for impact. UoA1's capability to handle large data sets will be expanded through formation of a £45M Big Data Institute (BDI) in 2015.

- This will enable UoA1 and its academic and commercial partners to define genetic, molecular and physiological responses in large-scale population studies, and stratify patients within clinical trials.
- It has the potential to create a commercial focus for health informatics in the UK. Its commercial partners Illumina and Life Technologies seek the analytical skills capable of relating genetic variants to disease; other partners, Microsoft and Oracle, want to develop healthcare tools that will track disease and define how patients should be treated.
- This initiative will be underpinned by an expansion of computing, including the development of high-speed Internet connections between Oxford, the Harwell Campus and other HEIs.

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- It will invest in the ethical framework around the use of human data, through collaboration between the UoA1, OUHT and the Ethox Centre in Population Health (UoA2).

**2. Improving healthcare provision in the UK**

Building on its current research and aspirations for commercial partnerships, UoA1 plans to build at least two new clinical research centres that are capable of proof-of-principle and early-phase trials of the novel probes, therapeutic and diagnostic innovations that emerge from core research.

**2.1 Oxford Targeted Cancer Research Centre**

This will be a £107M research institute with inpatient services on the Churchill Hospital site, in partnership with the Oxford University Hospitals NHS Trust, Cancer Research UK, Roche Diagnostics, GE Healthcare and others. It will:

- Focus on minimally invasive, curative treatments for patients with early-stage cancer, for whom minimising side effects will have substantial personal, societal and economic benefits.
- Have significant input to adjacent Institutes, such as the Wellcome Trust Centre for Human Genetics, TDI and BDI, and will perform genomic characterisation, and molecular and functional imaging and pathology, to devise personalised treatment plans.
- Alongside molecular agents, investigate robotic surgery, particle therapy, image-guided intensity modulated radiotherapy, high-intensity focused ultrasound, cryotherapy, photodynamic therapy, radioablative therapies and applications of nanotechnology. The scale and scope will be unique in the world, since no other international cancer centre takes this all-encompassing approach to patients with early-stage disease.

**2.2 Translational Gastroenterology Unit**

This will conduct studies similar to the Targeted Cancer Research Centre in inflammatory bowel disease, linking groups in infection and immunity (Powrie and others) with the Oxford University Hospitals Trust (OUHT) clinical services.

**3. Influencing healthcare on a global scale**

UoA1 will continue to grow and sustain its overseas programmes, responding to major hazards, with increased focus on the challenge of emerging infections and chronic metabolic and cardiovascular disease in developing countries. Strategic plans to enhance impact include:

**3.1 Respond rapidly to emerging infections and new challenges**

In the experience of UoA1, effective research in global health is often limited by delays in obtaining ethical approval and infrastructure support. The UoA1 Tropical Medicine Units have worked to establish generic approvals and a series of contingency plans to provide a rapid response to future emergencies.

**3.2 Create new and flexible overseas partnerships**

UoA1 has opened 5 major units in China addressing topics ranging from emerging infections and medical aspects of disaster response, to large-scale multi-centre clinical trials. It has recently established a University-owned company based in Beijing to provide local support for research.

**3.3 Capitalise on the digital revolution to bring impact to developing countries**

With links to the Big Data Institute, an important aspect of the emerging digital revolution in medicine will be the ability to better track the pattern and burden of disease on a global basis.

**4. Developing innovative industrial partnerships and activity**

Finally, this strategic plan argues the need for a step-change in the environment for science-based business in the UK. Too few mid-sized commercially viable companies have been created, and venture capital returns have been below expectations. If the UK is to remain competitive, commercial activity needs to work more closely with the major scientific hubs, and a better environment for start-up companies, with lower costs but access to specialised facilities, needs to be created. This will enhance the chances of early proof-of-concept studies. The right location is critical; for biotechnology, the optimum location is at the intersection of research and hospital communities such as Oxford.

#### 4.1 Establish the BioEscalator Institute

Oxford University has formed a partnership with Oxford Brookes University, the OUH Trust, Oxford City Council, and the Thames Valley High Technology Cluster to build a 5500m<sup>2</sup> BioEscalator Institute on the Old Road Campus/Churchill Hospital site, a planned £35M investment. This will provide:

- Cost-effective space for both proof-of-concept work and the initial growth of mid-sized firms.
- Direct access to University infrastructure, basic research and clinical facilities, critical for early proof-of-principle experiments.
- Mentoring in management, partnerships with financiers and other forms of support.
- Links to the major science parks at Milton Park and Oxford Science Park.

#### d. Relationship to case studies

UoA1 case studies illustrate each stage of its approach to impact.

##### 1. Promoting impact through basic and clinical research

- **Strength in basic science** and the ability to translate discoveries to major impact is illustrated by safe prenatal diagnostics based on DNA in the maternal circulation, and new diagnostics based on antibody reagents, exemplified by ALK1 and FOXP1.
- **Multidisciplinary research in drug development.** The development of anti-TNF $\alpha$  therapy provides the prototypical example of the multidisciplinary approach to drug discovery by basic scientists and clinicians at the Kennedy Institute. The structure-based design of NNRTI inhibitors for HIV treatment is another example of a multidisciplinary research leading to drug design.

##### 2. Improving healthcare provision in the UK

- **World-leading local and global clinical trials units** have underpinned the UKPDS Diabetes Trials, International Subarachnoid Aneurysm Trial, the ability to respond rapidly to global emergencies including the H1N1 pandemic, and most advances in Tropical Medicine.
- **The benefits of a close association with the NHS.** The advantage of a direct relationship with the NHS is illustrated with impacts from the field of orthopaedics (Oxford Knee, assessment tools, metal-on-metal hips), which is also widely acknowledged to be an area of unmet need. In UoA1, application of the principles of basic science to clinical problems, which underpins its tradition of molecular medicine is illustrated by its impact on the diagnosis and treatment of craniofacial disorders. A recent case study on paternal age and sperm donation shows how this approach can lead to changes in national and international guidelines.

##### 3. Influencing healthcare on a global scale

- **Inequality, hazards and risk in global health** are addressed within our tropical medicine units and have led to a wide range of beneficial changes in the treatment of malaria, tuberculosis, dengue, melioidosis, and other diseases.
- **Determining international policy and WHO guidelines.** The Tropical Medicine trials and surveys have had multiple and global impacts and have frequently changed WHO policy.
- **Influencing UK Government policy and NICE guidelines.** Trials in Oxford of H1N1 vaccines and by UKPDS Diabetes have changed UK government policy and NICE guidelines. The development of vaccines against meningococcal meningitis has introduced protection against this leading infectious killer of children in the UK.

##### 4. Developing innovative industrial partnerships and activity

- **The world's leading biologic therapy.** The benefits of commercialising new therapies are in evidence in the case of anti-TNF $\alpha$  therapy, which is the world's leading biologic agent for rheumatoid arthritis (RA). 500,000 people suffer from RA, and anti-TNF $\alpha$  therapy currently has annual sales worth US\$24.4 billion. UoA1 will use the experience of the Kennedy Institute in bridging the gap between the University and industrial partners.
- **Commercialisation of diagnostics.** UoA1's historical ability to generate impacts of high commercial value is illustrated by intellectual property and income developed through the use of ALK1 for ALCL, prenatal diagnosis using fetal DNA, tetramer technology and T-SPOT for the diagnosis of tuberculosis.