National Institute for Health Research

NIHR BIOMEDICAL RESEARCH UNITS

Annual Report 2009/10

Note: The accompanying *NIHR Biomedical Research Units – Guidance on Completion of Annual Reports for 2009/10 Financial Year* contains essential guidance on the information you need to provide when completing this proforma.

Please complete the form using a font size no smaller than 10 point (Arial). The completed form should be no longer than 10 pages in total.

1. UNIT DETAILS

Name of the NIHR Biomedical Research Unit:

Bristol Heart Institute Biomedical Research Unit

Name, job title, address, email and telephone number of an individual to whom any queries on this Annual Report will be referred:

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2. DECLARATIONS AND SIGNATURES

Name and address of the NHS Organisation administering the NIHR Biomedical Research Unit award:

University Hospitals Bristol NHS Foundation Trust (UH Bristol), Trust Headquarters, Marlborough Street, Bristol, BS1 3NU

Name of the Chief Executive of the NHS organisation:

Mr Robert Woolley

I hereby confirm, as Chief Executive of the NHS organisation administering the NIHR Biomedical Research Unit award, that this Annual Report has been completed in accordance with the guidance issued by the Department of Health and provides an accurate representation of the activities of the NIHR Biomedical Research Unit:

Signature of Chief Executive: …….. Date: ……

3. PROGRESS REPORT

Please provide a progress report for your NIHR Biomedical Research Unit for the 2009/10 financial year, describing any changes to the strategy for your Unit and any highlights of patient- and people- focused translational clinical research activity supported by the NIHR Biomedical Research Unit award:

Changes to the strategy

The benefits of the BRU are now beginning to demonstrate robust impacts in 2009-10. These impacts are becoming evident in the infrastructure available to the BRU (new staff in post, the MRI scanner commissioned and being used for BRU projects), new projects being developed and older projects being brought to successful conclusions and being published. The UH Bristol and the University of Bristol have strengthened their partnership through excellent communication between the Clinical Trials and Evaluation Unit (CTEU, University) and the UHBristol's Research and Innovation Department (R&I) and the very recent appointment of a full-time senior manager for both the BRU and the wider research remit of the CTEU. The hard work invested in writing contracts between the partners has, as anticipated, benefited other collaborations such as an NIHR programme grant on blood conservation and, conversely, contracts required for clinical research where funding has been awarded to the University.

The UH Bristol and the University of Bristol are founder partners in the Bristol Research and Innovation Group for Health (BRIG-H). This group is a vibrant and ambitious Bristol-wide strategic research and innovation partnership. It is dedicated to fostering excellence in people and infrastructure to realise the full potential of research and innovation to benefit patient health. Cardiovascular research is a key theme within BRIG-H. In addition, one of the work streams for BRIG-H is to develop systems and processes to provide seamless support to researchers around grant applications and regulatory approval applications. The work of the partners in setting up the BRU has been invaluable in informing the priorities for this work.

We have made good progress with the projects described in our original BRU application. We have successfully substituted a new theme relating to cardiac anaesthesia and critical care for the original theme 3 (which became non-viable with the move of Prof Zacharowski back to Germany), involving the initiation of one project and the adoption of two others (one externally funded). Table 1 provides an update on the projects described within our bid, with the additional three projects substituted for theme 3. We have eight projects actively recruiting and we expect to open another two to recruitment in 2010-11.

Table 1. Progress of BRU projects referenced within the bid

Bid ref.	Title	Progress
Protecting the heart and the patient during cardiac surgery		
1a	A single-centre randomised controlled trial of propofol cardioplegia on blood myocardial biomarkers of stress and injury of patients having isolated coronary artery bypass grafting (CABG) and heart valve surgery. (ProMPT)	All approvals are now in place. There was initial concern from the UHBristol pharmacy about the stability of propofol, which was assuaged by tests carried out independently by Cardiff University. Two patients were recruited before 31 Mar and 15 since.
1b	A prospective randomised study comparing normoxic vs. standard cardiopulmonary bypass in cyanotic children undergoing congenital cardiac surgery. (OXIC 2)	Project open and recruiting. Recruitment was completed in 2009-10 for the genomic and biomarker outcomes and continues for clinical outcomes. One paper on gene expression analysis in relation to the presence of cyanosis has been published, one has been submitted and one is in preparation.
1c	Shortening cardioplegic arrest time during combined coronary and valvular surgery (SCAT): a single centre randomised controlled trial	Staff in place. Project open and recruiting. 21 patients recruited in 09/10.
1d	A randomised controlled trial of median sternotomy vs. anterolateral left thoracotomy on morbidity and healthcare resource use in patients having off-pump coronary artery bypass surgery (SteT)	Staff in place. Recruitment completed in Sep 2009, with follow-up to one year after surgery continuing. Analyses of the data up to 3 months after surgery are almost complete and a manuscript has been drafted for publication.

Interventions to prevent vein graft failure		
2a	A randomised controlled trial to assess the extent of intimal hyperplasia and atherogenesis in bypass vein grafts following different surgical preparation (HArVeST)	All approvals are now in place. Approving information for patients about radiological exposure caused a delay but 3 patients were recruited before 31 Mar and 11 since.
2b	Effect of once daily folic acid on vein graft thickening and oxidative stress in diabetic patients undergoing coronary artery bypass graft surgery	This trial is still in development (draft protocol). Recruiting patients sufficiently far ahead of their surgery to provide the intervention is challenging. The primary outcome measure is intravascular ultrasound (as for project 2a). Both MHRA and REC are still required.
Interventions to improve anaesthetic and critical care for patients having cardiac surgery		
3a	Pulmonary protection with low frequency ventilation during cardiopulmonary bypass: a randomised trial	REC application reviewed, feedback received, response being drafted. Application for external funding in preparation but the funder advised that pilot data are required. This experience emphasises the importance of the BRU for 'seed corn' funding.
3b	Preoperative volume replacement vs. usual care in diabetic patients having CABG surgery: a RCT	Externally funded project for which REC and MHRA approvals were sought in 2009-10. First patient just recruited.
3c	Effects of epidural anaesthesia on inflammatory and stress responses, myocardial cell damage and clinical outcomes in patients undergoing beating heart coronary surgery: a prospective randomised trial	Originally BHF-funded project but recruited slowly for longer than planned. In 2009-10, analyses of data and submission of manuscript have been expedited by BRU infrastructure/funding. Manuscript now accepted for publication.
Therapeutic Angiogenesis and stem cell research		
4a	Relating progenitor cell number and function to Diabetes Mellitus	Staff in place. All approvals in place and recruiting. Three patients were recruited before 31 Mar and 10 since. Analyses on blood samples are extremely time consuming, approx 24 hours per patient and day 0 and 4 sampling severely limits the time window for recruitment.
4b	Bone-marrow derived stem cell transplantation in patients undergoing left ventricular restoration surgery for dilated ischaemic end-stage heart failure: a pilot randomised controlled trial. (TRANSACT II)	Because of delays since receiving REC approval, required re-review for confirmation of sponsorship (agreed Nov 09). Two REC amendments required for changes in protocol. There was no recruitment in 2009-10 but the first patient was recruited in May 10.
Autonomic function in children undergoing cardiac surgery		
5a	Coarctation of the aorta and hypertension: a prospective longitudinal cohort evaluation of autonomic and vascular influences on blood pressure control	Staff in place. Project open and recruiting. 45 patients recruited in 08/09. First paper published by Hypertension. Second paper accepted (published Aug 10) by Annals of Thoracic Surgery.
Vulnerable atherosclerotic plaques		
6a	Relating novel plasma and plaque biomarkers derived from the adverse macrophage gene profile to the prevalence of vulnerable atherosclerosis characterised by carotid and coronary MRI/MS-CT	'Recruiting' atherosclerotic plaque samples from 2 sources; coronary samples from cadavers in Bristol; carotid samples from Dutch biobank of endarterectomy patients having clinical follow-up. Hence, 2 projects: (a) cross sectional analysis of biomarkers and plaque characteristics in cadaver samples and (b) nested case control study in Dutch biobank cohort, comparing plaque samples among patients who have had a cardiovascular event during follow-up or not.

Changes to the strategy

We consider that there have been five major changes in strategy during 2009-10.

1. We have successfully recruited Dr Chiara Buchiarelli-Ducci to the advertised consultant senior lecturer post in cardiac magnetic resonance imaging (CMR). (Unfortunately, because of a serious injury, she was unable to take up the post until April 2010.) Dr Buchiarelli-Ducci previously worked at the Brompton Hospital, with Prof Dudley Pennell, which has created a natural link between our two BRUs and provides the opportunity for fruitful collaborations. Not only has Dr Buchiarelli-Ducci been trained in the protocols used at the Brompton, but the MRI scanners at both sites are identical. As well as working to support existing BRU projects that involve CMR, Dr Buchiarelli-Ducci is developing her own research portfolio. Consequently, in our activity and outputs proforma, we have added a seventh 'theme', namely research on CMR as an investigational tool in its own right.
2. The link with the Brompton with respect to CMR is just one aspect of a wider strategic collaboration that Prof Angelini negotiated in 2009-10. He has taken up the position of Clinical Chair of Cardiothoracic Surgery and Head of Cardiac Surgery at Imperial College, Hammersmith Hospital, and divides his clinical and research time between both sites. Senior Members of the Bristol Heart Institute have also been given honorary status at Imperial College London. The Hammersmith and Brompton hospitals are closely linked with respect to CMR and other aspects of their clinical services. The attraction of this collaboration is three-fold: (a) a larger pool of patients from which to recruit to translational cardiovascular research studies (about 2,500 surgical patients per year), (b) a more ethnically diverse patient population (important for studies of patients with diabetes, a frequent comorbidity among patients with cardiovascular disease) and (c) the opportunity to deploy our BRU infrastructure to translate innovative basic science at the Hammersmith into the clinical arena.
3. The third change in strategy is the substitution of theme 3. As is evident from the adoption of two existing projects under this theme, research to improve cardiac anaesthesia and critical care has been part of our portfolio for some time. Establishing this new theme will embrace our anaesthetic colleagues and facilitate collaborations. The PROTECTION trial of low frequency ventilation during cardiac surgery with cardiopulmonary bypass (CPB), led by Prof Ascione, will start recruiting in the next 3 months. This trial represents the kind of innovation that we expect to emerge from this theme.
4. The BRU infrastructure is facilitating the realisation of our potential for cardiovascular research in cardiology. This is happening for 3 reasons. First, initiation of and recruitment to the ProMIS project (4a in Table 1) has brought about a better understanding of the logistical problems that cardiologists face when doing research, especially in the context of primary percutaneous coronary intervention (PPCI). Second, the fact that Dr Buchiarelli-Ducci is a cardiologist has already (within 4 months) helped to promote research interest among her colleagues. Thirdly, on-going research initially outside the BRU has brought together an academic haematologist, Dr Mumford, with two of our cardiologists (Dr Baumbach & Dr Johnson) to study platelet activity in patients having PPCI. Understanding platelet activity is essential for optimising anti-thrombotic protection for patients during PPCI and in ensuring the long term benefits of PPCI. Therefore, platelet activity during PPCI has been added as a new theme (8). The potential for research on PPCI is high because of the large volume of patients treated in Bristol; UHBristol has recently joined a commercially-sponsored trial of coated versus bare-metal stents (COMFORTABLE) and has been the fastest recruiting site in the UK over the last 3 months.
5. The final change in strategy is also about the creation of a new theme, namely inflammatory markers in cardiac surgery. The theme has emerged from genomic research funded by the BRU (see examples of the value added by the BRU) and from early discussions between basic scientists at the Hammersmith and BRU researchers (showing, we believe, the future fruitfulness of this collaboration). The Hammersmith has a team of researchers with a special interest in inflammatory markers; the BRU includes several clinical projects researching interventions to reduce inflammation during cardiac surgery (theme 1). It has always been challenging to identify outcomes for the clinical projects which are sensitive and objective (required in order to avoid 'detection bias' since researchers and study participants often cannot be blinded to random allocation).

Significant developments

Within the various BRU themes, there have been a number of significant developments.

1. Theme 1: During 2009-10 we have been discussing an exciting new project with a commercial partner, Antipodean Pharmaceuticals (based in New Zealand). This company has a product, mitoquinone (MitoQ) which is hypothesised to reduce the oxidative stress (arising from ischaemia reperfusion injury) that damages mitochondria in myocytes during cardiac surgery. This collaboration is currently on-hold, subject to Antipodean raising venture capital for the project. In this theme, Mr Caputo is also carrying out early phase evaluation, gaining experience in a small case series, on a new intervention for paediatric cardiac surgery, namely using warm blood cardioplegia to reduce ischaemia reperfusion injury. This idea is a natural extension to children of our pioneering research on warm blood cardioplegia in adults (see 4 below).

2. Theme 3: There is great excitement about the PROTECTION trial which will soon start recruiting. This excitement arises from the promising results in our pre-clinical pig model of CPB, the simplicity of the intervention and interest in its wider potential applicability in paediatric cardiac surgery. The latter interest will be pursued if the findings from the PROTECTION trial show similar promise to the pre-clinical pig model. This development elegantly illustrates the seamless nature of translation in our BRU from pre-clinical to clinical research. A new development in 2010-11 is a joint project between the Hammersmith and the BRU on remote pre-conditioning in patients having coronary artery bypass surgery. Study participants will be recruited at the Hammersmith and myocardial biopsies will be analysed by Prof Suleiman's laboratory in the BRU. None of these projects are recorded in the 2009-10 activity and outputs proforma since they are not formally designated as 'initiated'.
3. Theme 7: Dr Buchiarelli-Ducci is rapidly formulating her plans for CMR research, which will be the foundation for external funding applications. Two main areas are emerging: (a) investigation of how CMR is being used, and informs clinical decision-making, by cardiologists; (b) investigation how CMR can be used as a diagnostic or prognostic tool in the clinical follow-up of children having cardiac surgery to correct congenital defects. These areas are important for the NHS and patients. CMR is an expensive investigation which is being requested with increasing frequency by cardiologists, largely depending on its availability; however, little is known about the characteristics of patients that cause the cardiologists to request CMR, whether cardiologists use CMR results to inform their clinical management of the patients (and, if yes, how) and whether having CMR improves health outcomes. Advances in paediatric cardiac surgery now mean that most children with congenital heart defects reach adulthood but experience progressive morbidity; CMR may provide an important tool for prognosis or for improving post-operative clinical management. A clinical research fellow is being appointed to work with Dr Buchiarelli-Ducci on these research areas and we are considering investing in a PhD studentship as well. Dr Buchiarelli-Ducci has also recently been appointed as the Clinical Director of the partnership's new Clinical Research Imaging Centre, which has a new 3T MRI scanner. This facility will also be available to the BRU for selected projects and for collaborations with the Brompton (which has a similar scanner).
4. Theme 8: A new project is being developed to investigate platelet activity during PPCI (with Dr Tom Johnson, cardiologist; Dr Andrew Mumford, haematologist). The project involves using point of care technology to describe changes in platelet activation over time in patients presenting with heart attacks, from arrival at the hospital ('door' time), through the PPCI procedure ('balloon' time) to recovery over the next 24 hours. The research will investigate how well new treatment guidelines safeguard patients against stent thrombosis. The project interfaces well with existing research of Dr Mumford's on platelet activity immediately before and after cardiac surgery (NIHR programme grant).
5. Theme 9: The aim of the interventions investigated under themes 1 and 3 is almost uniformly to reduce the iatrogenic harm that arises during cardiac surgery. With existing markers, and recently with genomics (see examples of added value), it is clear that the inflammatory response is a key part of this harm. In collaboration with basic science researchers at the Hammersmith, we will investigate new and potentially more sensitive biomarkers of inflammation. Our aim is to investigate the feasibility of developing an objective, biomarker-based, outcome measure representing physiological recovery from the iatrogenic harm of surgery / fit for discharge. This is a research area that would be extremely amenable to a PhD studentship, which we will try to recruit to in 2010-11.
6. Collaboration in the wider UK research effort: We have recently started to collaborate with British Heart Foundation Prof Shoumo Bhattacharya, in Oxford. Prof Bhattacharya has been trying to establish a biobank to investigate the genetics of congenital cardiac defects. This project has been struggling because of the difficulty of obtaining tissue samples for genotyping, especially with the cessation of paediatric cardiac surgery in Oxford. UHBristol is now a high volume paediatric cardiac surgery centre and, subject to consent, is now routinely contributing anonymised tissue samples to Prof Bhattacharya's biobank, with supporting clinical data and outcomes; since the collaboration started, we have consented over 100 families, obtained tissue samples and sent the samples to Oxford. We hope that this collaboration may also be beneficial to our research using genomics and that our example will persuade other centres who adopt our clinical database to join the collaboration.

Highlights of PPI translational clinical research activity supported by the BRU in 2009-2010

Professor Reeves and other CTEU staff have attended local (University of West of England) and national workshops, the latter specifically in a translational context (John Radcliffe Hospital Oxford, Oct 09 and Guy's Hospital London, Apr 2010). These latter workshops have prompted us to consider carefully the various ways in which patients and the public truly participate in research to improve its design, conduct and dissemination and which are most appropriate for the 'early phase' projects that mainly make up the BRU portfolio.

The content of the workshops made us aware of the limitations of the RAG with respect to PPI and we have formed another group consisting of patients who have participated in one of our previous trials. About 40 patients have expressed an interest in contributing to the group. We are extremely excited by this initiative and describe in more detail in section 5 the ways in which we believe patients can improve our research.

Examples of effective translation or significant progress

In describing examples below, details are only described if not described elsewhere (cross-referenced to relevant section).

1. The findings of the trial of epidural anaesthesia as an adjunct to general anaesthesia during coronary artery bypass surgery on the beating heart surgery suggest important benefits from this technique to patients and the NHS (substituted project 3c). We use this trial as an example of value added and describe the significance of the findings and their implications in more detail in that part of the reporting process.
2. The findings of our genomic research on gene activation in on and off-pump CABG in adults, and in children with congenital heart defects both before and after surgery, represent a vivid example of translation (project 1b). Gene activation can be seen as an outcome measure in its own right in 'early phase' research (conventional translation) and as a tool to demonstrate the mechanisms that are likely to explain more tangible clinical effects ('reverse' translation, feeding back into the design of new innovations). Again, we use this as an example of value added and describe it in more detail in that part of the reporting process.
3. Completion of recruitment to the SteT trial (project 1d) represents significant progress. Although follow-up to one year continues, and the analysis of outcomes at 3 months are not yet complete, it is clear that the left anterolateral thoracotomy approach is safe and represents an important innovation for cardiac surgeons. Again, we use this as an example of value added (see that part of the reporting process for more details).
4. Publication of recent research on angiogenesis in Circulation this April represents significant progress in translation.[Campagnolo et al., 20110] With support of the BHF, and a 25% contribution from the BRU, we succeeded in extracting and expanding human pericyte progenitor cells from saphenous vein leftovers of patients undergoing CABG surgery. We demonstrated that patients' perycites are superior to endothelial progenitor cells from young healthy individuals in supporting vascular regeneration in a mouse model of limb ischaemia. Now, we propose to investigate if transplantation of pericytes alone or in combination with human cardiac progenitor cells obtained from the right atrial appendix (CPCs) could improve post-MI recovery. This example demonstrates the integrated nature of our clinical and pre-clinical research.
5. Theme 5, investigating changes in cardiac baroreceptor, autonomic function and vascular stiffness in children with coarctation of the aorta over time (from presentation, through corrective surgery to adulthood), have successfully described the association between these changes and the development of hypertension in affected children significant. These findings have implications for monitoring progression and optimising therapeutic interventions in the future with respect to the choice of hypothensive agents.
6. Research on samples of atherosclerotic plaque (theme 6) has found that MMP-12 and -14 positive foam cells are highly over-represented, and TIMP-3 positive macrophages are highly under-represented, in vulnerable compared to the stable plaques. MMP-14 correlates and co-localises with markers of classical macrophage activation and TIMP-3 with markers of alternative macrophage activation in carotid and coronary plaques and in isolated human macrophages in culture. Three papers describing this work are being prepared for publication.
7. Important statistical research, relevant to all themes investigating biomarkers, has explored ways to optimise these laboratory measurements in order to minimise 'noise' and maximise statistical power. Biomarker measurements may sometimes be missing (e.g. at one of multiple time points for an individual subject, or at baseline), below or above the limit of quantification by an assay, and are rarely provided to the analyst with information about calibration. We have found that modern statistical methods for interpolation, and for taking information about calibration into account, better utilises the information available and may change the conclusions of the analysis. Two papers describing this work are being prepared for publication.

Initiation of new research projects of areas of research

Initiation of new research projects and themes has been covered under 'significant developments' above. In summary:

1. We have substituted one theme (theme 3: Interventions to improve anaesthetic and critical care for patients having cardiac surgery) and added three new themes to the BRU, namely (a) cardiac imaging, (b) platelet activation in the management cardiovascular disease and (c) development of

novel and sensitive inflammatory markers.
2. Three projects, one new and two existing, have been adopted under the new theme 3. These projects are, or have, evaluated epidural anaesthesia, pre-operative volume replacement and low frequency ventilation in patients having cardiac surgery. An additional project on remote pre-conditioning, is also being included under this theme from 2010-11.
3. Two main areas of research are being developed under the cardiac imaging theme, namely investigation of how CMR is being used/informs clinical decision-making by cardiologists; and how CMR can be used as a diagnostic or prognostic tool in children having cardiac surgery.
4. One new project is being initiated under the platelet activation theme, point of care platelet activity measurement in primary PCI.
5. New inflammatory biomarkers will be investigated alongside existing biomarkers in some of the existing projects.

Major new grants
We have had four major new grants awarded during 2009-10. Two are BHF programme grants (themes 6 and 8) and one is an MRC project grant (theme 4).

Prof Suleiman and Prof Halestrap have been awarded a BHF programme grant for the period 2009-2014 on "The role of mitochondria in the life and death of the heart" (£834,066). Although some the research undertaken with this grant will use pre-clinical models, as well as human tissue, it will fund the basic science that is likely to underpin future innovations that will be translated under theme 1.

Prof Newby has been awarded a BHF programme grant for the period 2009-2014 on "Vulnerable atherosclerotic plaques, foam cell phenotypes and extracellular proteinases" (£714,569). This will allow the excellent basic science research of Prof Newby's laboratory (usually using human tissue samples) on factors contributing to the instability of atherosclerotic plaque to progress.

In collaboration with a consortium (Universities of Bristol, Birmingham and Sheffield), Dr Mumford has been awarded a BHF programme grant on "Mapping and functional investigation of genetic mutations in patients with mild platelet bleeding disorders" (£1,369,073). This project seeks to identify novel proteins that mediate the platelet activation response and which are, therefore, pertinent to the pathogenesis of atherothrombotic cardiovascular disease. This award has enabled a new platelet research laboratory to be established at the Bristol Heart Institute that works in close partnership with our existing laboratories performing research within theme 6.

Prof Madeddu has been awarded a MRC project grant on "Function based enrichment of pro-angiogenic cells for cardiac repair" (£299,620). This grant aims to investigate methods for expanding populations of human progenitor cells, obtained from bone marrow of patients and surplus to requirements in an existing BHF-funded trial led by Prof Ascione, with a view to applying such methods for producing viable angiogenic therapies.

Examples of the creation of, or the addition of significant value to, intellectual assets
The nature of our research portfolio, based mainly on simple clinical interventions, does not lend itself to the creation or addition of significant value to intellectual assets. No patent applications have been filed or granted in 2009-10.

4. IMPACT ON HEALTHCARE PROVISION

Please provide descriptions of impacts/benefits to patients arising from translational clinical research undertaken by the partnership. You should provide examples of impacts that the Unit's research has had on health services or health policy, detailing how research findings have led to changes in the way services are delivered to patients, both locally and further afield:

Contributions to NICE guidance, etc.
Our research on the effects of the off-pump (or beating heart, OPCAB) method for doing coronary artery bypass surgery, published over the last 10 years, has been cited in various forms of guidance:

- Interventional Procedure Guidance 35, National Institute for Health and Clinical Excellence
- Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP-S)

overview of OPCAB
- 2008 editorial in NHS evidence: http://www.library.nhs.uk/theatres/page.aspx?pagename=ED13
- Feb 2010 'Eyes on Evidence' in NHS Evidence: cites the CRISP trial (ongoing, hosted by Bristol CTEU) http://www.evidence.nhs.uk/aboutus/Documents/EoE10.pdf

Our research on the effects of transfusion (Murphy et al. Circulation, 2007; Reeves and Murphy, Current Opinions in Cardiology, 2008; NIHR HTA CET project grant 06/402/94; NIHR programme grant RP-PG-0407-10384) have informed the deliberations of both national and international guidelines groups on blood transfusion through Mr Murphy's influential membership. Mr Murphy is negotiating various research proposals with the National Blood Service.

Evidence that has influenced National Service Frameworks
We are not aware of examples of our research influencing National Service Frameworks

Substantial, well-documented changes in practice or service delivery either locally, nationally or internationally
There are several examples of well-documented changes in practice or service delivery arising from our research. Most of these examples pre-date the formation of the NIHR and associated funding streams. Historically, our research has been funded mainly by two BHF chairs (Prof Angelini and Prof Newby), programme grants from the BHF and Garfield Weston Trust, and projects from NHS R&D, the BHF and other charitable sources.

One of the first examples was a randomised trial of angioplasty versus minimally invasive direct coronary artery bypass (MIDCAB) surgery (AMIST, funded by the NHS R&D HTA programme). MIDCAB involved a small left anterior thoracotomy which allowed revascularisation by direct visualisation of the left anterior descending coronary (LAD) artery with the left internal mammary artery on the beating heart. The trial did not reach its target sample size, largely because of cardiologists' unwillingness (cardiologists are the gate-keepers to cardiac surgery) to approach patients who they believed to be suitable for angioplasty. The trial has been important because it showed that operating on the beating heart was possible and gave surgeons in Bristol the confidence and experience to explore this avenue further. The limitations of MIDCAB, in allowing revascularisation only of the LAD, provided the direct impetus to develop OPCAB.

The development and evaluation of OPCAB is what the Bristol Heart Institute is best known for. As described above, our research on OPCAB, from small randomised trials on biomarkers for inflammation and cardiac injury, through to large trials with clinical outcomes, has been cited widely in several forms of guidance. OPCAB now accounts for 70-75% of all CABG operations carried out in Bristol and 15-20% in the UK, with 'hot spots' of high volume seeded by new consultants who trained in Bristol. OPCAB has been taken up more widely elsewhere in the world, notably India, China and other less developed countries in which the resources for cardiopulmonary bypass (CPB) are less available, and in Japan (whose surgeons are renowned for surgical innovation and technical surgical quality).

Alongside OPCAB, there were two other 'revolutions' in practice taking place in Bristol. Historically, when using CPB, usual practice was to cool systemically CABG patients during surgery and to use a cold crystalloid cardioplegia solution to stop the heart and protect it from ischaemia reperfusion injury. Detailed translational studies based on biomarkers and myocardial biopsies underpinned local changes first and, latterly, more widespread adoption of normothermia (almost universal adopted over the last 5-10 years) and warm blood cardioplegia (adopted less universally but used exclusively for CABG with CPB in Bristol). Similar studies have informed optimisation of cardioplegia for patients having valve surgery.

Biopsy studies have also underpinned parallel changes in cardioplegia to protect the heart for paediatric cardiac surgery. Importantly, these studies (and others) have shown that the heart undergoes maturational changes over time which may have implications for optimising the cardioplegia solution depending on the age of the child at the time of surgery. A shift from cold crystalloid to cold blood with 'hot short' cardioplegia has been adopted locally on the basis of the research. We are also beginning to gain experience using warm blood cardioplegia for paediatric cardiac surgery, which we intend to evaluate in a randomised trial (see section 3, significant developments, theme 1).

Prof Angelini's previous research on surgical preparation of saphenous vein graft has led to local adoption of a no touch technique and vein distention to check for side branch leaks with systemic pressure rather than using a syringe (avoiding the risk of high pressure damage to the media and endothelium). Continuing uncertainty around this intervention, and the possible benefit of harvesting vein with a fatty pedicle, has led directly to the HArVeST factorial randomised trial (project 2a in Table 1).

Finally, our research on the effects of blood transfusion in patients having cardiac surgery has been influential locally and (more patchily) elsewhere. The very act of auditing transfusion practice and quantifying associations with adverse outcomes in our observational database has brought about a clinical important reduction in the rate of transfusion locally over the last 2-3 years – ironically making it more difficult to recruit sites and participants to our HTA-funded TITRe2 trial which aims to answer, finally, the question of whether transfusion after cardiac surgery causes significant net harm to patients' health.

5. PATIENT AND PUBLIC INVOLVEMENT

Please provide specific examples of how patients and the public have been actively involved in the research undertaken within your Unit (*e.g.* in informing or developing strategy, identifying research priorities, participating in the research process itself), detailing the nature of their contribution and the impact this has made:

We have had a Research Awareness Group (RAG) for over 2 years. This group consists of members of the public who are stakeholders in the use of, or delivery of, healthcare and healthcare research and includes patients, those who commission or deliver healthcare services and those who fund healthcare research. The RAG met in 2009-2010 to consider the research proposals that constituted a full, application for a NIHR programme grant on strategies to improve health outcomes in patients with undiagnosed diabetes mellitus undergoing cardiac surgery. With the input and support of the RAG, the application was finalised and submitted but the programme grant was not awarded.

The workshops on PPI in translational research (cf. late phase, applied clinical research) discussed in depth the various ways in which patients and the public and can participate in research, for example:

- Designing information sheets and other materials for communicating with prospective study participants, especially during the process of invitation to join a study and obtaining informed consent.
- Helping to optimise the logistical arrangements around recruitment and participation with respect to their acceptability to prospective participants.
- Advising on appropriate methods of dissemination of research findings (in addition to conventional academic outputs).
- Providing their perspective on the choice of health outcomes assessed to quantify the effects of treatments and highlighting on aspects of patients' experiences which they consider to be important and which are neglected by researchers
- Discussing the strength of prospective participants' preferences for treatments and the extent to which these are well informed. If strong preferences are prevalent this will slow recruitment to a trial and may limit the applicability of its findings but preferences can be influenced by providing trustworthy information.

The content of the workshops made us aware of the limitations of the RAG with respect to PPI and, in the autumn of 2009, the CTEU decided to form another group consisting initially of patients who have participated in one of our previous trials. At present, these are only patients who have had CABG (not valve or combined valve and CABG) surgery although, when on-going trials that are recruiting patients having other types of cardiac surgery are completed, we intend to expand the membership. About 40 patients have expressed an interest in contributing to the group, some through face-to-face discussion groups and others through postal or telephone surveys. The inaugural face-to-face meeting will take place on 22 Sep 2010. This initial meeting will focus on the experiences of members of the group when they were actively taking part in research, their satisfaction with the information presented to them about the studies they were invited to join and will elicit comments from them about a draft patient information sheet for a new trial (project 3a in Table 1).

As described in our 2008-9 report, we have also made links with the recently funded, joint university (Universities of Bristol and the West of England) National Co-ordinating Centre for Public Engagement. Prof Reeves participated as a stakeholder in scoping study on how organisations can collaborate to improve public involvement carried out by Rosie Davies and David Evans (University of West of England), the findings of which were presented and discussed at a meeting in April 2010 (attended by 3 CTEU staff).

Prof Reeves has collaborated with Prof Ann Bowling and Dr Gene Rowe on the design and evaluation of a self completion questionnaire to assess patients' preferences for alternative treatments for angina. This research was motivated by evidence of inequity by age and gender in access to revascularisation procedures and unequal take-up of such procedures by ethnic background. The work involved developing

an information booklet about the advantages and disadvantages of medical, cardiological (angioplasty) and surgical treatments. The questionnaire then quantifies the strength of preferences by eliciting responses on 5-point Likert scales to standardised attitude statements developed from earlier qualitative interviews, e.g. "I'd have surgery if I could avoid being a burden on others in the long term." A paper describing use of the questionnaire in a general population was published in Mar 2010 but is not included in the appendix because it did not acknowledge our BRU. A further paper on the stability of patients' preferences over time has just been submitted for publication.

Please also describe how you keep patients and the public informed of the research being undertaken within your Unit:

During 2009-10 we have continued to disseminate the findings of our research in a newsletter to patients who have had previous cardiac surgery. This newsletter is enclosed with an annual questionnaire about their current health and major cardiovascular events they may have experienced in the last year.

6. LINKS WITH INDUSTRY

Please outline your Unit's progress in engaging with industry (pharma, biotech and devices) describing any significant successes and/or any challenges faced during 2009/10. Please also outline any strategic plans for increasing engagement with industry:

As hinted at in section 3, our research portfolio does not lend itself to the creation or enhancement of intellectual assets. We continue to participate in selected commercial studies, e.g. COMFORTABLE (see section 3, changes to strategy #4) and PARADIGM-HF (see section 7). With respect to cardiac surgery, we participate in commercial studies less often because of the number of investigator-led non-commercial studies we are currently recruiting to. We are now consistently inviting over 90% of all cardiac surgery patients to join at least one study, and over 50% to join a randomised trial; of eligible patients invited to join a study, over 80% consent for observational studies and about 45% consent for trials.

Our link with Antipodean Pharmaceuticals is different. This came about through academic links (a scientist working in the University of Cambridge and with Antipodean) involving Prof Suleiman. The hypothesised mode of action of MitoQ on the mitochondria inside myocytes fits perfectly with Prof Suleiman's research on the way in which ischaemia reperfusion injury is mediated by the effect of oxidative stress on mitochondrial pores. Consequently, we feel that this is truly collaboration. This project may yield intellectual assets or a financial interest but this is subject to on-going contractual negotiations.

Dr Chris Jackson is a basic scientist who collaborates with industry (most recently Astra Zeneca) to develop pre-clinical models of atherosclerosis and to use them to test novel therapeutic strategies.

7. USE OF NIHR CAPITAL INVESTMENT FUNDING

Please describe progress in procuring the capital assets funded via the NIHR Capital Investment Funding award(s) to your Unit, indicating which capital assets have been procured and which are not yet in place. Where capital assets have yet to be procured, please provide an explanation and an indicative timescale for procurement. There is no need to report on capital assets procured prior to 2009/10 which were described in previous Annual Reports:

During 2009-10 we have successfully procured, installed and commissioned both our Siemens 1.5T MRI scanner and the Vivid E9 3-D echocardiography equipment.

The MRI scanner is vital for original projects 4a and 4b, and is the basis for Dr Buchiarelli-Ducci's developing research on CMR (theme 7, see section 3, changes to strategy and significant developments). The business case for the scanner is based on mixed clinical and research use. It is important to emphasise that data obtained during both of types of use will contribute to Dr Buchiarelli-Ducci's research, since she is instituting standard protocols (identical to those in use at the Brompton Hospital) to be

implemented routinely. This initiative will create an important observational database, identical across two sites, which will be used to address questions about the characteristics of patients that cause the cardiologists to request CMR, how cardiologists use CMR results to inform their clinical management of the patients and whether having CMR improves health outcomes. The importance of the research use of the MRI scanner is self evident; MRI represents the primary outcome measure for projects 4a and 4b, and for another externally funded project. New projects using the scanner are currently being discussed.

The new Vivid E9 3-D echocardiography equipment is currently being used in two randomised trials. The first is the Randomised Ischaemic Mitral Evaluation (RIME; NCT00413998) Trial, funded by the NIHR-HTA, in which Bristol is a participating site. This multi-centre trial is coordinated from the Brompton Hospital and is comparing CABG alone or CABG plus mitral annuloplasty in patients with moderate functional ischaemic mitral regurgitation undergoing CABG. The second is the PARADIGM-HF commercial trial (sponsored by Novartis) which is comparing a new drug (LCZ696) with enalapril in patients with heart failure and reduced ejection fraction (<40%). A grant application is currently being written in collaboration with Prof Julian Paton (University of Bristol) to use the equipment to investigate ablation of the renal afferent nerve in patients with high sympathetic activation and hypertension. The hypothesis is that ablation will provide improved control of hypertension but the research is needed to document the effects on both vascular and heart function.

8. FORWARD LOOK

Please identify any significant developments (*e.g.* major research findings or planned initiatives) anticipated in 20010/11, particularly those that are likely to generate media interest:

We expect that 2010-11 will see the publication of the first results of two recent trials and the early results of Prof Newby's research on theme 6. The research carried out on OPCAB by Profs Angelini, Ascione and colleagues is being show-cased at the forthcoming event, "Changing Worlds: the Impact of University Research", on 13 October 2010. The objective of the event is to promote investment in universities by industry, the Innovation Fund, charitable and other non-governmental organisations. This event will present selected examples of the impact of research led by the Universities of Bristol, Southampton, Bath and Surrey to senior members of the Houses of Commons and Lords, industry representatives, policy makers and the media. Examples were selected by panels who undertook the 2008 Research Assessment Exercise (RAE), under the auspices of the Higher Education Funding Council for England (HEFCE).

We will prepare joint press releases, in combination with the UHBristol and University, when papers describing the findings of two of our recent trials, Epidural and 'SteT' (Sternotomy vs. Thoracotomy), are published. The Epidural trial found statistically significant reductions in the frequency of post-operative arrhythmias and the average duration of ventilation and post-operative hospital stay. We expect this paper to generate a debate with cardiac anaesthetists about whether these benefits are 'worth' the very small risk of a serious complication from epidural anaesthesia.

The results of the SteT trial up to 3 months follow-up are currently being written up and cannot be described here. However, anterior lateral thoracotomy represents such an innovative approach to OPCAB surgery that we expect the results to generate intense interest whatever the results. It is also unusual to evaluate a purely surgical innovation in a randomised trial at such an early stage in its development. As described in section 3, the trial has shown at the very least that the left anterolateral thoracotomy approach is a safe and, even if not more effective for first-time elective OPCAB, it represents an important new technique that can be used in technically difficult scenarios such as "re-do" CABG avoiding existing scar tissue. The expertise learnt in this trial may also be applicable to other innovative and less invasive techniques avoiding sternotomy, e.g. for aortic and mitral valve surgery.

This form, together with a completed *Activity, Outputs & Finances* proforma, a publication list for 2009/10, and any specific examples of the value of NIHR Biomedical Research Unit funding (using

the structured template provided) must be submitted, by email, no later than **midnight** on **Monday 16th August 2010** to Julian Hughes (julian.hughes@nihr-ccf.org.uk).

A signed copy of this report should be sent, as soon as possible after this date (and no later than Friday 27th August, 2010), to:

Dr Julian Hughes
NIHR Central Commissioning Facility
Grange House,
15, Church Street,
Twickenham TW1 3NL