Institution: UNIVERSITY OF OXFORD

Unit of Assessment: 2

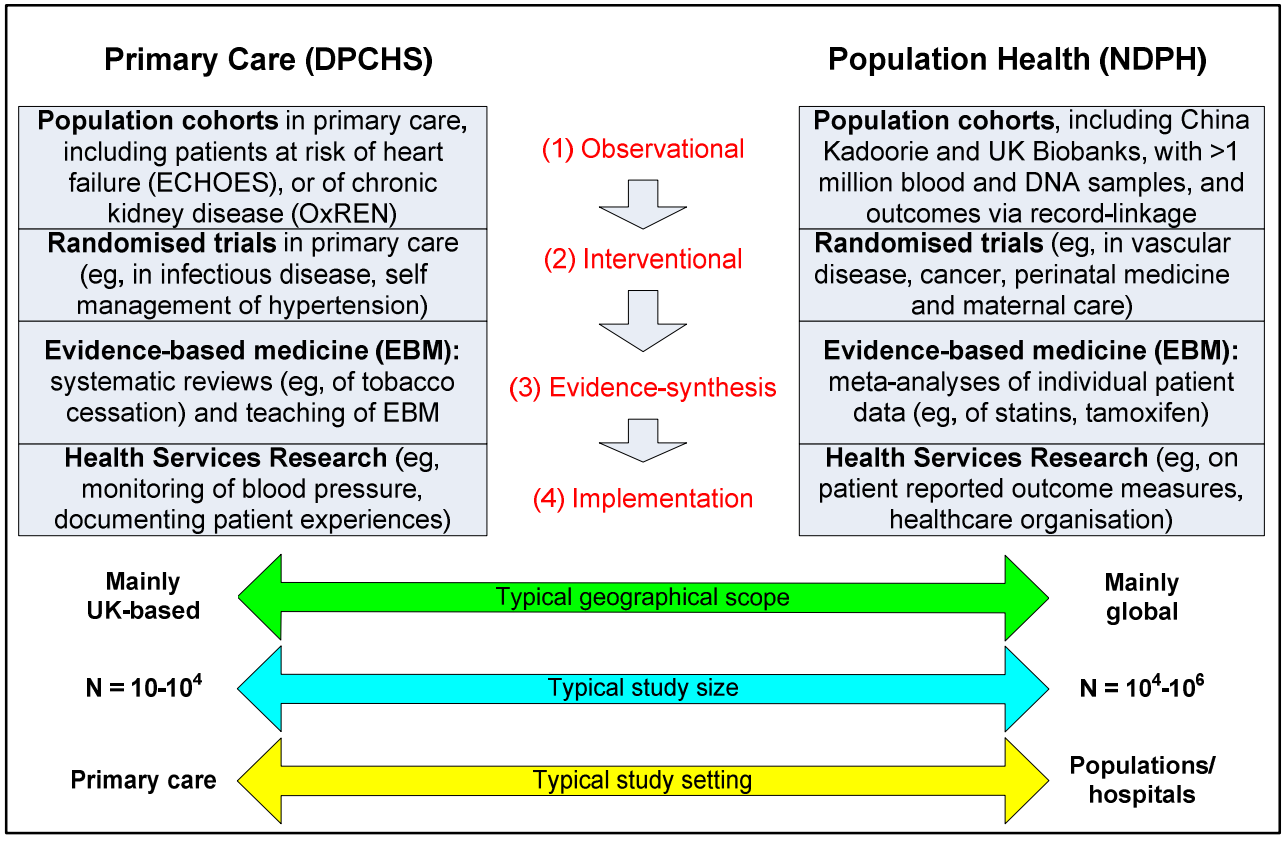
A. OVERVIEW

Aims: The core aim of Oxford University's research strategy for primary care and population health is to generate and disseminate reliable evidence from a range of robust study designs that directly leads to improving health outcomes or to a better understanding of disease mechanisms.

Structure: Since RAE 2008, Oxford University has re-structured and invested in both primary care and population health. In 2011, the **Department of Primary Care Health Sciences (DPCHS)** was formed under *Professor Richard Hobbs* and located in new purpose-built accommodation in central Oxford. Similarly, in 2013, the **Nuffield Department of Population Health (NDPH)** was created under *Professor Sir Rory Collins*, bringing together most of the University's major population health research groups, including the Clinical Trial Service Unit & Epidemiological Studies Unit (CTSU, *Collins* and *Peto*), Cancer Epidemiology Unit (CEU, *Beral*), and the former Department of Public Health (including the Health Economics Research Centre [HERC, *A. Gray*], the National Perinatal Epidemiology Unit [NPEU, *Kurinczuk*], and the Health Services Research Unit [*Fitzpatrick*]), based on the University's Old Road Medical Sciences Campus in Headington.

Research resources (Figure): Oxford's UoA2 research assets are distinctive because of their **exceptional breadth** of **geographical scope and impact**, ranging from nationally influential research to some of the world's largest international collaborations, **study sizes** ranging from focused studies of patient experiences to population-based studies involving over a million people, and diverse **healthcare settings** including general practices, hospitals and populations.

Figure: Summary of UoA2's inter-related activities



Distinguishing features of Oxford's UoA2

- **Exceptional external grant funding**: £189M in the assessment period (corresponding to an average of ~£4M per staff member returned).
- **Some of the world's largest population cohorts and randomised trials**: China Kadoorie and UK Biobanks (both 0.5M individuals) and the Million Women Study (1.3M women); SHARP, THRIVE and REVEAL trials of lipid-modifying therapy in >60,000 patients.
- **Practice-changing research**: Major contributions to international guidelines (e.g., statins, aspirin, hypertension, pre-eclampsia, heart failure, serious childhood illness, infections).

- **World-class scientists**: 13 individuals with h-index >40, 2 with h-index>100.
- **Exceptional national leadership**: *Collins*, CEO/PI of UK Biobank; *Farmer*, Deputy Chair, NIHR HTA Commissioning Board (to 2011), Sub-Panel Chair, NIHR Applied Programme Grants; *Fitzpatrick*, Director, NIHR HS&DR Programme; *Hobbs*, Director, NIHR School for Primary Care Research; *Jebb*, Chair, NICE Public Health Advisory Committee, Chair, NICE Programme Development Group, DH Science Advisor on Obesity, Chair, DH Expert Advisory Group on Obesity, Expert Advisor, Cabinet Office Strategy Unit Review on Food.
- **National/international recognition for excellence**: *Beral* Dame Commander (2010); *Collins* Knighted (2011); *Jebb* (2008) and *Mant* (2011) awarded OBE.

B. RESEARCH STRATEGY

B1. STRATEGIC AIMS

Objective 1: Establish infrastructure for large prospective cohorts

Substantial investments in bioinformatics have transformed the way that we organise research, understand disease and practise medicine, such as:

- **Million Women Study** of 1.3M UK women, with follow-up via registries of deaths, cancer, health episode statistics, and primary care records; **UK Biobank** study of 0.5M individuals, with biochemistry and genotyping, other measures (e.g., imaging), and follow-up as in Million Women's Study; **China Kadoorie Biobank** study of 0.5M Chinese, with blood samples and follow-up via health insurance records; **ECHOES cohort** of 6162 adults screened for heart failure and 13 years follow-up.
- Oxford's new **Big Data Institute** (phase 2 of £45M **Li Ka Shing Centre for Technology and Health Informatics**; building starts in Q1, 2014), will manage data from molecular and genomic studies and analyse such data in combination with those from **electronic patient records**, epidemiological cohorts, deep phenotypic and disease surveillance data.
- Investment in **technological innovations** in both computing systems (e.g., touch-screen and web-based survey methods) and laboratory systems (e.g., assay development that optimises sample storage, utilisation and analysis for large-scale studies).

Objective 2: Establish infrastructure for randomised trials

Three trials units within UoA2 have full NIHR Clinical Research Collaboration registration:

- NDPH's **Clinical Trial Service Unit (CTSU)** runs investigator-led streamlined international trials capable of leading to drug labelling changes.
- NDPH's **National Perinatal Epidemiology Unit Clinical Trials Unit (NPEU-CTU)**, within NDPH, runs large multi-centre pragmatic trials in perinatal medicine and maternal care.
- DPCHS's **Primary Care Clinical Trial Unit (PC-CTU)** runs investigator-led multi-centred randomised trials in collaboration with local NHS Trusts, chiefly in primary care.

A distinctive feature of Oxford's approach to trials is that they are designed in collaboration with the NDPH's **Health Economics Research Centre (HERC)**, yielding health economic assessments as an integral part of trial analysis plans. There is also national expertise in the development and use of patient reported outcomes in NDPH's **Health Services Research Unit (HSRU)**.

Objective 3: Conduct meta-analyses and systematic reviews

Groups within UoA2 aim to improve clinical care through meta-analyses and systematic reviews:

- DPCHS's **Centre for Evidence-based Medicine (CEBM)** is internationally recognised for the development, teaching and promotion of evidence-based health care, influencing clinical guidance (e.g., on neuraminidase inhibitors, self-management of anticoagulation).
- NDPH (CTSU and George Institute) runs large **collaborative meta-analyses of individual patient data** yielding highly cited publications that influence guidelines (e.g., tamoxifen, statins, aspirin, antihypertensive treatments), as well as (CEU and CTSU) similar meta-analyses of observational studies, such as the **Collaborative Group on Hormonal Factors in Breast Cancer** and **Prospective Studies Collaboration**, yielding world-leading insights into hormonal causes of breast cancer and risk factors for cardiovascular disease.

Objective 4: Establish collaborations to support research excellence

Groups within the UoA2 have established a wide range of collaborations and partnerships that enhance the potential for scientific excellence:

- DPCHS's Head (*Hobbs*) is Director of the **NIHR School for Primary Care Research**, in

partnership with the 7 other leading UK primary care departments, investing £5M annually; DPCHS leads the Oxford **Collaboration for Leadership in Applied Health Research and Care** linking several NHS Trusts and Oxford University departments.
- NDPH (CTSU) has major collaborations with **industrial partners** (see E2 for details): including **Astra Zeneca**, **GlaxoSmithKline**, **Merck** and **Pfizer**; DPCHS has funding from **Roche** and **Omron**.
- **China Oxford Centre for International Health Research**: NDPH (CTSU) has a high profile partnership with the Fuwai Hospital in Beijing, and has helped establish the Chinese national Biocentre with Chinese government funding.
- **UK Biobank**: NDPH (CTSU) is contributing its expertise to help establish and manage UK Biobank, and to set up a £25M DH-funded state-of-the-art facility (**Biorepository South**) for the storage and analysis of biological samples from NIHR-funded researchers.

Objective 5: Facilitate cross-disciplinary research to exploit new technologies

A key objective of both primary care and population health research is to utilise advances in technology to promote research excellence. Examples include:
- DPCHS's **Oxford Centre for Monitoring and Diagnosis (MaDoX)** aims to improve monitoring and diagnosis in primary care; e.g., with 'telehealth' systems for monitoring of COPD, diabetes and hypertension (with **Oxford Department of Biomedical Engineering**).
- NDPH collaborates with the **Wellcome Trust Centre for Human Genetics (WTCHG)** and **Department of Cardiovascular Medicine** in UoA1 in studies of the genetic determinants of disease and drug effects. The new **Big Data Institute** will nurture and develop the skills and resources necessary to collate and analyse large, complex datasets (see section D3).
- DPCHS and NDPH lead 7 NIHR programme grants and collaborate on 4 more, each including **cross-disciplinary research** involving medicine, nursing, public health, statistics, social sciences and health economics.

Objective 6: Achieve excellence in staff development, teaching and training

Our strategy for capacity building is based on inspiring, recruiting, training and mentoring the most outstanding staff and students. Our success in this area is illustrated by:
- **Inspiring the next generation**: NDPH's **MSc in Global Health Science** is 5-times over-subscribed, and is being strengthened with additional epidemiological and statistical topics (see section C). Similarly strong, DPCHS's **MSc in Evidence Based Medicine**, has a 50% international intake and the second largest part-time DPhil programme at Oxford University.
- **Academic staff development**: Around 10-15 research students join UoA2 each year. Many progress to post-doctoral research positions, or joint clinical/academic appointments. There is also a thriving clinical academic training programme, including 2-3 NIHR ACF and 2 NIHR ACL posts competitively allocated to and recruited within UoA2 in most years.
- **Recruiting and nurturing leaders**: Since 2008 there have been 14 new professorial posts in Oxford UoA2, including 2 of the 12 nationally appointed NIHR Professorships (*Knight*, *McManus*), and it is anticipated that this will accelerate in conjunction with the recruitment of senior staff for the Big Data Institute.

B2. RESEARCH ACHIEVEMENTS

The distinctiveness and vitality of research (see Figure above) is illustrated by representative examples from the broad range of achievements in UoA2.

Observational studies: population cohorts

Key achievements
- DPCHS maintains the **ECHOES cohort** of over 6000 patients at risk of heart failure: publishing sub-studies reporting the reliability of natriuretic peptides as diagnostic and prognostic indicators of heart failure, 10 year survival, the potential for heart failure screening; and the optimum diagnostic strategy for heart failure.
- NDPH's (CEU) **Million Women Study** of over 1.3 million UK women has published several key papers, including the recent demonstration that cessation of cigarette smoking before 40 by women avoids over 90% of the risk.

Future plans
- The **Big Data Institute** adjacent to NDPH, construction of which is planned to commence in early 2014, will develop detailed processes and bespoke IT systems for linking genetic,

imaging and pathological information with electronic patient records (such as NHS hospital and primary care data) in very large population studies.
- Oxford's uniquely large population studies (e.g., Biobanks) will provide unprecedented opportunities for understanding disease causation; e.g., a £2M MRC-funded genome-wide association study of 20,000 well-characterised strokes and 20,000 controls in the **China Kadoorie Biobank** will provide insights into stroke aetiology.
- DPHCS is recruiting to a new 6000 patient chronic kidney disease cohort (**OxREN**), with sub-studies developing to test better biomarker identification of disease, predictors of rapid decline, and interventional studies.

Interventional studies: randomised trials

Key achievements

- DPCHS's **Hypertension Research Group** published the **TASMINH-2** trial showing that self-management of poorly-controlled hypertension resulted in better blood pressure control compared with usual care, influencing 2011 NICE hypertension guidelines.
- In NDPH, the NPEU's 16,000 patient **CORONIS** trial showed the similarity of different caesarean section techniques; CTSU's 9000 patient **SHARP** trial showed that reducing LDL-cholesterol reduces vascular risk in chronic kidney disease, its 25,000 patient **THRIVE** trial showed that niacin is both ineffective and unsafe for the prevention of cardiovascular disease, and its 13,000 patient **ATLAS** trial showed that, as compared to 5 years, 10 years of tamoxifen reduces 15-year breast cancer mortality.

Future plans

- DPCHS is leading a suite of NIHR-funded trials, including a trial of electronic reminders to improve rates of anticoagulation and reduce stroke risk in AF in 49 general practices (**AURAS-AF**) and the **BARACK-D** trial to assess whether spironolactone reduces cardiovascular risk and the decline in renal function among 2600 patients with CKD.
- NDPH (CTSU) is leading the **REVEAL** trial of lipid-modification with CETP-inhibitor therapy in 30,000 patients with cardiovascular disease; NDPH's (CEU) **breast cancer screening trial** to assess the efficacy of earlier (age <50) and later (age >70) screening within the existing NHS screening programme will become the world's largest trial (n=3 million).

Evidence synthesis: evidence-based medicine (ebm)

Key achievements

- DPHCS's systematic reviews on clinical and laboratory features to identify serious infection influenced NICE guidance for managing illness in children and provided the world's first centile charts for vital signs in children.
- NDPH's (CTSU) highly-cited Lancet papers showed that: tamoxifen reduces 5-year breast cancer mortality in both estrogen-receptor positive and negative disease (**Early Breast Cancer Trialists' Collaborative Group**); more intensive statin regimens reduce vascular risk, and statins are both effective and safe for primary prevention (**Cholesterol Treatment Trialists' (CTT) Collaboration**); aspirin is not typically of net benefit in primary prevention (**Antithrombotic Trialists' (ATT) Collaboration**) and that diclofenac increases cardiac risk (**Coxib and traditional NSAIDs Trialists' (CNT) Collaboration**), which led to revised European Medicines Agency guidance.

Future plans

- DPHCS leads individual patient data meta-analyses of self-monitored blood pressure (in hypertension and pregnancy), and of self-management of anticoagulation and diabetes.
- In NDPH (CTSU), EBCTCG will collect data on gene expression indices and other tumour characteristics; CTT is establishing meta-analyses of the side-effects of statins and the efficacy and safety of new agents (e.g., PCSK-9 inhibitors); and ATT is conducting a major update of meta-analyses of antithrombotic agents in high-risk patients.

Implementation: health services research

Key achievements

- In DPCHS, the **Health Experiences Research Group (HERG)**, with its **award-winning** **www.healthtalkonline.org** website, has conducted 30 new condition studies; its **Cochrane**

Tobacco Addiction Review Group's systematic review established that reduction programmes for smokers who were not ready to quit in one step produced long-term cessation and was introduced into government policy, reinforced by NICE guidelines.

- The NDPH's (HSRU) **Parkinson's Disease questionnaire (PDQ-39)** has been used in Parkinson's-specific trials worldwide and its **Oxford Hip and Oxford Knee Scores** were mandated for monitoring NHS joint replacements; DH-Policy Research Programme-funded work evaluating stroke outcomes in primary care led to the **short form (8 item) Stroke Impact Scale** which correlated highly with the standard 56-item parent questionnaire.

Future plans

- In DPCHS, the **Oxford Collaboration for Leadership in Applied Health Research and Care** (CLAHRC) £18M grant will address key NHS priorities, such as: the frail elderly presenting to acute medical services, people with dementia in care homes, and patient self-management in chronic enduring illnesses and comorbidities.
- NDPH (HSRU) will develop different computer platforms (such as 'tablets') for electronic data capture of PROMs, which will align with technological innovation work elsewhere in NDPH (e.g., the George Institute smartphone apps being developed for use in India) and with DPHCS's tablet computer-based self-management platforms, including COPD and heart failure applications. In addition, in HSRU, a European Brain Council-funded project is developing a *generic* (utility-weighted) PROM relevant to a range of long-term conditions.

C. PEOPLE

C1. STAFFING STRATEGY AND STAFF DEVELOPMENT

Our staffing strategy focuses on recruiting and retaining the highest quality researchers, with established policies to support and develop careers.

Equality and diversity

Our commitment to equality and diversity is illustrated by the Athena SWAN silver award for NPEU (2013) and bronze awards for DPCHS (2013) and the University as a whole (2012), with the new NDPH applying at the end of 2013. Future commitment will be supported by the Vice-Chancellor's £1M Diversity Fund. Of 15 professors returned in NDPH, 5 are women and in DPCHS of 7 professors, 2 are women. Activities in response to the issues raised during preparations for Athena SWAN include: reviewing appraisal systems establishing specific mentoring schemes, supporting the balance between the demands of work and other responsibilities, advice on writing CVs and applying for regrading, and expanding part-time DPhil programmes.

Support and mentorship

Members of staff are entitled to a range of benefits to enhance their research careers, including:

- Generous maternity, paternity and adoption leave entitlements (such as maternity and adoption paid leave of 26 weeks, compared to 18 weeks in many other institutions).
- Comprehensive range of childcare services, and family-friendly policies (e.g., part-time, flexible and home-working), enabling staff to combine productive research careers with other demands.
- Applications for paid and unpaid leave are considered on a case-by-case basis and are granted, for example, to support researchers in personal development and specialised training.
- Encouragement and financial support to attend conferences and personal training courses.
- NDPH engages in training in trials methodology of external staff working on its collaborative studies worldwide, both in Oxford (such as symposia for selected Chinese doctors) and abroad.

Career development of researchers

All staff are offered regular personal development reviews and career development discussions with their supervisor or line manager. Discussions cover teaching, research, administration, pastoral and outreach work, and aim to identify needs. Junior researchers are further supported by regular meetings, coordinated through research groupings, where individuals present (and get feedback on) preliminary research ideas in a supportive setting and can discuss funding and publication issues with senior academics. There has been an increase in senior academic staff numbers since 2007 (DPHCS has doubled in size since 2011). This increase will accelerate with the structural reorganisations of both Departments and, in particular, the high degree of institutional resource devolution (enabling departments to commit reserves to posts) and the availability of significant new resources (the Li Ka Shing £20M donation) that will allow the recruitment of high-

quality research leaders to chairs and other posts within Oxford University's new Big Data Institute.

Supporting and integrating clinical academics

We recognise that clinical academics have particular needs, and have dedicated ways to support and integrate them, including:

- DPCHS created 4 year academic training options for GP vocational trainees in 2001/2, which developed into an NIHR academic clinical fellowship (ACF) programme with at least three ACFs in post at any one time. Since 2008, the DPCHS academic career 'pipeline' has included staff holding awards at every grade of the NIHR national competitive training schemes, including NIHR Professorship, Clinician Scientists, Career Development Fellowships, 4 NIHR Lecturers, Doctoral fellows and 10 NIHR ACFs. Similar early career support is provided to non-clinicians.
- In NDPH, 13 specialist registrars have undertaken out-of-programme training to obtain an MD or DPhil in topics related to randomised trials or epidemiology prior to completing training, and 5 of these returned after completing their training to continue research, with honorary NHS consultant positions. At senior level, NDPH holds one BHF Chair and 2 career MRC Scientists.
- In addition, Oxford UoA2 research groups provide world class methodological research training: for example, in evidence appraisal and synthesis by the CEBM, in statistical methods and diagnostic modelling from the PCCTU (supports NIHR methodology training fellowships), and in health economics research with the HERC. In addition, with the Department of Continuing Education, NDPH (Health Promotion Research Group) runs short courses on Prevention Strategies for Non-Communicable Diseases (NCDs), and NDPH (Ethox) has launched a free e-learning module on the ethics of genomics research in low-income country settings.

C2. RESEARCH STUDENTS

UoA2's teaching mission is integral to its research. During the REF2014 period, the new NDPH was established by combining several groups working in population health research, and one aim of the new department is to expand, broaden the scope of, and enhance its graduate teaching programme. This programme enriches scientific work across the NDPH, and there have been major contributions from students to research activity. For example, during the REF2014 period, UoA2 students have published several first author papers in the Lancet (*Bhala*, *Bulbulia*) and the New England Journal of Medicine (*Link*, *Reith*), have been awarded national fellowships, and several have progressed to become independent investigators in Oxford and elsewhere.

Recruitment and funding

The REF2014 period has seen several steps made to improve access to graduate programmes in UoA2, and increase the number and quality of research students. This is underpinned by strong collaboration between departments and the formation of Oxford University's **Medical Sciences Graduate School** (2011), which has created a single point of entry for applications and administrative support. Notable achievements have included the:

- **Establishment of a central division-wide funding model (2009)**, which allocates unrestricted University and RCUK funds on the basis of academic merit to students worldwide.
- **Establishment of the Nuffield Department of Population Health (2013)** which has enabled plans for significant expansion of the graduate teaching programme (see below 'Future strategic developments in research student training').
- **More competitive stipends (>£18,000/yr) and four-year studentships as norm** (except for 3 year clinical trainees).

Support

Students are members of Colleges which provide independent pastoral support through college advisors who can act as student advocates when necessary, and specific support is available through the University's student counselling service. In addition, for UoA2, DPCHS and NDPH provide significant support through DPhil Student Support groups, providing workshops/seminars (e.g., CV writing, writing a grant proposal), disseminating information, organising social activities, supporting the use of WebLearn and providing weekly DPhil student seminars during term-time. In addition, student representatives sit on the Graduate Studies Committees of DPCHS and NDPH, and on the Medical Sciences Division's Graduate Joint Consultative Committee.

Supervision
During the REF2014 period, the Medical Sciences Division strengthened supervision, planning and feedback, and introduced dual supervision as standard practice, led in DPCHS and NDPH by a Director of Postgraduate Education (*Ward*, *Shepperd*) with close links to the Oxford Department for Continuing Education and the Medical Sciences graduate committees. In UoA2 more than 80% of doctoral students finish their doctorate or MD within 4 years.

Student numbers
Across the UoA2 from 2008-13, 46 students were awarded doctorates. In DPCHS there are currently 13 full-time DPhil students and 26 part time DPhil students (registered for up to 8 years and from many countries). Improving the capacity for doctoral training is a major UoA2 priority.

Future strategic developments in research student training
The NDPH MSc in Global Health currently has an annual intake of around 25 students and from 2014 will have enhanced teaching of epidemiological and statistical topics, as well as additional material on chronic diseases. From 2014, NDPH will provide 10 fully-funded Prize Studentships each year, with around half of these providing 4 years' funding for the MSc in Global Health, followed by a DPhil. Oxford's unique Biobanks and other large cohort studies provide an unrivalled resource for such doctoral training. The DPCHS MSc in EBM is also expanding from a similar base to Global Health, with half of places competed for internationally.

Both UoA2 departments deliver Special Studies Modules offered to final year undergraduate medical students. These 2-3 week blocks allow students to select learning experiences around personal interests from a list of options on offer and usually include literature reviewing, secondary data analysis or professional shadowing e.g., NDPH offers opportunities to study a broad range of population health topics with particular strengths in the causes, prevention and treatment of chronic diseases in developed and developing settings (i.e., cancer, coronary vascular disease and stroke) and through a range of research disciplines (e.g., genetic epidemiology, bio-informatics, large-scale observational studies and clinical trials, health economics, medical statistics, biomedical ethics). DPCHS also offers intercalation research projects for Year 3 undergraduates.

D. INCOME, INFRASTRUCTURE AND FACILITIES

D1. INCOME
The strategic funding priority in UoA2 is to match its long-term research goals with secure and sustainable long-term grant income. UoA2 has increased its grant income by 42% over the period of the REF, diversifying its funding sources during a period of financial stringency. It has secured substantial new support from the National Institute for Health Research and increased funding from several industrial partners, including Bayer, Merck and Novartis. Its work is underpinned by several major funders, including the MRC, BHF and CRUK, with renewal of large core grants.

Summary of UoA2 research income (main sources & overall totals) during the REF period

Year	BIS/RCUK	UK Charities	UK Govt	Non-EU Industry & Public Corps.	NIHR	Totals, inc all sources
2008-09	£4.34M	£6.56M	£7.41M	£12.00M	£0.21M	£31.80M
2009-10	£3.81M	£6.95M	£7.58M	£13.37M	£1.12M	£34.70M
2010-11	£3.63M	£6.62M	£7.63M	£12.35M	£2.20M	£33.90M
2011-12	£3.51M	£6.34M	£6.84M	£20.17M	£2.69M	£42.90M
2012-13	£3.73M	£7.72M	£6.50M	£19.07M	£5.06M	£45.30M
TOTALS	£19.02M	£34.19M	£35.96M	£76.95M	£11.28M	£188.70M

D2. BUILDINGS
During the assessment period, DPCHS moved into brand new purpose-built accommodation (New Radcliffe House) which is co-located on the University's new Radcliffe Observatory Quarter site with the New Jericho Health Centre, within which several departmental members also work. The University recently released a heritage building on this site which is to be re-developed to locate the remainder of DPCHS (currently in office space close to the Railway Station). For NDPH, half of

the department (CTSU, CEU and NPEU) are based in the superb purpose-built Richard Doll Building (completed 2005) on the University's Old Road Medical Sciences Campus in Headington and the remainder of NDPH (which is currently in the adjacent Rosemary Rue Building) will occupy part of the adjacent new building that is to be built to house the Big Data Institute.

D3. RESEARCH INFRASTRUCTURE

Within UoA2 there is significant research infrastructure. The key assets are:

- **Large research collaborations**, including the **Thames Valley CLRN** (*co-director Farmer*) and the **Thames Valley hub of the Primary Care Research Network** (*Hobbs*) **South East (PCRN-SE)** with 278 practices supporting a population of approximately 2.3 million; NDPH has established collaborations to conduct some of **the world's largest epidemiological cohorts**: UK Biobank (500,000), China Kadoorie Biobank (500,000), and Million Women Study (1.3 million), plus, in collaboration with local scientists, various other international cohorts. NDPH also coordinates international collaborations between trialists to produce regularly updated meta-analyses in vascular disease (*Baigent*) and cancer (*Peto*).
- **NIHR School for Primary Care Research**: Director (*Hobbs*) and 5 year funding of £32M.
- **Trials Units**: 3 separate NIHR HTA fully registered trials units provide state-of-the-art facilities for designing and running randomised trials (**Primary Care and Vaccines Collaborative Clinical Trials Unit [PCVC-CTU]**, **Clinical Trial Service Unit [CTSU]** and **National Perinatal Epidemiology Unit [NPEU]**).
- NDPH's **Health Economics Research Centre** underpins UoA2 trials with research on the economic aspects of health and disease, costs and benefits of prevention and treatment, and design and evaluation of health systems, and NDPH's **Ethox** provides advice on ethical aspects of large-scale population studies (e.g., in UK Biobank).
- **Wolfson Laboratories**: 600m^2 of laboratory facilities located within NDPH are accredited to ISO 17025:2005 standard, and have high-throughput automated liquid handling facility to allow rapid sample handling and array plate work for sample testing in population studies.
- **Sample storage capacity**: Two offsite liquid nitrogen storage units provide 170m^2 and 460m^2 of space respectively, with storage of over 2 million aliquots from large-scale epidemiological studies and randomised trials.

A major strategic aim in UoA2 is to develop research infrastructure to ensure that Oxford is at the forefront of advances in bioinformatics and the use of technology to extract maximum value from the nationally-important open-access epidemiological assets managed within UoA2. Several pivotal developments will provide national leadership in the analysis of large population cohorts:

- A new Centre (the **Li Ka Shing Centre for Technology and Health Informatics**) is to be dedicated to generating and analysing large datasets. Phase 1 of this Centre, the recently completed Target Discovery Institute, is applying high-throughput molecular technologies to contribute towards a better definition of disease and the characterisation of improved drug targets. For Phase 2, Oxford has been offered a £20M contribution from the Li Ka Shing Foundation towards establishment of the new **Big Data Institute**, an adjacent facility to handle large data sets emerging from a variety of other sources, including population health science. Massive datasets from molecular and genomic studies can be analysed alongside those from electronic patient records, epidemiological cohorts, deep phenotypic data, and disease surveillance. University matched funding of £10M from the Research Partnership Investment Fund (RPIF) will help meet the costs of construction of a new building on the Old Road Campus site which will start in early 2014. NDPH will provide epidemiological and bioinformatics leadership within the new Big Data Institute.
- NDPH is responsible, with UK Biobank, for establishing **Biorepository South**, funded by a £25M DH grant to the University, which will house laboratory and storage facilities for projects conducted by the NIHR-funded Biomedical Research Centres, of which Oxford is one. CTSU will provide laboratory expertise and leadership, and this initiative will greatly enhance the UK's ability to archive and analyse samples from large studies cost-effectively.

D4. SUPPORT SERVICES

Research and Legal Services: The Medical Sciences Division's Research Services facilitate research across the Division, and knowledge exchange between the University's researchers,

government, community organisations and industry. For UoA2, they perform a particularly vital service for the conduct of large-scale randomised trials, which operate with the University as sponsor and require a complex hierarchy of contracts with pharmaceutical companies, regional coordinating centres and hospitals in multiple jurisdictions worldwide. During the REF period, Research Services have managed research income totalling around £189M on behalf of UoA2.

Libraries: UoA2 is supported by the Radcliffe Science Library, part of the Bodleian Library with over 1 million volumes of printed materials, over 120,000 books and 1400 print journals available. The Radcliffe Science Library provides complete electronic access to conference proceedings and journals from all professional societies and all major publishers.

Computing: Oxford's UoA2 computing facilities are distinctive because they have evolved to include world-leading systems that acquire, store, analyse and distribute data for a variety of large-scale studies, holding detailed and confidential medical records on over 3 million people. Currently this requires around 50 server-scale systems on-site, with additional nodes deployed within the main University system, at the **Oxford Supercomputing Centre**, and in China. Smaller custom designed systems are also deployed throughout the UK and internationally; for example, the SHARP, THRIVE and REVEAL trials involved 400 NDPH-managed computers spread across up to 20 countries; UK Biobank involved 400 PCs within the UK; and the Kadoorie Biobank deployed 100 PCs and a dozen servers across China. These systems are designed and managed by in-house IT teams comprising over 50 specialist programming and systems personnel, working closely with medical and statistical staff to produce bespoke systems of any required complexity. In addition to in-house use, NDPH computer staff provide an open-access data exposition and analysis service to researchers worldwide as part of UK Biobank, supplying both data and a secure high-power computational infrastructure to facilitate their work. Currently 570 researchers have joined this service and 30 projects are using it, with several hundred more in the pipeline.

Over the next 3 years, the core databases will be enlarged to produce the world's largest combined repository of multi-modal imaging (MRI, OCT, DXA, ultrasound), biometric (ECG, accelerometry) and genomic data, linked to NHS records and existing/accruing epidemiological data, and making the whole database accessible. NDPH's current storage of around 400TB will be expanded to over 2PB during this phase. A pilot project in whole-genome sequencing is under way and as this is extended to the biobank projects the data requirements will exceed 100PB. Effectively using such large and rich resources will require massive computational power and the new **Big Data Institute** combining expertise within the NDPH and the WTCHG (UoA1) is aimed expressly at such tasks. This substantial new facility will bring together existing genomics and epidemiology experts, add additional bioinformatics researchers, and provide them and their collaborators with the world-class hardware infrastructure that will be required to manipulate these large and complex datasets.

E. COLLABORATION OR CONTRIBUTION TO THE DISCIPLINE OR RESEARCH BASE

E1. BUILDING COLLABORATIONS WITH OTHER UOAs

DPCHS collaborates widely within Oxford, for example, with Biomedical Engineering on evaluating 'telehealth' systems in COPD and hypertension (Wellcome Trust & NIHR funded) and Psychiatry on the treatment of mental health problems in diabetes (NIHR School for Primary Care Research). Similarly, **NDPH** has established substantial collaborations with UoA1: for example, with the Department of Cardiovascular Medicine on the C4D and PROCARDIS studies of the genetic determinants of coronary disease, and on the STICS trial of statin therapy for the prevention of atrial fibrillation after cardiac surgery; with the Wellcome Trust Centre for Human Genetics on the Big Data Institute and the China Kadoorie Biobank; the Nuffield Department of Surgery on the 3C trial involving 18 of the UK's 23 transplant units, and on joint prostate cancer projects in EPIC, including studies of emerging potential biomarkers of risk. NDPH (George Institute) is also collaborating with Oxford University's Institute of Biomedical Engineering to develop and evaluate a simple heart failure monitoring and risk prediction system (SUPPORT-HF) for patient use at home.

E2. EXTERNAL COLLABORATIONS

The constituent groups within UoA2 are active in multiple collaborative ventures. Two main categories of collaboration can be distinguished: (i) regional, national or international collaborations designed to facilitate **areas of research activity**; and (ii) **collaborations on specific projects**.

Salient examples of collaborations that **facilitate areas of research activity** include leadership of: the **NIHR School for Primary Care Research** (with 5 year funding of £32M from 2008); the **Sensible Guidelines Group** (a collaboration between NDPH, Duke University, and McMaster

University) which is working to reduce barriers to randomised trials by engaging with regulators, pharmaceutical companies and other research governance stakeholders; and **the Oxford-India Health Research Network** (OIHRN) comprising established and emerging researchers/students at Oxford engaged in, or aiming to establish, collaborations with health researchers and research organisations in India supported by the NDPH (George Institute), the INDOX Cancer Research Network, and the Institute of Biomedical Engineering.

Some representative examples of the wide range of **collaborative activity on specific projects**, subdivided by the main categories of studies identified in the Figure (see Overview), include:

Observational studies. **DPCHS**: EchoNormal, a heart failure collaboration (*co-led* by Oxford & Auckland), collating and curating data from the world's largest echo cohort studies (UK, US, NL, Sweden, NZ) for meta-analyses. **NDPH**: Biobanks (China Kadoorie and UK Biobanks) and other prospective studies (~4.2 million participants in total) involve collaborations in the UK, China, Latin America (Mexico and Cuba), India, and Russia; International Collaboration on HIV and Cancer involves links with the US Centres for Disease Control and Prevention; NCI Breast and Prostate Cancer Cohort Consortium involves work with principal investigators from six large US cohort studies for studies of breast and prostate cancer genetics and gene-environment interactions. NPEU (UKOSS) links to every UK obstetric unit to capture rare complications of pregnancy.

Interventional studies. **DPCHS**: EU funded programmes in infection (>€48M) e.g., leadership of FP7 R-Gnosis consortium (POETIC); FP6 GRACE (delivered largest recruiting trials on infections ever in primary care); FP7 PREPARE Consortium (from 2014); Science Foundation, Translational Research on Antimicrobial resistance in Europe (TRACE); EU European Research Network on Recognising Serious Infection (ERNIE) with Belgian and NL. Major programmes in impoverished countries e.g., HURAPRIM (Human Resources for delivering care in Africa) programme with Gent and Vienna and six universities in Africa (Uganda, Mali, North Sudan, Botswana and South Africa). FP7 SupportingLIfe programme (€3M) with UC Cork, Lund Univ, and Malawi on child care in rural Malawi using diagnostic and mobile phone technology. A number of stroke and diabetes projects link with universities in CapeTown and Australia. **NDPH**: The ATLAS trial of a longer versus shorter course of tamoxifen in 13,000 women involved collaborating hospitals in 38 countries, and the series of lipid-modifying treatments (SHARP trial of ezetimibe/simvastatin in chronic kidney disease, THRIVE trial of niacin in CHD, REVEAL trial of anacetrapib in CHD) involved up to 400 hospitals in up to 20 countries; CEU's breast cancer screening trial to assess the efficacy of earlier (age <50) and later (age >70) screening incorporates the whole of the NHS screening programme; in NPEU, the CORONIS trial involved 16,000 women in 7 countries.

Evidence synthesis. **DPCHS**: Results from individual patient data meta-analyses of self-management in anticoagulation, diabetes and hypertension have changed international clinical guidelines and research on the recognition of serious illness led to publication of the world's first validated centile charts in children for standard signs such as respiratory rate. **NDPH**: Collaborative meta-analyses of individual patient data from randomised trials of cardiovascular treatments (e.g., for aspirin and statins [CTSU], antihypertensive treatments [George Institute]), and meta-analyses of treatments for breast cancer (CTSU) each involve hundreds of collaborating groups worldwide.

Implementation. **DPCHS**: Madox (Monitoring and Diagnosis Oxford) involves collaboration with international research groups in Engineering Science, Paediatrics and Health Economics; the childhood disease team collaborates internationally with a range of multidisciplinary teams including Departments of Primary Care, Engineering Science, Paediatrics, and Nursing. **NDPH**: the George Institute has collaborated with Indian scientists to develop Systematic Medical Appraisal Referral and Treatment (SMART) Health India, utilising smartphone-based technologies to provide healthcare workers with personalised clinical decision support to guide care of individual patients. HERC collaborates on providing economic evaluations within trials with Universities in the UK, US and China; HSRU collaborates with a number of trials units, charities and industry through its work on PROMs; and the BHF Health Promotion Research Group collaborates with institutions as diverse as NICE, European Heart Network, Children's Food Trust, European Food Information Council, Cochrane Collaboration, US Centre for Disease Control, and WHO Obesity Observatory.

Collaboration with industry. In **DPHCS**, the heart failure and anticoagulation research teams have collaborated for over a decade with **Roche Diagnostics** and **Abbott Laboratories** through grants and the supply of assays and point-of-care analysers. Roche have also provided research funding for secondary analyses and consultancy reports. Hypertension and diabetes telehealth work has been supported by **Omron**, **Vodafone** and **T+-Medical**. **NDPH** (CTSU) collaborates with

several pharmaceutical companies in order to conduct large-scale randomised trials. For example: **Merck** have provided £61M for the THRIVE and REVEAL trials during the assessment period; **Astra Zeneca** have collaborated on the STICS trial of rosuvastatin for the prevention of post-bypass arrhythmias; and **Pfizer** helped to fund the 3C trial in renal transplantation. CTSU licensed its discovery of genetic variants associated with statin-related myopathy for patient testing. HSRU licenses its portfolio of PROMs to the pharmaceutical sector, healthcare providers, medical device companies and the academic sector (http://www.isis-innovation.com/outcomes/index.html).

E3. CONTRIBUTIONS TO WIDER DISCIPLINE SINCE 2008

Leadership contributions

Within the REF2014 period, senior staff contributed substantially to healthcare research through leadership roles in national organisations. Within **DPCHS**: *Hobbs* is Director of the NIHR School for Primary Care Research, Chair of the European Primary Care Cardiovascular Society, and was Chair of the Council of Cardiovascular Primary Care, European Society of Cardiology; *Farmer* is Deputy Chair of the HTA Commissioned Research Board; *Butler* is Director of the Welsh School for Primary Care Research; and *Jebb* is Scientific Advisor on Obesity to the Department of Health. Many staff sit on NICE bodies and national funding boards. Within **NDPH**: *Beral* is a Non-Executive Director, Medicines and Healthcare Products Regulatory Agency; *Alastair Gray* serves as Advisor to International Society for Pharmaco-economics and Outcomes Research (ISPOR) Consolidated Health Economic Evaluation Reporting Standards (CHEERS) Task Force; *Collins* is CEO/PI of UK Biobank; *Peto* is a Founding Member of the European Academy of Cancer Sciences, a Board Member of the Washington Center for Disease Dynamics, Economics & Policy, and served as a member of the WHO Expert Advisory Panel on Cancer; *Fitzpatrick* is Chair of the NIHR Health Services and Delivery Research Board; *Parker* is Chair of the Ethics Advisory Board, Genomics England (100,000 Genomes Project), Non-Executive Director of Genomics England (100,000 Genomes Project), Chair of Wellcome Trust Consortium Data Access Committee for Case Control Consortium, and Deputy-Chair, Expert Review Group, WT Ethics and Society Investigator Awards.

Markers of esteem

During the REF2014 period, the major contributions made by senior members of UoA2 have been recognised by numerous national and international accolades. Within **DPCHS**: research excellence has been rewarded with the award of an NIHR Research Professorship (*McManus*) and 4 members have become NIHR Senior Investigators (*Mant*, *Hobbs*, *Farmer*, *Ziebland*); *Jebb* received OBE for services to public health (2008), Honorary Fellow, Faculty of Public Health (2009), Society of Biology, Science Communicator Award (2009) and Rank Prize (2010); *Hobbs* was made Life Fellow of Stroke Society of Australasia (2009) and, with *McManus*, won the RCGP Stroke Paper of the Year Award (2011). Within **NDPH**: *Beral* was made Dame Commander of the British Empire, Companion of the Order of Australia, awarded honorary degrees (DUniv, Oxford Brookes University; DSc, University of Glasgow), and made an Honorary Fellow at the London School of Hygiene and Tropical Medicine; *Collins* was knighted for services to science and medals for the British Cardiovascular Society Joy Edelman Lecture and European Society of Cardiology Geoffrey Rose Lecture on Population Science; *MacMahon* received the Pickering Award from the British Hypertension Society, a Research Achievement Award from the National Health and Medical Research Council of Australia, the John P. McGovern Award from the Association of Academic Health Centers, the Lewis A. Connor Award from the American Heart Association, the Ernst & Young Social Entrepreneur of the Year award, and the RT Hall Prize from the Australia and New Zealand Society of Cardiology; *Peto* received the WHO International Agency for Research on Cancer Medal of Honour for outstanding contribution to cancer research, the Heineken Prize from the Royal Netherlands Academy of Arts and Sciences, the Brupbacher prize for cancer research, Zurich, Lifetime Achievement Prize from Cancer Research UK, Lifetime Achievement Award from the British Medical Journal Group, Doctor of Medical Science, Yale University Commencement, USA (2011), was made an Honorary Fellow by the Royal Society of Medicine, served as Harveian Orator for the Royal College of Physicians, received the Society of Apothecaries' Galen Medal in Therapeutics, received the Chinese Government Friendship Award, State Administration of Foreign Experts' Affairs (SAFEA), and was elected Membre Associé Étranger de l'Académie Nationale de Médicine, France.