Trust Board Meeting: Wednesday 10 September 2014
TB2014.104

<table>
<thead>
<tr>
<th>Title</th>
<th>NIHR Oxford Biomedical Research Centre (BRC) report</th>
</tr>
</thead>
<tbody>
<tr>
<td>Status</td>
<td>For information</td>
</tr>
<tr>
<td>History</td>
<td>Regular report to the Trust Board</td>
</tr>
<tr>
<td>Board Lead(s)</td>
<td>Dr Tony Berendt, Interim Medical Director</td>
</tr>
<tr>
<td>Key purpose</td>
<td>Strategy</td>
</tr>
</tbody>
</table>


Executive Summary

- The Oxford BRC is a translational research partnership between the OUH and the University of Oxford, supported by an award of £95m over 5 years (2012-17) from the National Institute for Health Research (NIHR).
- The Oxford BRC has recently submitted its second annual progress report to the NIHR, summarising key achievements, research productivity and examples of benefit to NHS patients.
- The Mid-Term Review of the BRC is currently assessing the progress of all BRC Themes and working groups, through systematic peer review and consideration by an external Review Panel on 4-5 September 2014.
- The Oxford BRC is making important contributions to national programmes such as the NIHR Health Informatics Collaborative and Genomics England.

Recommendation

The Board is asked to note this report.
1. Summary of BRC Progress and Achievements 2013-14


Project Activity
- During 2013-14 financial period there were 350 active clinical studies and 150 non-clinical projects.
- Over two thirds assessed the efficacy of interventions that may go on to directly benefit patients.
- Many were clinical trials (267; 42 phase I, 16 phase IIa, 82 phase IIb, 85 other trials) providing gold standard evidence.
- A great number of projects investigated drug new biomarkers and interventions (44 and 124 respectively).

Training and Investigators
- Nearly 400 students have been trained as a result of the BRC award (2012-13 = 177; 2013-14 = 176).
- For 2013-14 there were over 200 investigators ranging from clinical scientists to allied health professionals.
- During the same period over 180 NIHR trainees engaged in pursuing doctorates or masters programmes.

The Themes have published >700 papers in peer reviewed Journals during 2013-14 including: Nature, Nature Genetics, The Lancet, BMJ and New England Journal of Medicine, acknowledging the NIHR Biomedical Research Centre.

Staff: The NIHR Oxford BRC includes 23 NIHR Senior Investigators, 231 NIHR Investigators employed by the BRC, 303 NIHR Associates and 166 NIHR Trainees with specific BRC funding. Approximately 85 OUH-employed consultants are partly supported by the BRC, amounting to 28 whole-time equivalents.

External Funding: During 2013/14 the NIHR Oxford BRC attracted £270 million of external grant income, representing a leverage ratio of more than 11.5 fold. The external funding includes £66 million from research councils, £91 million from research charities, £55 million from DH/NIHR, £34 million from other non-commercial sources, £22 million from industry collaborative and £1.4 million from industry contracts.

Business Development and Intellectual Property: During 2013/14 we filed 13 patents and spun out 3 companies (OxeHealth, Run3D, Perspectum Diagnostics).
1.1 BRC Theme Achievements

All 14 Themes of the NIHR Oxford BRC have made excellent progress in addressing the aims and objectives of the BRC:

- **The Biomedical Informatics and Technology Theme** has developed digital solutions for patient-centered self-management, and for improved patient monitoring and ‘early warning’ systems (e.g. in ITU, A+E and hospital wards), leading to major changes in hospital practice.

- **The Blood Theme** has generated novel diagnostics and therapeutics for blood disorders, based on stem-cell biology and stem-cell transplantation, used genomics to better diagnose both common leukaemias and rare inherited anaemias, and changed NHS practice through innovations in blood transfusion procedures.

- **The Cancer Theme** is developing new treatment combinations through the concepts of synthetic lethality and oncogenic vulnerability, using tumour genomics and novel biomarkers to target specific mechanisms in melanoma, sarcoma, ovarian and GI cancers.

- **The Cardiovascular Theme** uses the Oxford Acute Vascular Imaging Centre (AVIC) to conduct unique imaging studies, during the emergency phase of acute stroke and heart attack. Imaging also underpins studies in inherited cardiomyopathies and valve disease, including OxVALVE, the largest prospective cohort study of incident valvular disease, world-wide.

- **The Cerebrovascular and Dementia Theme** has grown large cohort studies, focusing on better phenotyping and prognostication, through imaging and biomarkers, leading to internationally-used scoring systems for stroke and new insights in to the importance of blood pressure control. In dementia the Theme has identified “secondary insults” and delirium in accelerating cognitive decline.

- **The Diabetes Theme** has improved phenotyping and genotyping techniques for personalised medication, and to understand disease mechanisms related to beta cell function, including the largest UK islet transplantation resource. The translational trials group tests new treatments and develops new technological innovations such as disposable electronic oral glucose tolerance test, in conjunction with SmartSensor.

- **The Functional Neurosciences Theme** has evaluated non-invasive stimulation treatment for tremor, for enhancing recovery after stroke, in phantom limb pain, and first in man studies of closed loop deep brain stimulation for Parkinson's disease, which shows improved therapeutic efficacy and efficiency over current deep brain stimulation approaches.
The Genomic Medicine Theme is discovering novel disease genes and developing novel genetic diagnostic tests based on whole genome and exome sequencing in diseases including cranial malformations, cardiomyopathies, myasthenias, epilepsy, and congenital anaemias. The Theme is applying genome-wide sequencing for clinical diagnosis, clinical trials, translational research and discovery of novel targets, with strong links to Genomics England.

The Immunity Theme has developed a core BRC translational immunology lab, to generate and validate novel cellular immune assays, and supports work in viral infection (HCV and HIV) and immunogenetics.

The Infection Theme translates genome sequencing and informatics technologies to transform the diagnosis, management and surveillance of infectious diseases, such as Norovirus, C Difficile, S Aureus, and minimising antibiotic use to reduce antimicrobial resistance.

The Prevention & Population Care Theme provides a route of rapid translation of research to healthcare delivery and prevention, at the interface between primary and secondary care in key clinical areas that have high national priority- including chronic kidney disease and heart failure, trialling of technological advances such as telehealth.

The Translational Physiology Theme has developed new technologies such as hyperpolarized Xe MRI, laser gas analysis and MRI tissue oxygen imaging to understand ventilation and hypoxia in lung disease, anaesthesia and ischaemia.

The Surgical Innovation and Evaluation Theme has established the Oxford Surgical Intervention Trials Unit (SITU), the first of its kind in the UK, recognised by the Royal College of Surgeons. SITU evaluates new surgical technologies and supports novel trials in retinal gene therapy.

The Vaccines Theme generates and evaluates new vectored vaccines leading to clinical trials e.g. in TB, and evaluates childhood vaccinations, providing key evidence for UK national vaccination recommendations.

Significant Developments in Implementing the Strategy: Working Groups to Build New Capacity and Critical Mass. The Oxford BRC has formed Working Groups to support new activity in key, cross-cutting domains that are critical to the strategy of the BRC, and align with national priorities. These include:

- Clinical Informatics: to link NHS clinical data, through the EPR, with clinical research studies, and forming the basis for the Oxford BRC's leadership as the coordinating centre for the NIHR Health Informatics Collaborative (NIHR HIC).

- Molecular Diagnostics: to translate BRC advances in genomics and bioinformatics to provide an NHS, CPA-accredited diagnostic service, based
in the hospital clinical laboratories, through genome sequencing in cancers, haematology and rare diseases. The BRC Molecular Diagnostics Laboratory has developed techniques for optimising clinical samples in whole genome sequencing, establishing pathways for clinical samples and data, and formed important links with Genomics England.

- **Cognitive Health:** to build additional BRC capacity in dementia, leveraged by the award of NIHR funding to the Oxford BRC for work in cognitive health and dementia.

- **Patient and Public Involvement and Engagement:** We appointed a new lead for PPI&E, Dr Sophie Petit-Zeman, as the NIHR Oxford BRC Director of Patient Involvement. The working group prioritises PPI&E activities across the Oxford BRC, and strengthens the profile and importance of PPI&E locally and nationally, including high profile publication (Petit-Zeman & Locock. *Nature* 2013), and links with INVOLVE and the James Lind Alliance/NETSCC.

- **Progress with Leadership, Governance and Management Arrangements:** The BRC Steering Committee oversees the scientific direction and progress of the BRC Themes. During 2013-14 the Oxford BRC is preparing for a major Mid-Term Review of BRC progress and strategy, to be held in early September 2014, led by an external scientific review board. The BRC is a key focus of the NHS-University Partnership, governed by the Strategic Partnership Board, including the OUH CEO and Chairman, and the University of Oxford Vice-Chancellor and Dean of Medicine. The ability of the BRC to operationalize personnel, estates and research governance are facilitated by NHS-University Joint Committees, and RM&G functions that are key to BRC performance are managed by a Joint Research Office that co-locates all grants, contracts, administration and governance teams. The BRC has strong links with the newly-designated Oxford Academic Health Sciences Centre, and the Oxford Academic Health Sciences Network, providing further opportunities for NIHR BRC translational research to benefit NHS patients across the Region, and to drive innovation and wealth creation. The BRC operational team achieved renewal of our ISO9001 designation in 2013-14 and is currently using the NIHR hub to disseminate information to the Themes. The BRC website provides comprehensive and up to date information including details of the BRC Open Day and the Mid-Term Review process.

2. **Specific Examples of BRC Research 2013-14**

2.1 Data Fusion for Integrated Patient Safety Monitoring in Hospital

Our strategy for digital healthcare in the hospital, based on the development of real-time data fusion techniques, is also delivering improvements in patient care. In 2010 we established a new evidence-based early warning score for recognizing clinical deterioration in hospital patients.
During the past year, we have undertaken extensive clinical trial evaluations of our data fusion technology and algorithms. These have taken place on several hospital wards, including the Emergency Department, and have involved the recruitment of nearly 8,000 patients, and a 1,200-patient clinical trial on the trauma wards at the John Radcliffe Hospital. We have shown how the use of an electronic track-and-trigger system can enable nursing staff to spend a greater proportion of their time on the highest-risk patients.

We have applied the results of these studies to roll out an electronic track-and-trigger system across every ward in all of the OUH hospitals during 2014-15, attracting additional financial support from the “Safer Hospitals, Safer Wards” post-Francis report initiative (NHS Technology Fund).

Our work has also revealed that the most effective strategy for early identification of unanticipated clinical deterioration needs patient-specific personalisation, moving from generic early warning scores to scores which are targeted at specific patient populations. We have therefore begun to develop scores for patient groups where physiological states are altered, including:

- The CALMS2 study, showing that post-surgical patients have characteristic patterns of recovery following surgery, necessitating the design of an early warning score, which takes the changing physiology into account.

- The 4P study (Predicting Physiology Patterns in Pregnancy) is constructing risk models for vital signs in pregnant women, so that we can design an evidence-based Modified Early Obstetric Warning Score (MEOWS) for identifying abnormal physiology during pregnancy as well as unexpected deterioration during labour. Such a score currently does not exist anywhere in the world.

Patients on a general ward experience major deterioration when they are not brought to the attention of clinical teams equipped to deliver timely, often life-saving treatments, sufficiently early. The available data (demographics, admission diagnosis, laboratory results, vital-sign observations) are not currently integrated to provide clinically useful information and support decision-making based on an overall risk index. We are starting to develop new risk-prediction algorithms integrating physiology (the vital signs) with the multiple types of patient data available within the electronic patient record (EPR).

We anticipate that developments in ‘Big Data’ at the Oxford BRC will integrate vital-sign data with all clinical data recorded in the EPR during a hospital stay, including digitised data from pathology slides and radiology. Analysis of such diverse datasets will help identify strategies to improve patient outcomes and deliver more efficient hospital treatment.
2.2 New Insights to Clostridium Difficile Infection and Hospital Outbreaks using Genome Sequencing

Infection such as Clostridium difficile (C. difficile) cause healthcare-associated infections that may cause outbreaks in hospital patients, with major implications for hospital logistics, potential patient-patient infection, and the need for patient isolation. Researchers in the Oxford BRC Infection Theme have tracked C. difficile infections over 5 years, representing >96% of all clinical cases identified by the service Microbiology Laboratories at the John Radcliffe Hospital. Using this unique resource, linked with clinical data from hospital admissions, the programme used whole genome sequencing of the C. difficile genomes from >1200 infections, discovering that only a minority could be attributed to direct spread in hospital. Furthermore, of the likely transmitted cases based on close genetic similarity, more than one third had no hospital or community contact. Distinct new genetic subtypes continued to be identified throughout the study, suggesting that new cases arise from a considerable reservoir of C. difficile. Interventions targeting transition from exposure to disease, rather than just transmission, likely played a major role in recent CDI declines.

This study, published in the NEJM in September 2013, conclusively demonstrated that genetically diverse sources, in addition to symptomatic patients, play a major part in C. difficile transmission. The unique resource of genetically-sequenced C difficile infections is now being exploited in bacterial association studies of C. difficile severity, and studies estimating the impact of antibiotic use on the dynamics of different C. difficile strains. Further, this study impacts on the national Clostridium Difficile Ribotyping Network (CDRN) to move to whole genome sequencing for its reference laboratory activities.

2.3 Direct Sequencing of mycobacterial culture as a replacement technology for routine TB diagnostics

The current approach for recovering the information necessary for managing patients with TB is complex and lengthy. It requires culture locally in liquid medium, which takes from a week to two weeks to yield growth. Once growth is achieved samples are referred to a reference laboratory and fragments of information by various methodologies including molecular and routine culture techniques to produce the complete test results which take two to three months. The key information is as follows: species identification, anti-mycobacterial resistance, and TB typing to identifying clusters of transmission.

The Oxford BRC working jointly with awards from UKCRC and The Health Innovation Challenge Fund has developed methodology for producing the full diagnostic information content from whole genome sequencing. An evaluation of the prototype has been completed as follows:
I. A method for extracting and preparing DNA directly from a positive liquid culture sample has been developed. This yields sufficient DNA of adequate quality of first-day-positive cultures so that the sample can be prepared for whole genome sequencing.

II. The samples have been successfully sequenced on a MiSeq yielding high quality DNA sequences.

III. The data is downloaded from the MiSeq machine via a connection to the Amazon Cloud, managed by Illumina named BaseSpace.

IV. The downloaded sequenced data from BaseSpace is processed through an assembly and analysis pipeline set up by the OxBRC and the Modernising Medical Microbiology Consortium. Reports recording the mycobacterial species and, for those that are *Mycobacterium tuberculosis* complex, the resistance determinants and the nearest genomic match are returned in 48 to 72 hours of receiving the sequenced data.

V. The evaluative study was an international collaboration between Vancouver, Canada; Dublin, Ireland; Borstel (Hamburg), Germany; Lille, France; Leeds, England; Birmingham, England; Oxford, England; and Brighton, England.

VI. Over 400 samples have been processed and successfully yielded the required information with high sensitivity and specificity, with much more rapid turnaround than the routine processing.

VII. A health economic evaluation is being performed.

As a consequence of the preliminary results from this successful evaluative investigation, the Oxford-based BRC and MMM TB sequencing solution has been adopted for the Genome England 100,000 genome project. This has now been funded and will commence, in the first instance, for one year starting July 2014. It is expected that once the process is running smoothly it will be extended and implemented into the NHS.

2.4 Smartphone-Based Self-Management of Gestational Diabetes

Gestational diabetes mellitus (GDM) affects 5% - 16% of all pregnancies in the UK, with important implications for the health of the mother and baby. Furthermore, there and major lifestyle and resource impacts due to the need for intense monitoring and treatment adjustments, typically achieved by glucose monitoring, diary keeping and frequent hospital visits.

The newly-developed Oxford GDM-health management system both improves the management of GDM and reduces the number of clinic visits. The system has been designed with extensive input from both patients and clinicians, comprising a smartphone app, with a Bluetooth-enabled blood glucose meter, for the patient; and a secure website, with optimised data presentation and alerting algorithms for healthcare professionals. The app automatically transmits the blood glucose measurements to the website, along with annotations entered by the patient. In addition, the app provides visual feedback on blood glucose control to the patient. The system has built-in capability for communication between healthcare professionals and the patient, using text messages to support self-management.
A randomized controlled pilot trial is currently underway comparing clinical, economic and satisfaction measures between women using the Oxford GDm-health management system and those receiving usual care (TREAT-GDm, clinicaltrials.gov NCT01916694).

Working in partnership with the Oxford Academic Health Sciences Network (OxAHSN), the Oxford GDm-health management system will be adopted by 2 large partner Trusts, the Royal Berkshire NHS Foundation Trust and the Milton Keynes NHS Foundation Trust, with plans for further implementation of this system across the region in 2015

2.5 The Oxford Acute Myocardial Infarction (OxAMI) Study to Evaluate New Treatments in Emergency Cardiac Care

The OxAMI study builds on the expertise and platforms provided by the Oxford Acute Vascular Imaging Centre (AVIC) to undertake detailed clinical research studies in patients presenting with acute myocardial infarction (MI; heart attack), in the emergency phase, within minutes of arrival at the hospital and during emergency treatment to unblock the coronary artery. Key outputs and impact include:

- Establishing a rigorous ethical and regulatory framework for enabling patient participation in clinical in the research emergency setting.

- Establishing the infrastructure for acquisition of physiological data, aspirated thrombus and cardiac blood sampling and processing in the emergency setting, on a 24 hour-a-day basis, to enable recruitment in the emergency setting.

- Establishing new imaging platforms and protocols, using the AVIC cardiac MRI capability, to allow scanning of acute MI patients in the immediate period after myocardial infarction.

The OxAMI study establishes a new approach to undertake clinical research in emergency setting - by complementing highly specialised and sophisticated clinical research facilities with the NHS patient pathway and direct involvement of NHS emergency clinical staff in clinical research.

OxAMI studies are:
(I) Identifying circulating biomarkers and invasive physiological measures that quantify effective reperfusion of the ischaemic myocardium.

(II) Developing and validating novel MRI techniques for understanding myocardial injury and recovery after MI

(III) Testing strategies to stratify patients to predict those that will recover well with minimal myocardial injury, from those where new therapies may be targeted to improve recovery and clinical outcomes

2.6 Emergency Magnetic Resonance Imaging to Diagnose and Stratify Acute Stroke

A unique multidisciplinary research programme brings together the Acute Stroke Programme and Neuroradiology at the John Radcliffe Hospital, with researchers in the University's Centre for Functional Magnetic Imaging of the Brain (FMRIB) and in the Institute of Biomedical Engineering. The programme is based around the Oxford Acute Vascular Imaging Centre (AVIC), which provides state-of-the-art high-field MRI scanning, with an integrated vascular intervention lab, co-located in a dedicated clinical research facility adjacent to the A+E department, enabling patients presenting with acute stroke to participate in research studies in the emergency setting.

These studies have achieved the following outputs and impacts:

- Refined emergency consent process accommodating the requirements of the Mental Capacity Act (published in *Emergency Medicine Journal* 2013).

- Demonstrated feasibility and safety of undertaking clinical research in acute stroke, from the Emergency Department directly into the Acute Vascular Imaging Centre.

- Improving sequence acquisition aimed at minimizing poor images, particularly at peri-imaging motion correction techniques rather than standard post-imaging processing.

- Seamless assimilation of clinical research in to the acute stroke clinical pathway.

- Patient involvement and feedback at follow-up incorporated into new study protocols (July 2013).

- Award of external funding from the Dunhill Medical Trust (2013-15) to support a larger cohort study in acute stroke.
250 patients will be recruited to participate in studies which will reveal new insights in to the diagnosis, stratification and outcomes of acute stroke, through immediate and repeated MRI scanning during the first 24 hours following stroke symptom onset. These studies will develop and validating novel physiological MRI approaches to predict brain injury, recovery and outcome in acute stroke. Using sophisticated imaging techniques in clinical research studies will be used to identify and validate diagnostic biomarkers to improve management of acute stroke patients across the NHS, and find potential new treatment targets.

2.7 Telemetric Home Monitoring to Improve Blood Pressure Treatment After Stroke

Consistent control of blood pressure (BP) after TIA and stroke is vital to preventing recurrent stroke, but is hard to achieve in routine practice. Recurrent strokes, cognitive decline and acute coronary events can all be triggered by peaks in BP due to under-treatment or non-compliance and by troughs in BP due to over-treatment. In collaboration with the Department of Bioengineering and with industry (t+ Medical, Abingdon, UK), we have developed telemetric home BP monitoring early after TIA or stroke to titrate medication and achieve consistent personalised BP control.

Patients measure BP in their homes using a Bluetooth-equipped monitor, with multiple readings transmitted automatically in real time via a secure web page, enabling rapid titration of medication to achieve optimal BP control.

In a study of 1000 patients (23% aged ≥80 years) almost 99% of patients monitored for at least one month, leading to major changes in BP management. These included: (1) Missed hypertension in >30% of patients; (2) initiation or increase in medication in >70% of patients, and, (3) 28% of patients stopping or decreasing medication. Overall BP control improved during home monitoring, and patient satisfaction rate were very high.

The superior predictive value of home BP versus 24 ambulatory BP monitoring is likely to changes in clinical practice and current NICE guidelines. Additional studies, now published, have revealed new insights in to BP variability in diabetes, in intracerebral bleeds versus ischaemic stroke, and physiological Correlates of Beat-to-Beat, Ambulatory, and Day-to-Day Home BP Variability;

This work has also led to collaborations with University of Leicester, University of East Anglia and University of Dundee, with BHF funding, to determine the prognostic implications of increased BP variability after TIA and stroke and to a number of randomised trials of morning versus evening administration of BP-lowering medication.

2.8 New Techniques for Brain Stimulation Therapy in Parkinson’s Disease

- Brain pacemaker therapy is a growing field with over 100,000 patients operated on worldwide. The treatment is usually used in Parkinson’s patients
and other indications are being trialed. The brain stimulation takes a simple form that is continuous and fixed, independent of the nature of the underlying pathological brain activity. It has been speculated that this may limit efficacy and increase side-effects, as the brain is being stimulated both when necessary but also when unnecessary. It is, in effect, rather like having central heating without a thermostat.

- We demonstrated that we can detect and quantify a signal from the brain of patients with Parkinson’s disease that closely follows symptom severity. We have shown that we can use this signal to guide when and if to stimulate, using a brain pacemaker. The new approach is significantly more effective than standard therapy, and uses less than 50% of the pacemaker battery than before, so reduces the need for operations to change the pacemaker device. This simple improvement is analogous to adding a thermostat to central heating!


- It was the subject of a commentary in the same journal: Starr PA, Ostrem JL. Annals of Neurology, 74:447-8 and in an article in Nature (Shen H. Tuning the Brain. 2014; 507; 290-292).

- Considerable media interest included a BBC News Feature & was featured in many sites including:

  http://www.ox.ac.uk/media/news_stories/2013/130712_1.html;
  http://oxfordbrc.nihr.ac.uk/personalised-brain-stimulation-could-improve-life-for-parkinsons-sufferers/
  http://www.jwatch.org/na32545/2013/10/30/adaptive-dbs-parkinson-disease?query=etoc_jwneuro
2.9 New Interventions for Cure of Chronic Hepatitis C and HIV Infection

The NIHR Oxford BRC has combined basic science advances in viral immunology and genetics to work with other BRCs in national initiatives to optimize the treatment of important chronic viral infections- Hepatitis C (HCV) and Human Immunodeficiency Virus (HIV).

In Hepatitis C, genetic testing of HCV genotype is being tested for impact on the health sector will be significant, as with the major expense of the new drugs, defining their best use is really an imperative and since we focus on the major UK strains (notably genotype 3A), this is of specific interest to the NHS. The NIHR Oxford BRC work and support was instrumental in the award of an MRC Stratified Medicine grant (STOP-HCV) across several BRCs and other centres.

Furthermore, this consortium has already attracted major industry funding through collaboration with Gilead, to test the impact of new agents in genotype 3A disease. This has a major academia-led component including creation of a tissue bank from liver biopsies and an intensive sampling protocol, and will provide a first-class model for future BRC-Industry collaborations in this area.

In HIV, the NIHR Oxford BRC contributes to the leadership of CHERUB - a pan-BRC consortium to develop new approaches to HIV cure. Development of cure strategies would have a huge impact on HIV therapy, allowing cessation of lifelong drug therapy with associated costs and side-effects. There is strong focus on this aspect of HIV medicine and the development of cohorts of patients and groups of clinical triallists backed by excellent lab scientists has been dependent on BRC support. This collaboration of triallists will be further strengthened in future and several new trials are in progress or planned (see below). The team has recently published high-profile results from an international early intervention study (SPARTAC trial investigators, NEJM, 2013).

2.10 Gene Therapy for Blindness Caused by Retinal Degeneration

Clinical trials led by Oxford BRC researchers have tested new gene therapies to treat choroideremia, Stargardt's disease and retinitis pigmentosa. Choroideremia is a degeneration of the retina (light-sensitive lining of the back of the eye) leading to blindness by middle age. The gene therapy tested by Prof Robert MacLaren at the OUH's Oxford Eye Hospital uses a modified adeno-associated virus, AAV.REP1 as a vector to deliver the correct version of the choroideremia (CHM) REP1 gene to cells in the retina of the eye (published in Lancet, 2014). The gene therapy trial involved the injection of viral vector particles into the back of an eye in six participants, underneath the retina, in order to permit the virus to deliver working copies of the gene to the cells that particularly needed it (i.e., photoreceptors, and pigmented epithelium). The initial aim was to achieve the prevention or slowing
down of any further degeneration of the retina caused by choroideremia. The first part of the clinical trial (2012/13) showed very promising initial results, surpassing the expectations of the researchers involved, and has been widely publicised in the international media. Six months after treatment with this therapy, the first six patients showed improvement in their vision in dim light and two of the six were able to read more lines on the eye chart. The next phase of the gene therapy clinical trials will use higher doses of the viral vector in six further participants.

2.11 Functional Lung Imaging using Hyperpolarized Xenon-MRI

Work at the NIHR Oxford BRC has established hyperpolarized xenon (Xe) MRI techniques to image lung function in patients with lung diseases such as COPD. Studies to compare imaging modalities (Xe-lung MRI, CT, ventilation: perfusion scanning) and phenotyping (dyspnoea, lung function and exercise tolerance) in patients with COPD will test how Xe-lung MRI can better predict dyspnoea and exercise tolerance, and provide a quantitative readout of changes in lung function in response to therapies. Further studies in the normal population and in patients with lung cancer are now recruiting.

This novel lung imaging technique has the potential to revolutionise the clinical management of patients with a wide range of chronic respiratory conditions, and change the design of clinical trials in respiratory disease.

2.12 Improving Childhood Vaccination Against Group B Meningococcus

Group B meningococcus (MenB) is the last major cause of bacterial meningitis and septicaemia in children, with more than 10,000 cases in England and Wales in the past decade, and it is the leading infectious cause of childhood death in the UK. Immunisation against MenB is a public health priority, but has been difficult because the MenB outer capsule does not generate an adequate immune response.

The NIHR Oxford BRC Vaccines Theme has led national and European studies of a new MenB vaccine (4CMenB; Bexsero), in collaboration with industry, which was licensed in Europe in 2013 and has been recommended in 2014 for immunisation of all infants by the Department of Health’s Joint Committee on Vaccination and Immunisation. A national study (CHIMES), coordinated by the Oxford BRC, is investigating the current causes and presentation of meningitis in the United Kingdom.

With BRC support we have developed and evaluated a new vaccine, MenPF, based on 2 proteins from the organism’s outer-membrane, and we have also developed an entirely novel approach to meningococcal vaccines using a viral vector to deliver key antigens, attracting MRC funding to advance this project to phase I.
2.13 Translating Advances in Genomics into Benefits for NHS Patients

The NIHR Oxford BRC has established a BRC Molecular Diagnostics Laboratory to develop, evaluate and apply next generation sequencing technologies and bioinformatics. The BRC Molecular Diagnostics Laboratory is led by a BRC-funded NHS Consultant, and is fully integrated within the OUH’s core clinical diagnostics labs. The Oxford BRC Molecular Diagnostics Laboratory is unique across the NHS by providing state-of-the art NGS diagnostics to patients across the region and enabling rapid, gene-specific recruitment to clinical research studies and clinical trials in cancer, haematology and rare diseases.

For example, in cancer and iron overload conditions (e.g. haemachromatosis) we provide NHS patients with information on a panel of specific cancer genes which can tailor specific treatments so that the patient benefits in getting the right treatment first time. These tests are affordable at £400 for 20 genes (Iron-overload) or 50 genes for the Cancer panel, national and international referrals (MiSeq), patients’ tumours to be profiled and treatments selected accordingly where available, or to be entered into clinical trials on the basis of mutation analysis (see press release in Jan 2013 GenomeWeb) (Ion Torrent platform). We are now using genome testing in ‘real time’ to stratify patients for entry into the DOCMEK oncology clinical trial based on data from the cancer gene panel.

Further panels are being developed, including:

1. A Rare inherited anaemia panel has been developed in the MDC, this is expected to become a national service.
2. A Myeloid panel, targeting 24 genes, has been developed in the MDC which is currently being reported on a research basis only until further validation is carried out.
3. A haem-oncology panel is being co-developed with Illumina and MDC is about to beta test the product
4. Breast cancer panel – we are developing a breast cancer panel of 47 gene ‘hot-spot’ regions.

We are now working on a national QC assay for this new NGS technology. An interlab validation of Next Generation Sequencing has been set up between Oxford, Leeds, Glasgow, Sheffield, Manchester and Liverpool. Samples will be analysed using amplicon sequencing on NGS platforms and resulting variations that are detected will be compared between all participating laboratories by a means to compare and cross-validate the technology, platforms and tests being used in participating labs.

2.14 Expanding Techniques for Pancreatic Islet Cell Transplantation in Diabetes

The publication of the “Edmonton protocol” from Canada in 2000 transformed islet cell transplantation in many countries, including the UK. Since that time islet cell
transplantation has moved from a research activity into a clinical service, supported by NICE guidance published in 2008.

The Oxford islet isolation facility, with support from the NIHR Oxford BRC, is one of only two such facilities in England and provides islets for transplantation in Oxford and in centres in London, Newcastle, Manchester and Bristol. Oxford performs the largest number of islets transplants nationally with a programme strongly supported by basic science and clinical research. In addition to cutting edge research into enhancing both yield and function of transplantable islets, the Oxford BRC group, also supported by an EU FP7 award, is also leading on the optimisation of the first in man bioartificial pancreas.

Oxford has led an NIHR QIDIS initiative to establish 'hub and spoke' islet transplant networks within England and has pioneered a regional network that includes an established satellite clinic in Birmingham, and new clinics being created in Southampton and Exeter. In addition, we have initiated a network in the Thames Valley using both real and virtual (spoke) clinics based around the central Oxford (hub) facility. This new initiative is a key activity of the newly formed diabetes clinical network as part of the Oxford Academic Health Science Network (OAHSN) and represents a clear example of translational research within the Oxford BRC feeding innovation across the AHSN to deliver better care for people with type 1 diabetes.

2.15 Targeting Stem Cells in Therapies to Treat Myeloid Leukaemias

The NIHR Oxford BRC has developed new anti-cancer stem cell therapies based on a humanized anti-CD47 monoclonal therapy.

Phagocytic cells recognize "eat-me" signals present on cancer cells that are counter-balanced by specific "don't eat-me" signals. On the surface of cancer cells the CD47 molecule transmits a "don't-eat" signal when it binds to its ligand, SIRP1-α, on phagocytic cells. Work by the Blood Theme of the NIHR Oxford BRC, in collaboration with investigators at Stanford University, showed CD47 is highly expressed on leukaemic stem cells (LSC) in acute myeloid leukaemia (AML) and other tumours.

The Oxford BRC, in collaboration with the UK AML Working Party, have tested 547 bone marrow samples from the UK NCRN AML clinical trials, demonstrating that CD47 is the only universally expressed antigen on AML leukaemic stem cells (LSC) and bulk cells.

Working with Stanford, the CD47 “don’t eat me” signal can be blocked by humanized anti-CD47 monoclonal antibody Hu5F9-G4, allowing tumour cells to be destroyed.
Following an initial preclinical development programme for Hu5F9-G4 at Stanford, including GLP toxicology in non-human primates, the Oxford BRC has finalized the first-in-man Phase I AML trial protocol, and attracted additional funding from the MRC. The Oxford BRC will lead the AML trial, with 7 other large UK centres. Furthermore, the work of the Oxford BRC with the anti-CD47 antibody has led to CRUK funding for a solid tumour trial and CRO and EU sponsor representative function (CRUK DDO). This unique academically driven and funded (NIHR BRC, MRC and California State Government) trans-Atlantic collaboration between The Oxford BRC and Stanford is a blueprint for a novel path to take discoveries into clinical practice without commercial stakeholders until late in Phase II, thus maximizing value and accelerating implementation.

2.16 New Genetic Diagnostics Tests to Improve the Utility of Genomics in Medicine

The Oxford BRC Genomic Medicine Theme have developed whole genome sequencing (the WGS500 programme) and exome sequencing projects to identify new genes for rare disease including inherited adenomas, cranial malformation syndromes, cardiomyopathies, myasthenic syndromes, epilepsy and congenital anaemias. These studies have: (a) revealed new genetic causes of disease in families where prior tests had not been informative, and, (b) expanded the repertoire of genes for which diagnostic testing can be offered in people with these conditions.

The Oxford BRC is working to make genome-wide sequencing accessible across several medical specialties for clinical diagnosis, clinical trials, translational research and discovery of novel therapeutic targets. A single research ethics framework has been established, and REC approval gained to provide documentation for tiered consent for targeted and genome-wide sequencing for all constitutional/inherited disorders. A Genomic Medicine Multidisciplinary Team (MDT) oversees the clinical use of exome/genome sequencing through highlighting availability and ensuring appropriate sample selection and return of results. The BRC Genomic Medicine Theme has attracted substantial external funding from the Health Innovation Challenge Fund (HICF) to translate WGS into the clinic and is providing the necessary technical expertise and clinical pathways for developing these approaches nationally, with Genomics England.

3. Biomedical Research Centre Mid Term Review

3.1 The NIHR Oxford Biomedical Research Centre is now halfway through its current five-year term. In light of this, Oxford BRC is undertaking a comprehensive Mid-Term Review in order to evaluate its progress against its stated aims and to establish new goals for the remainder of the current term. To provide a robust and independent review process, 54 national and international reviewers have been selected to cover the full breadth of the BRC’s work, and the progress of each Theme and Working Group will be reviewed by at least two external reviewers. The feedback they provide, along with written and oral submissions by each Theme/Working Group Leader, will be considered by the BRC’s Mid-Term Review
Panel on the 4th and 5th September. The Panel will be chaired by Prof Jonathan Knowles, and comprises nine other distinguished scientists from both within and outside Oxford to complete the Review. The members of the Mid-Term Review Panel do not have direct leadership roles in any of the BRC’s themes, and the review process will therefore provide valuable independent insight into the success of the BRC, and future direction.

The BRC Mid-Term Review Panel will review the progress of the BRC Themes and Working Groups according to the following criteria:

- Significance
- Approach
- Progress
- Budget Support
- Innovation and Commercialization
- Impact

Specific aspects of impact include:

- Number and impact of publications, including acknowledgment of NIHR/BRC support
- Gender equity in the allocation of BRC funding (Athena Swan)
- Patients recruited into studies
- External grant awards received
- Patient and public involvement and engagement
- Contribution to the UK growth agenda
- Links with other NIHR infrastructure
- Development of intellectual property (IP)

Following the Mid-Term Review, a feedback report will be provided to each Theme and Working Group, following approval by the Mid-Term Review Chair and the BRC Steering Committee.

The overarching aim of the BRC Mid-Term Review is to provide a critical evaluation of progress and achievements in the BRC, in order to assist the BRC Steering Committee and the BRC Themes to select priorities and identify new opportunities in the 18 months before the next BRC competition, expected to be announced in early 2016.

4. NIHR Health Informatics Collaborative and Genomics England

4.1 The Oxford BRC is the central coordinating site for the NIHR Health Informatics Collaborative (NIHR HIC), an initiative established to develop data standards and information systems that allow safe and appropriate sharing of NHS clinical data to support clinical research. The BRC Clinical informatics working group provides the foundation of the Oxford NIHR HIC activity both from a theme specific perspective and as the coordinating centre. The initiative has reached the half-way point, at one year since funding began.
4.2 The NIHR HIC Board met and received an annual report from each of the five themes, demonstrating good progress against the aims of the initiative, standardising clinical data and sharing that data across organisations.

4.3 Each of the five BRCs participating in the NIHR HIC [Oxford, Cambridge, Imperial College, UCH, Guy’s & St Thomas’] has now entered into a framework Data Sharing Agreement permitting transfer of clinical data throughout the collaborative for research purposes.

4.4 NIHR HIC continues to develop the framework for the data component of Genomics England, with the Ovarian Cancer theme of NIHR HIC providing the exemplar for the Genomics England oncology pipeline.

Dr Tony Berendt
Interim Medical Director

Paper prepared by:

Professor Keith Channon
Director of Research and Development
Director of the Biomedical Research Centre

2 September 2014