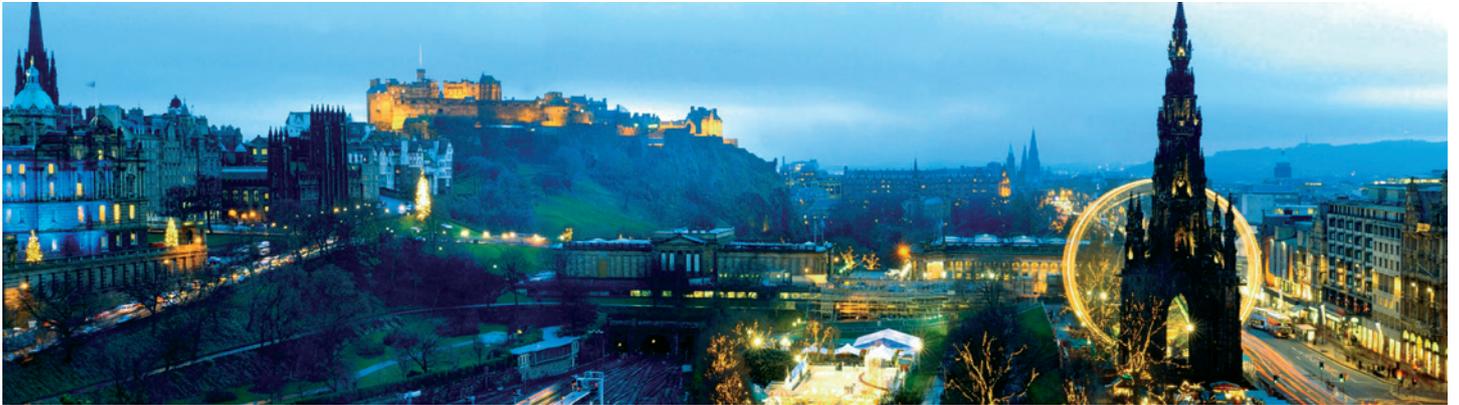




clinical
research
facility
EDINBURGH

August 2012



Delivering excellence
in clinical research



Key Milestones in the Development of Edinburgh's Clinical Research Facilities

- **1997** Edinburgh awarded Millennial Funding to develop Wellcome Trust Clinical Research Facility (WTCRF)
- **1998** Pilot Facility opened at Western General Hospital (WGH) and Satellite Facility opened in Royal Infirmary Edinburgh (RIE)
- **2001** Official Opening of WTCRF by HM Queen Elizabeth II
- **2003** Launch of WTCRF Education Programme
- **2003** Sister Facility (RIECRF) opened in New Royal Infirmary of Edinburgh
- **2005** Scottish Clinical Research Facilities Network Inaugural Meeting
- **2006** Launch of Academic and Clinical Central Office for Research and Development (ACCORD) supporting joint working between NHS Lothian and University of Edinburgh (UoE)
- **2006** SHEFC Brain Imaging Research Centre (now Brain Research Imaging Centre – BRIC) integrates with WTCRF to form Imaging Core
- **2006** Paediatric CRF Service launched with appointment of Scottish Medicines for Children Network (ScotMCN) Research Nurse
- **2006** NHS Education Scotland (NES) funds nationalisation of WTCRF Education Programme
- **2006** Clinical Research Infrastructure Award for Clinical Research Imaging Centre (CRIC) under Directorship of Professor Newby
- **2006** Translational Medicine Research Collaboration (TMRC) established with Wyeth Pharmaceutical Co
- **2007** Community Research Nurse Service initiated
- **2007** Launch of Scottish Imaging Network a Platform for Scientific Excellence (SINAPSE)
- **2008** UK Clinical Research Facilities (UKCRF) Network officially launched
- **2008** Edinburgh hosts the 4th Annual UKCRF Network Conference
- **2008** Edinburgh CRF Director Professor Newby appointed Director of R&D for NHS Lothian
- **2009** First WTCRF Public Open Day
- **2009** Paediatric CRF opened in Royal Hospital for Sick Children (RHSC)
- **2009** Launch of the Scottish Academic Health Sciences Collaboration (SAHSC) – now known as Health Science Scotland
- **2010** CRF Mass Spectrometry Core receives £750,000 Wellcome Trust equipment award for major new investment
- **2010** Official opening of the CRIC by HRH Prince Phillip, Chancellor of the University of Edinburgh
- **2011** Edinburgh CRF becomes the first non-commercial unit in the UK to achieve supplementary Phase I accreditation with the MHRA
- **2011** Neurology Research Nurse appointed in collaboration with the Anne Rowling Regenerative Neurology Clinic
- **2011** Investigational Supplies Group (ISG) established to provide GMP compliant investigational products for studies conducted within UoE and NHS Lothian
- **2011** Edinburgh CRF celebrates its 10th Anniversary
- **2012** Trial of Gene Therapy in Cystic Fibrosis starts in the purpose built suite in the WTCRF

Introduction

2011 marked ten years since the Wellcome Trust Clinical Research Facility (WTCRF) was opened by HM Queen Elizabeth II. We celebrated this important anniversary with a special event to showcase scientific highlights and major initiatives from our first decade. Key stakeholders joined us for a day of presentations that illustrated the range and quality of clinical research that we support in our facilities. The event provided a welcome opportunity to reflect on our many achievements to date and to outline our future plans.

Central to our achievements last year was our successful application for Phase I Accreditation with the Medicines and Healthcare products Regulatory Agency (MHRA). In July 2011 we became the first non-commercial clinical research centre in the UK to attain supplementary accreditation with the regulatory authority. This was a significant achievement for an academic centre and it has paved the way for other clinical research facilities to follow suit. Further details about our accreditation status and associated developments are outlined later in this brochure.

In addition to our accreditation endeavours and 10th anniversary celebrations, regular business continued apace across all areas of the CRF. We supported over 350 projects during the year and received 159 new applications to access our resources. We tracked an impressive haul of 197 publications from studies that were conducted through the CRF and we enjoyed another consecutive increase in the number of unique investigators using our facilities. All of our activity data are managed using CRFManager™, the information management system that was developed by our IT team. As described later, CRFManager™ has been adopted by colleagues throughout the UK and our team continues to develop it in line with local and national reporting priorities.

A notable milestone worthy of special mention, is the commencement of patient dosing in a pioneering clinical trial of cystic fibrosis transmembrane receptor (CFTR) gene therapy.

A key development in 2011 was the creation of pressure controlled dosing cubicles for this trial and we are pleased to report that the first patient was dosed on the 19th of June 2012. As reported last year, researchers in Edinburgh are part of the UK CF Gene Therapy Consortium, a team comprising investigators from Imperial College London, the University of Edinburgh and the University of Oxford. In 2011, the consortium won two prestigious Medical Futures Innovation Awards for this programme of research: the Best Therapeutic Innovation (Respiratory) and the MRC Translational Research Award. Following detailed project planning and significant structural modifications to the WTCRF building, we are delighted to support the research team as they embark upon this important study.

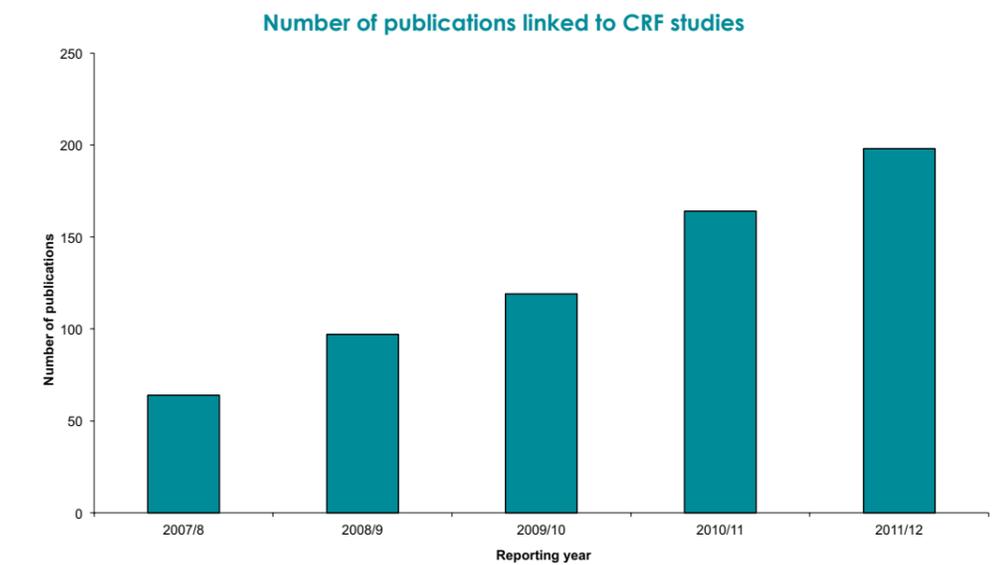
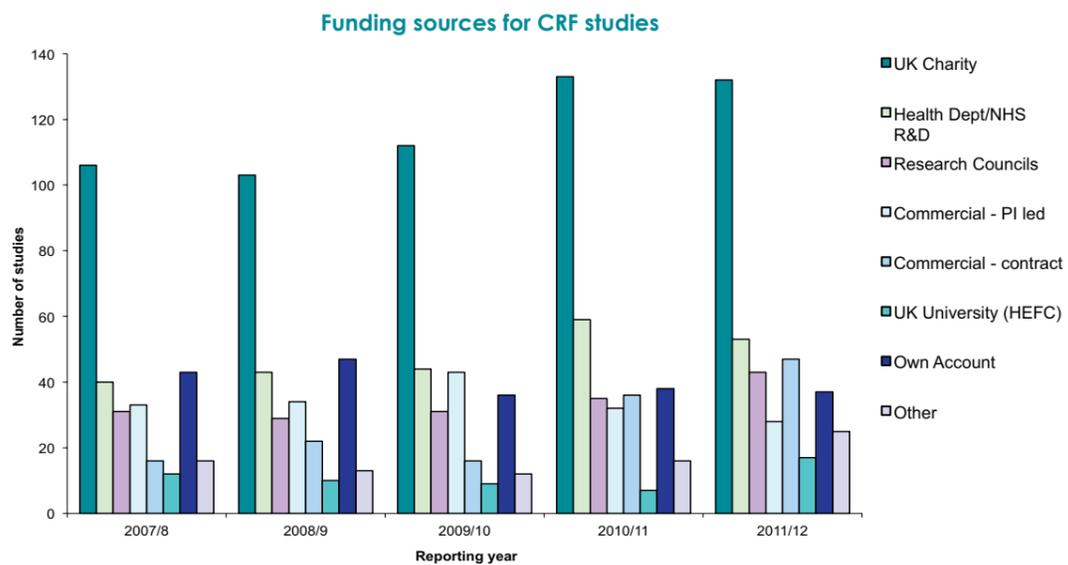
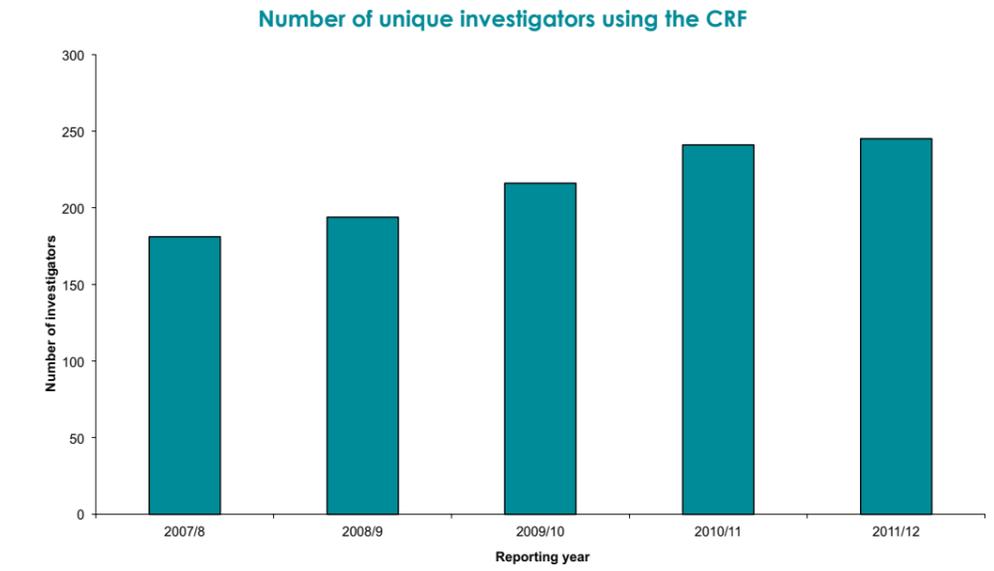
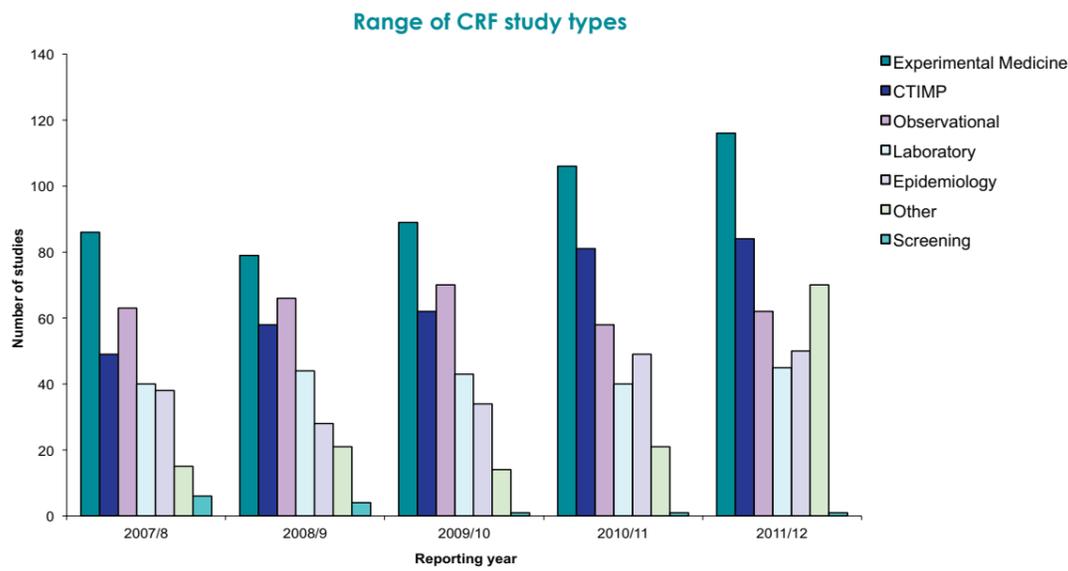
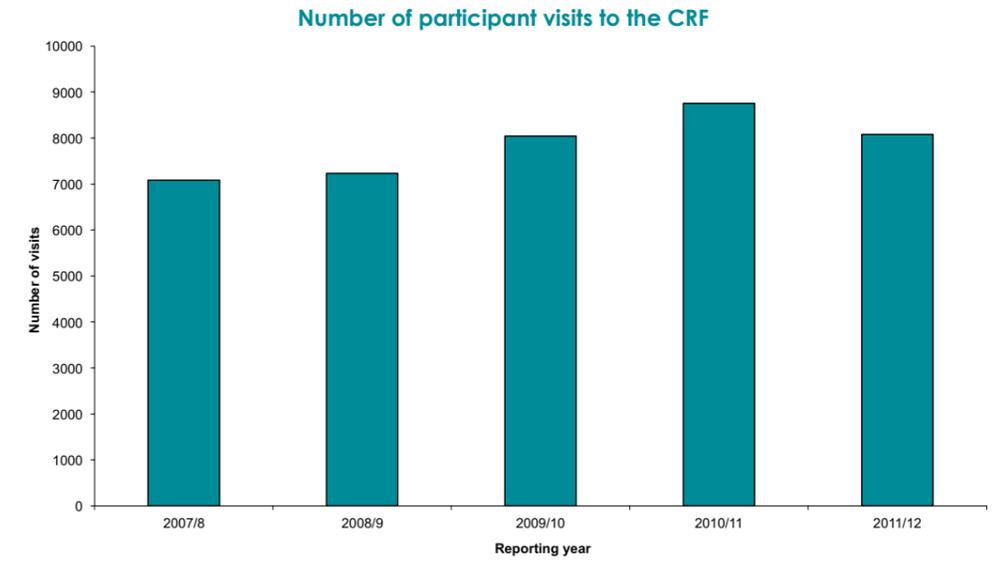
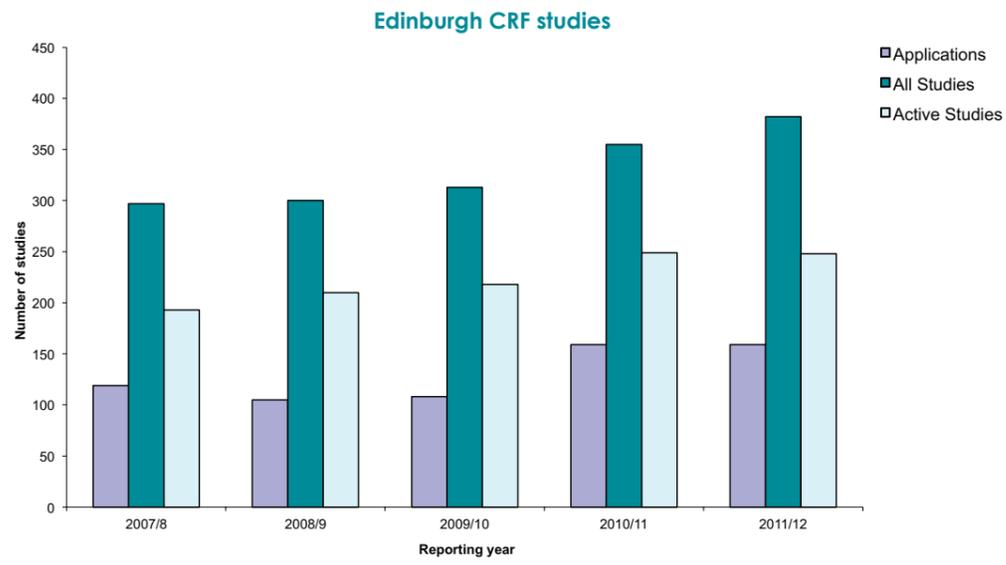
Our annual brochure provides an overview of the past 12 months in Edinburgh CRF. It has been another exceptionally busy year and our team is to be commended for their energy, innovation and dedication. Our specialist Core areas provide supporting detail to highlight developments and advances within their services. We hope that you will enjoy reading about key projects and publications that we have supported. We feature articles from three of our investigators, describing how they have benefited from conducting their studies through the CRF. Please enjoy this publication and feel free to contact our team if you would like further information.

We look forward to hearing from you!



THE UNIVERSITY OF EDINBURGH





Key projects and initiatives from Edinburgh's Clinical Research Facilities

First Academic CRF in the UK to achieve Supplementary Phase I Accreditation *Fiona McArdle*

On the 4th of July 2011 Edinburgh Clinical Research Facility became the first non-commercial clinical research centre in the UK to be awarded supplementary Phase I Accreditation with the Medicines and Healthcare products Regulatory Agency (MHRA). During the course of our accreditation we worked closely with the MHRA to demonstrate the key differences between commercial research units and academic Clinical Research Facilities (CRFs). A major difference between commercial units and academic units is the level of clinical pharmacology training that Principal Investigators have undertaken. PIs in academic CRFs rarely possess the post graduate qualification in clinical pharmacology that is currently required by the MHRA Phase I Accreditation Scheme.



Certificate of supplementary Phase I accreditation with the MHRA

To address inconsistencies in clinical pharmacology training among our PIs we established a Phase I / First in Human (FIH) Study Review Committee (PISRC) to assess all Phase I and FIH studies that are undertaken in our CRF. The PISRC comprises an expert panel of clinical pharmacologists, senior researchers, pharmacists, statisticians, research managers and quality management staff. The committee provides scientific review, robust risk assessment and ongoing mentorship for PIs who are conducting these early phase trials. To complement the PISRC support and optimise training opportunities for our researchers, we have also introduced an intensive Translational Pharmacology course to our education programme. This short course is being developed into a module for a new online MSc in Clinical Trials that we are launching in September 2013.

Edinburgh's Phase I / FIH Study Review Committee model has been recognised as an important quality management system to underpin the conduct of early phase experimental medicine studies and it is being adopted by other CRFs across the UK. The MHRA has acknowledged the strengths of the PISRC structure and is considering how the model might be integrated within a revised Phase I Accreditation Scheme. As the first academic facility to achieve accreditation status, we have worked proactively with colleagues in other CRFs to share our experience and to provide advice on preparing for Phase I inspection. In November 2011, we delivered a workshop for prospective accreditation applicants within the UKCRF Network and we disseminated key documents that we have developed to comply with the accreditation criteria.

Our Phase I Accreditation status has stimulated a lot of interest from commercial organisations and academic research teams alike. Given our firm integration within Edinburgh's acute hospitals, we are particularly well positioned to support first into patient trials as well as healthy volunteer studies. We enjoy firm links with senior investigators from a broad range of clinical specialties and our close longstanding partnership with the Academic & Clinical Central Office for Research and Development (ACCORD) supports the efficient delivery of world class scientific outputs. Please contact us if you would like to discuss placing a trial in Edinburgh CRF.



Poster presentation at 2012 UK CRF Network Conference

The Genetics of Influenza Susceptibility *Professor Tim Walsh*

Influenza is a major threat to human health. During most seasons influenza affects many people, but only results in severe illness in the elderly or those with significant co-morbidity. However, new influenza variants can cause life-threatening respiratory illness in young healthy individuals (Figure 1). This was the case for the 2009 H1N1 "swine flu" world pandemic. Recent estimates suggest 16-20 billion people worldwide were infected, of whom the majority had a mild illness or no symptoms. However, about 0.01% of previously healthy young people developed a severe life-threatening respiratory illness requiring intensive care admission. About 20% of these individuals died despite modern intensive care.

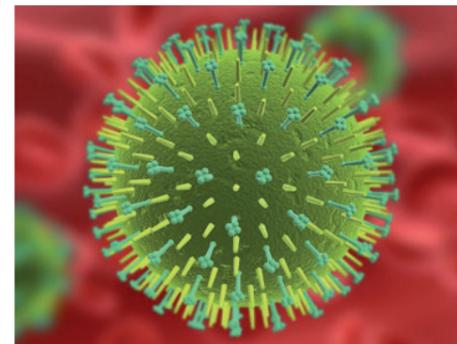


Figure 1: *The influenza virus*

It is highly likely that genetic factors determine why some individuals develop severe illness after influenza infection, because the virus was the same in these individuals and in those less severely affected. In 2009, a group of Lothian investigators realised that the "swine flu" pandemic was a unique opportunity to study this.

The Genetics of Influenza Susceptibility in Scotland (GenISIS) study was conceived in early September 2009 by Dr Ken Baillie at the Roslin Institute. Prof Tim Walsh took this to the Scottish Critical Care Trials Group meeting in late September, where the Scottish intensive care community supported it.

After informal contact with the Chief Scientist Office (CSO), an outline application for funding was submitted at the start of October, and after expedited peer review the CSO funded the project in early November.

With the help of the Lothian R&D office, who prioritised the research, full

ethics approval and R&D approvals were obtained from almost all of the Scottish R&D departments within 4 weeks. This remarkable performance resulted in a time from conceiving the project to recruiting the first patient of 2 months. The project ran alongside the Swine Flu Triage study (SwiFT), which the UK Department of Health commissioned ICNARC (the Intensive Care National Audit and Research Centre) to run in order to track the epidemiology of swine flu cases (Prof Walsh coordinated this for Scotland).

Scottish ICUs successfully obtained consent for almost all eligible patients in intensive care with swine flu to GenISIS after its initiation, and obtained blood samples for DNA. These were sent to the Genetics Core at the WTCRF where DNA was extracted and stored, together with clinical data collected in the SwiFT study. Between October 2009 and March 2011 96 previously healthy patients who required mechanical ventilation in ICU following H1N1 infection were recruited to GenISIS. Despite many others attempting similar studies, this was the largest genetics study of H1N1 undertaken worldwide.

The GenISIS investigators are collaborating with others to maximise the information that can be gained from their valuable resource. The first of these was work with scientists at the Wellcome Trust Sanger Institute, who were studying cell membrane proteins which were thought important in defending cells from a range of viruses, including influenza. In animal and cell studies one of these proteins, IFITM3, was found to profoundly affect the susceptibility to severe influenza. Scientists were able to study the DNA from patients in the GenISIS study and the MOSAIC study (an English study that obtained DNA from some cases) and compare them with DNA from the general population. Those patients who developed severe illness following H1N1 infection were more likely to have a genetic variant of the IFITM3 protein that was less effective at clearing influenza virus from cells.

This important research was published in the journal Nature, and will lead to further research to detect factors that may increase risk of life-threatening disease following influenza. It might also ultimately lead to new treatments. Without key collaborations between clinicians working at a national level, scientists, and the support from R&D departments that enabled this project to be set up so quickly this key discovery would not have been possible.

Tim Walsh, Professor of Critical Care, University of Edinburgh; Chair, Scottish Critical Care Trial Group
Ken Baillie, Wellcome Trust Research Training Fellow, Roslin Institute, University of Edinburgh

CRF Support used: Critical Care Research Nurses; Genetics Core

Key projects and initiatives from Edinburgh's Clinical Research Facilities

The Ring of Fire – imaging in heart disease *Dr Marc Dweck*

Aortic stenosis occurs when the aortic valve (the main outlet valve in the heart) becomes narrowed and it is the most common form of valve disease in the western world. Atherosclerosis is the process that leads to heart attacks and strokes and is therefore the biggest killer in the western world. The diseases share a similar pathology, characterised both by inflammation and calcification, the activity of which we can measure using a modern non-invasive imaging technique called positron emission tomography computed tomography (PET/CT) (Figure 1).

Over the last two years we have performed several studies using this technique. We are indebted to the Clinical Research Facility for their support in conducting these studies, in particular in helping us to perform all the baseline clinical assessments and echocardiograms. In the aortic valve we have demonstrated that we can reliably measure aortic stenosis disease activity using PET/CT and that calcification appears to be the predominant disease process (Figure 2). In the coronary arteries we can reliably image regions of increased calcification activity, which holds promise as a means of identifying plaques at risk of rupture and causing a heart attack or stroke (Figure 3).

Further projects are under way to study these issues in greater detail and to identify whether PET/CT might have a future clinical role in predicting disease progression or as an end-point in research studies of novel therapeutic strategies.

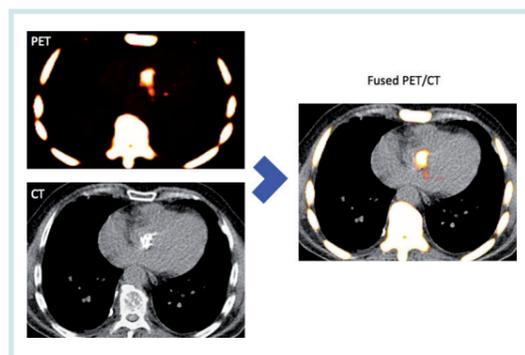


Figure 1. How PET/CT Works
Functional images provided by PET and combined with detailed anatomical images from CT. Fused PET/CT images then allow specific pathological processes to be localised to individual structures within the body. In this case calcification in the ribs, sternum and aortic valve (centre of the image).

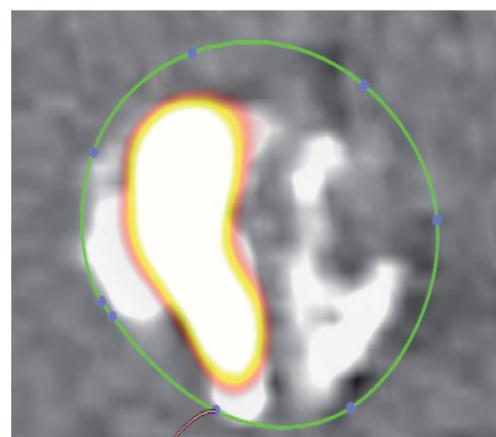


Figure 2. PET/CT of the aortic valve following administration of 18F-NaF. This tracer identifies regions of increased calcification activity in the valve (yellow/red areas). Areas of calcium already established in the valve are identified on the CT (white regions).

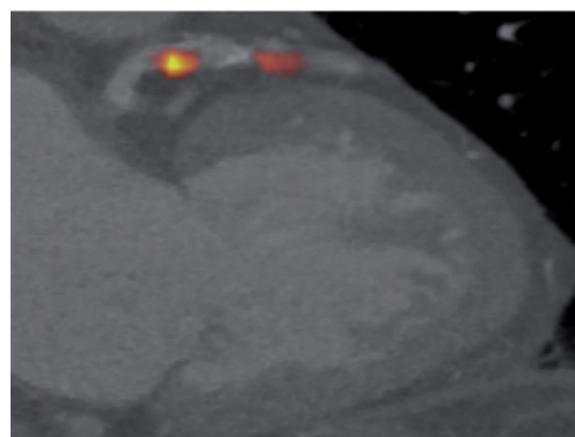


Figure 3. PET/CT images of the coronary artery following administration of 18F-NaF. Regions of novel or micro-calcification are again shown in yellow/red and are seen in a region of mixed non-obstructive coronary plaque in the proximal left anterior descending artery.

This work has resulted in several major publications and Dr Marc Dweck (PI) has been awarded the Young Investigator Award by the American College of Cardiology, the William W Parmley Young Author Award by the Journal of the American College of Cardiology, the Young Research Worker's Prize from the Radiology Society of North America and the President's Medal from the Royal Society of Medicine.

See our video on <http://www.youtube.com/watch?v=mWfm07QhHol&feature=youtu.be>

CI: Professor David Newby, BHF John Wheatley Chair of Cardiology
CRF Support used: Nursing Clinical; Image Analysis; CRIC

The kiss that tells men from boys *Dr Jyothis George*

Whilst killer diseases like heart attack, stroke, cancer and diabetes fill the airwaves and gobble up research pennies, it is easy to take some less urgent areas for granted. Research on reproductive matters is sometimes not seen as 'sexy' (pardon the pun), and some key questions on how we all achieve sexual maturation and maintain normal reproductive function remain unanswered: How does the brain know it's time to secrete the hormones that turn silk-skinned boys into bearded men with baritone boom boxes? How does the brain know when things are 'too stressful' for a woman and shut down the normal monthly release of eggs? Why do men with diabetes have lower testosterone concentrations than others?

The kiss that heralds puberty

Puberty begins with a kiss – or so they say. When researchers in Hershey (Pennsylvania, USA) discovered a new gene, they named it after the town's famous produce – Hershey's Chocolate Kisses. The hormone that's coded by the gene was hence named kisspeptin. Around a decade ago, our collaborators in Harvard were among the first to show that boys lacking normal kisspeptin activity do not go through puberty in a timely manner.

We synthesised the active end (C-terminal end) of kisspeptin hormone and undertook first-in-human studies of this peptide at the Edinburgh Clinical Research Facility. As predicted, we were able to demonstrate its stimulatory effect on the human reproductive system, as measured by Luteinizing Hormone (LH) concentrations in the blood. LH is secreted as discrete pulses and it is this ebb and flow of LH that controls the reproductive function. Newborn babies have robust LH pulses but this pulsatility remains suppressed in childhood until puberty kicks in. In women, the frequency of LH pulses reaches a crescendo just before the egg is released, and then dampens down until the next menstrual bleed. We were able to demonstrate, for the first time, that the rhythmicity of LH release can be accelerated using kisspeptin. These studies, some of them involving samples being collected at precisely 10-min intervals for up to 12 hours on consecutive days, would not have been possible without the professionalism of our CRF nursing team.

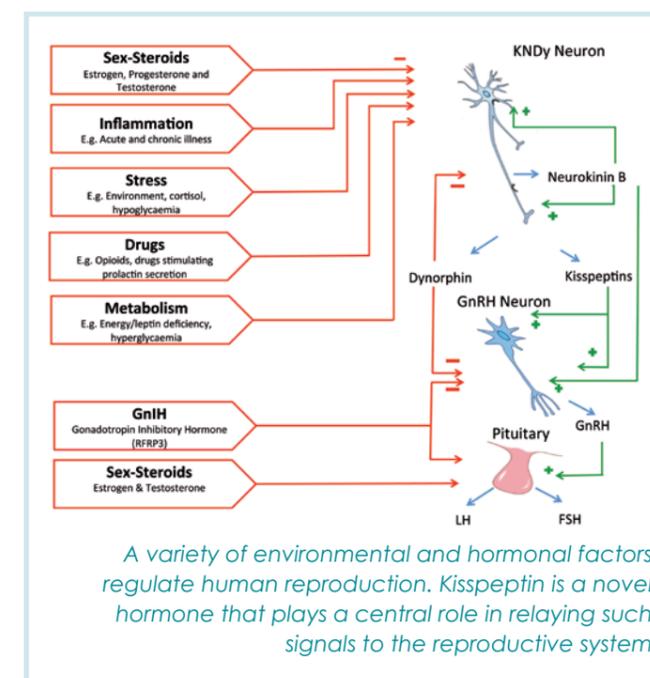
Beyond the first kiss

We have recently undertaken studies in children with delayed puberty – trying to develop a 'kiss test' that helps differentiate 'late bloomers' from those with underlying diseases of the reproductive system. We have also undertaken first-in-human studies of another hormone (Gonadotropin Inhibitory Hormone). Once again, the rigor and discipline demonstrated by the CRF team in ensuring regulatory compliance in these studies were exemplary. With Edinburgh CRF support, we have also entered into partnerships with multinational pharmaceutical companies to develop novel treatment paradigms for disorders of human reproduction.

The extensive support our team received from the Edinburgh CRF is a crucial factor for our success in taking two novel reproductive hormones to man in three years. Clinical academics in Edinburgh are blessed to have the CRF team to support translational research - long may they thrive!

This work has resulted in several presentations and publications.

Dr. Jyothis George (PI) has been awarded the Michael Harbuz Young Investigator Prize by the British Society for Neuroendocrinology, the trainee award from the Association of British Clinical Diabetologists and prizes for oral communications from the Society for Endocrinology (USA), British Society for Endocrinology and the Clinical Endocrinology Trust. He was also selected for visiting fellowships at Harvard (Royal College of Physicians) and the Mayo Clinic (Society for Endocrinology).



CI: Professor Richard Anderson, MRC Centre for Reproductive Health
CRF Support used: Nursing Clinical

Key projects and initiatives from Edinburgh's Clinical Research Facilities

Education Programme *Michelle Evans*

Courses and training



The Education Programme delivers over 70 training courses, workshops and seminars per year to meet the changing needs of clinical researchers locally and nationally across Scotland and the UK. In addition to face-to-face teaching, the programme utilises online learning, web streaming and videoconferencing technologies, to engage with a wider audience.

National Education & Training Strategy

In the present highly regulated research management environment clinical research projects must be designed and conducted to the highest standards. This can only be achieved if staff receive appropriate and adequate training. Over the past ten years various groups across Scotland's academic centres have developed and delivered a variety of education and training programmes related to clinical research. Representing all the Scottish CRFs, Clinical Research Training for Scotland (CRTS) www.crts.org.uk was set up in 2008. Its remit is to implement educational initiatives and infrastructural changes and coordinate the provision of clinical research education and training in order to ensure the further development of clinical research activity in Scotland. Current projects include A Blueprint for a National Education and Training Strategy for Clinical Researchers in Scotland.

Current Projects

MSc Clinical Trials (Phase I-IV)

To complement the accreditation in July 2011 of the CRF under the MHRA Phase I scheme, the Education Programme is developing an MSc level course in Clinical Trials (I-IV). In June 2012 as part of the Scottish Translational Medicine and Therapeutics Initiative (STMTI) led by our programme Director Professor David Webb, we piloted a one week course in Translational Pharmacology addressing key training requirements of Principal Investigators and other staff involved in Phase I Clinical Trials, and relevant to hospital, academic, industry or government sectors.

The next stage is to develop an online distance learning 3 year part-time course leading to the degree of MSc in Clinical Trials, this project is in collaboration with the Edinburgh Clinical Trials Unit (ECTU).

Event Planning

The Education team offers its expertise to other organisations planning events including courses, seminars, conferences and open days.

Events we have organised include:

- Scottish Research Nurse & Co-ordinator's Network Annual Conference
- The 'VITamins TO Prevent Stroke' (VITATOPS) trial participants meeting
- Translational Genomics Event for Illumina
- National Research Ethics Service (NRES) Training Days
- CRF Public Open Days

Patient & Public Involvement (PPI)

The Education Programme is developing a PPI advisory service that will facilitate meaningful interaction between researchers and participants during the design, conduct, analysis and dissemination of research activities at the WTCRF. The aim is to build partnerships with both research networks and the community testing a variety of methods of engagement, participation and education.

UK CRF Education Working Group

Our Education Manager is a member of the 'UK CRF Education Work Stream' and has been working with the group to deliver a number of projects, including a 'UKCRF Induction Framework'. Based on best practice from across a number of established CRFs, the Framework is designed to help Clinical Research Facilities (CRFs) develop a comprehensive induction programme for new staff.

Edinburgh CRF Education Programme provides a wide variety of training and courses

- Audit & Monitoring
- Consent
- Data Management
- Ethics
- Evidence-Based Healthcare
- Human Tissue
- Literature Searching
- Personal Development
- Qualitative Methods
- Questionnaire Design
- Regulation
- Statistics
- Trial Management
- Writing & Publication Strategy



CRF Public Open Day 2012: Cancer Research UK staff illustrate the effect of smoking on the lungs

Specialist research services in Edinburgh's Clinical Research Facilities

Nursing Clinical Team

Our research nurses have extensive experience in conducting detailed clinical studies. They have worked with hundreds of investigators on many highly successful projects and their knowledge and expertise has been fundamental to these achievements.

We support projects in the Wellcome Trust Clinical Research Facility (WTCRF) at the WGH, the Royal Infirmary of Edinburgh Clinical Research Facility (RIECRF) at Little France and the Children's Clinical Research Facility (CCRF) at the RHSC. Outreach and community research nurse support is also provided in the wider hospital and primary care setting.

The nursing team is supported by experienced Clinical Measurement Technicians, Clinical Support Workers, Project Assistants, reception staff and a ward clerk. Our staff receive regular ICH GCP updates and all work is underpinned by robust quality management systems that are monitored by our QA Manager.

2011 was a very busy year for the nursing team. Newly accredited with the MHRA, we completed an intensive Phase I drug trial involving patients with diabetes and otherwise healthy cigarette smokers. The study ran in both of our adult facilities and involved long subject visits of up to 14 hours duration. Study procedures included forearm plethysmography and pulse wave analysis to assess vascular function. The trial was conducted to Phase I Accreditation standards and the commercial Sponsor was delighted with the quality of the CRF support.

In addition to this, our nurses supported an extensive range of clinical studies throughout the year, many involving the acquisition of new clinical skills. Several nurses undertook training in chemotherapy administration and a number of nurses were trained to take skin biopsies. Skin samples can be used to generate induced Pluripotent Stem (iPS) cells for drug development and disease modelling. This capability will support local investigators including those working with the Anne Rowling Regenerative Neurology Clinic and the MRC Centre for Regenerative Medicine.

We look forward to another exciting year ahead as we commence a flagship clinical trial of cystic fibrosis transmembrane receptor (CFTR) gene therapy. We are delighted to support this pioneering project that will keep our team incredibly busy over the coming months.

Research Nurse Manager: Sharon Cameron - 0131 242 7185 - sharon.cameron@luht.scot.nhs.uk



Image Analysis Core

Established to meet the data-intensive demands of using modern medical imaging devices in clinical research, the Image Analysis Core computer laboratories are located in the Clinical Research Imaging Centre (CRIC) at Little France and in the CRF at the Western General site. Each laboratory is equipped with high-spec workstations and specialised software packages, and staffed by personnel with expertise in image processing, manipulation and quantification.

Experienced in dealing with images from a variety of sources including MRI, CT, PET, ultrasound, microscopy, and photography, we are available to train researchers in the use of specialised techniques, including 3D visualisation (i.e. volume and surface rendering), registration, segmentation, region of interest analysis, volumetric analysis and image enhancement.

The Image Analysis Core has Windows PCs, Apple Macs and Linux boxes and a variety of commercial and open-source software packages.

Our contribution to scientific research involves the development of new image processing and analysis methods and custom-written software to perform such tasks as analysing retinal images, post-processing contrast enhanced MRI scans to reveal areas of inflammation, and analysis of intima-media thickness (IMT) along the length of the carotid artery from ultrasound images.

Retinal Imaging and Analysis

Imaging the retina allows direct, non-invasive study of the human microvasculature. Evidence suggests that features associated with retinal blood vessels may be early indicators of cardiovascular disease, stroke, MS, diabetes, hypertension and dementia.

Thanks to Optos, a Scottish-based company and world leaders in developing the technology, a scanning laser ophthalmoscope (SLO) has recently been installed in CRIC. This device, which generates wide-field images of the retina, will be used to support research programmes in a number of specialties including cardiovascular science, neuroscience, respiratory medicine and diabetes.

In collaboration with the University of Dundee (School of Computing) and international centres the Image Analysis Core is developing software (VAMPIRE) for automatic analysis of retinal images. The aim is to identify biomarkers, i.e. subtle changes to structural features such as vessel width, branching angles and vessel tortuosity. The VAMPIRE software enables robust, objective, and quick and easy to perform quantification of these features.

Current projects include the analysis of images from ORCADES, LBC1936, UKBiobank.



Wide-field retinal image

Specialist research services in Edinburgh's Clinical Research Facilities

Epidemiology and Statistics Core

The aim of the Epidemiology and Statistics Core is to improve the methodological quality of studies through the provision of expert statistical input. The Core is involved in studies at all stages from initial design through to analysis and dissemination. By encouraging investigators to approach the Core at an early stage we support the development of the highest quality study designs for submission to regulators, ethics committees and grant awarding bodies and provide an invaluable educational resource.

The Core has contributed to a substantial list of publications enhancing the profile of the CRF beyond the local setting. Some highlights of recent work of the Core statisticians include:

General Anaesthesia compared with Local Anaesthesia for carotid surgery (GALA) trial:

Through a secondary analysis of the GALA trial we examined whether exposure to nitrous oxide was associated with increases in mortality, stroke and myocardial infarction. Given the greater prevalence of vascular risk factors in the nitrous oxide group, and the lack of any definite effect on the primary outcome measure, these data did not support a clinically meaningful adverse effect of nitrous oxide on our composite outcome in patients undergoing carotid surgery.

Modified Rankin Score After Stroke: The modified Rankin score is a measure of disability commonly used as an outcome measure in large randomised stroke trials. Most trials will use the tick box version of the score and collect this information using a combination of postal and telephone follow up. However discrepancies in responses as a result of the method of collection and also the format [tick box compared to simplified version] could have a negative impact on trials. We were unable to identify any studies examining the feasibility and agreement between methods and consequently conducted a trial to examine this. We have used the results obtained to help guide the methods of data collection for a subsequent large scale stroke trial.

Core Manager: Catriona Graham - 0131 537 3350 - c.graham@ed.ac.uk



Genetics Core

The WTCRF Genetics Core was established in anticipation of the increasing role of genomics analysis in clinical research. The laboratory provides a secure, audited and quality-assured biobank with systems in place for the receipt and processing of biological samples from clinical research programmes. Standard operating procedures and a Laboratory Information Management System ensure accuracy and facilitate the long-term utilization of the biological materials gathered. Over 82,000 samples are held within a secure suite of freezers. High-throughput genotyping, gene expression, epigenetics and sequence analysis is provided through four different platforms:

- Applied Biosystems 7900HT
- Applied Biosystems OpenArray
- Illumina HiScan
- Ion Torrent

The reduction in the cost of sequencing a person's genome is increasingly allowing genomics to become part of standard healthcare, enabling us to predict disease and identify more effective therapies. The latest Genetics Core platform, the Ion Torrent Personal Genome Machine, is part of the revolution in technology that is allowing more sequence for less cost. Operating by emulsion PCR and semiconductor based sequencing, the Ion Torrent can be used for DNA sequencing, RNA-seq and ChIP-seq. This investment in new technology will ensure that researchers continue to have access to these top-of-the-range genetic platforms for their clinical research.

Core Manager: Lee Murphy - 0131 537 3370 - lee.murphy@ed.ac.uk



Information Technology

Information technology supports many aspects of clinical research today and good systems combined with trained system users mean that data collected for reporting are accurate and easy to analyse.

In Edinburgh's Clinical Research Facility (CRF), the IT team supports the CRF Cores and related areas by developing bespoke systems to meet user requirements.

Key software developments to date include

- **CRFManager™**, which manages studies, resource bookings, key study metrics, study finances and recruitment
- **Course Manager**, which manages courses and seminars from registration to payment
- **Forms Manager**, a forms builder eCRF system, which has been used to collect data for 5 studies over the past year

This past year we developed a **Trial Recruitment Register** for NHS R&D to capture data from investigators and their staff on study recruitment across Lothian. We are currently working on an **NHS R&D Finance system** to support R&D Finance with CSO requirements for collection of pre-award finance data.

CRFManager™ has been shared with colleagues across the UK and Ireland and it is now installed in 22 CRF sites. Additional sites are keen to adopt the system in the near future. We are working with the UKCRF Network to promote the use of **CRFManager™** as a common IT system for new facilities. The **CRFManager™** user group was established in 2012 and has proved a useful means of bringing together user sites to discuss functionality and provide training workshops. www.crfmanager.com.

The system has also been used to support non-CRF groups such as local research networks for study data input (forms) and resource scheduling.

Course Manager has contributed to the success of our Education Programme, and the connected Clinical Research Training Scotland (CRTS) website is used across Scotland to publicise clinical research related courses and events. Over the past 4 years, Edinburgh CRF IT team coordinated the IT for the Clinical Research Imaging Centre (CRIC) and we continue to support the CRIC staff with their IT needs.

Programme Director: Elizabeth McDowell - 0131 537 3353 - elizabeth.mcdowell@ed.ac.uk - www.crfmanager.com

Mass Spectrometry Core

A wide range of research projects have been supported by the Mass Spectrometry Core during the last year, covering basic and clinical studies in the fields of drug discovery, oncology, toxicology and steroid hormone action. These projects represent investigators from across the University of Edinburgh College of Medicine and Veterinary Medicine and NHS Lothian. We have strengthened our links with the School of Chemistry, enhancing the diversity of analytical approaches offered at both sites.

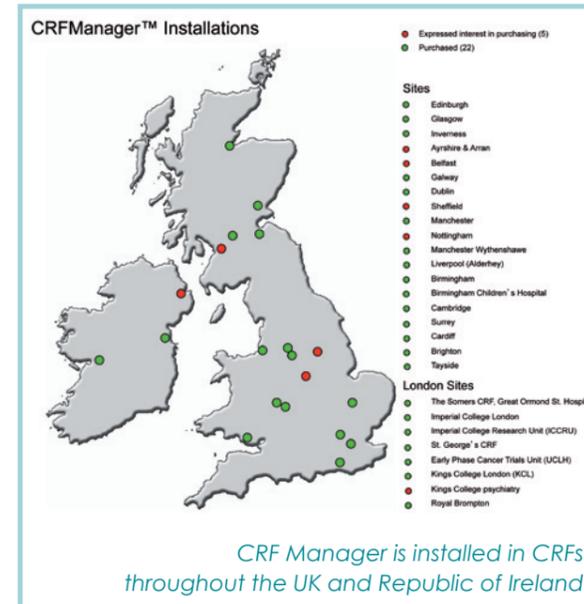
Within the laboratory, new equipment installed in 2011 is now operating fully and has increased our capacity considerably. Our major focus this year is to improve sample throughput, by the use of Ultra-high performance liquid chromatography and also the introduction of online sample preparation using the new Turboflow Aria system (pictured).

The work of the Core has been well received nationally and internationally, for example one of our PhD students won the Sir James Black Presentation award at the Scottish Society for Experimental Medicine and two of our Clinical Investigators have been selected for the Presidential Poster Award at the American Endocrine Society. We continue to support post-graduate students to develop skills in the field of Analytical Chemistry and, due to our unique facilities in Scotland, are hosting regular secondments for the University of Strathclyde, MSc programme in Pharmaceutical Analysis.



Joanna Collier is studying for an MSc in Pharmaceutical Analysis at the University of Strathclyde and performed her practical dissertation under the supervision of Core Manager, Dr Natalie Homer

Core Manager: Dr Natalie Homer - 0131 242 9333 - n.z.m.homer@ed.ac.uk



CRF Manager is installed in CRFs throughout the UK and Republic of Ireland

Specialist research services in Edinburgh's Clinical Research Facilities

Clinical Research Imaging Centre Professor Edwin J.R. van Beek
www.cric.ed.ac.uk



Formally opened by HRH the Duke of Edinburgh

In October 2010 the Clinical Research Imaging Centre (CRIC) is a highly successful example of partnership working between the University of Edinburgh (UoE) and NHS Lothian, and is rapidly developing into a flagship research centre

The facility currently houses a 3T Verio MRI system, a 128-MDCT mCT-PET system and a 320-MDCT Aquilion ONE system with supporting image-analysis facilities, as well as a GE cyclotron and a radiochemistry suite. Refinal imaging is a recent addition while installation of an ultrasonography unit is planned for late 2012.

CRIC continues to embrace a multidisciplinary research model, and currently has over 30 staff including radiographers, radiologists, physicists, image analysis specialists, radiochemists and support staff. 7 PhD students are based in CRIC, with a further 5-10 postgraduate students supported across the University. The group has formed close relations with many medical disciplines to facilitate the integration of imaging studies into

the mainstream research portfolio. Our state-of-the-art imaging technology and expertise have been at the centre of a number of large grant awards in the fields of Psychiatry, Fetal and Pregnancy Health, Care of the Elderly, Sports Sciences, Cardiovascular Sciences, Liver Diseases and Pulmonary Medicine.

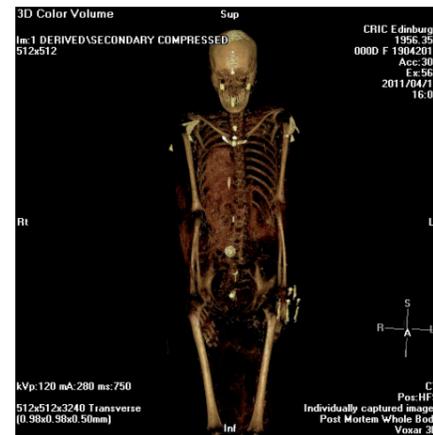
CRIC enjoys thriving collaborations with Heriot Watt, Stirling and Dundee Universities. Beyond the medical field, access to functional MRI has allowed the UoE Music Department to gain new insights into the performance of musicians.

In addition to its research portfolio, CRIC performs imaging for cardiology and oncology patients across NHS Lothian in a comfortable, patient-friendly environment.

CRIC has been actively engaged in public awareness, resulting in successful exhibitions at the National Museum of Scotland ('Fascinating Mummies' exhibition, science week), and presentations at local schools showcasing the University of Edinburgh's research capability.

As well as hosting the Edinburgh CRF Image Analysis Core, CRIC

administrative processes are integrated with the CRF study management systems ensuring that study work-up and documentation are managed according to the CRF's well-established streamlined processes. In particular, CRIC benefits from the bespoke electronic CRFManager™ system developed by the CRF IT team. Investigators can be reassured that their research is conducted in compliance with the Research Governance Framework, relevant legislation, national and local policies and the principles of Good Clinical Practice (GCP) in an appropriately regulated research environment.



'Mummy' courtesy of Dr Saeed Mirsadraee and National Museum of Scotland

Brain Research Imaging Centre Professor Joanna Wardlaw
www.bric.ed.ac.uk



The Brain Research Imaging Centre is a key component of the Edinburgh CRF Imaging Core. BRIC is home to multidisciplinary groups of researchers with experience in all aspects of

brain imaging encompassing specific disease areas such as Stroke, Dementia, Multiple Sclerosis and other Neuro-degenerative diseases, as well as Aging and Psychology research. Structural, Perfusion, Permeability, Functional, Tractography and Spectroscopy MRI scanning techniques are used. The quality of the staff and the dedicated research MRI scanner at the heart of the Centre allow BRIC to pursue its mission statement:

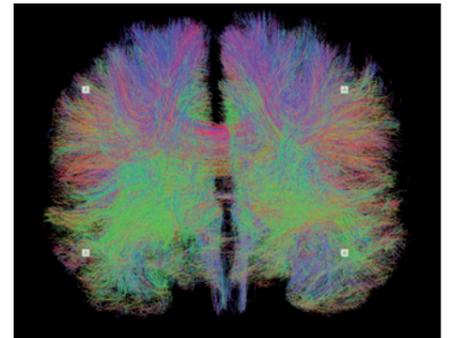
"Enabling high quality research using Magnetic Resonance (MR) and related imaging methods to improve understanding of the causes, pathophysiology and treatment of common neurological disorders"

BRIC forms the core of Neuroimaging Sciences, a functional unit within the Centre for Clinical Brain Sciences (CCBS) and is embedded within clinical space in the Department of Neuroradiology and Clinical Neurosciences (DCN) at the Western General Hospital (WGH). The mutually beneficial relationship between the University of Edinburgh research facility and the NHS department enables BRIC to carry out research work on critically ill subjects as appropriate emergency clinical support is on hand.

BRIC is a leader in excellence in imaging and disseminating knowledge through teaching and research. BRIC has been providing a Neuroimaging MSc since 2007 and in 2012 secured funding to lead a cross-disciplinary Imaging MSc.

BRIC is also leading the Centre for In Vivo Imaging Sciences (CIVIS) – an initiative that will integrate all imaging activity across the University of Edinburgh and other institutes, providing researchers with coordinated and collaborative access to imaging expertise and facilities. CIVIS will also have a commercial "face" with the development of Edinburgh Imaging, a single web portal allowing access for commercial scientific research to the CIVIS collaboration.

Integration of the BRIC administrative processes with the CRF means that the Centre can offer researchers collaborative support to design, implement, troubleshoot, data process and analyse imaging research studies and trials in compliance with the exacting requirements of Good Clinical Practice (GCP) in an appropriately regulated research environment.



Whole Brain Tractography Map

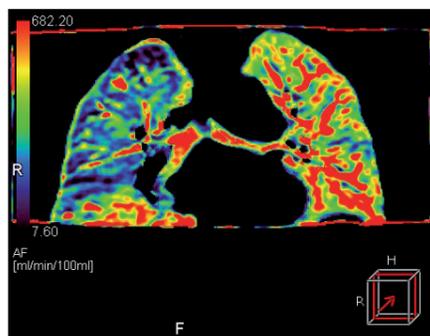


Edinburgh Imaging (the commercial face of CIVIS)

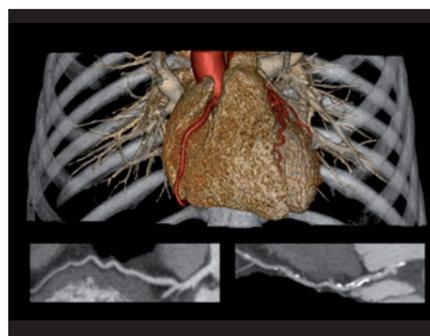
Professor Joanna Wardlaw, Chair of Applied Neuroimaging
Dr Duncan Martin, Scientific Business Manager

We welcome anybody with imaging needs to discuss potential collaboration and are willing and able to help set up projects, develop protocols and deliver imaging-based outcome measures.

Professor Edwin J.R. van Beek, SINAPSE Chair of Clinical Radiology



Post PE treatment perfusion defect Right lung



'Looking inside the heart' courtesy of Dr Michelle Williams

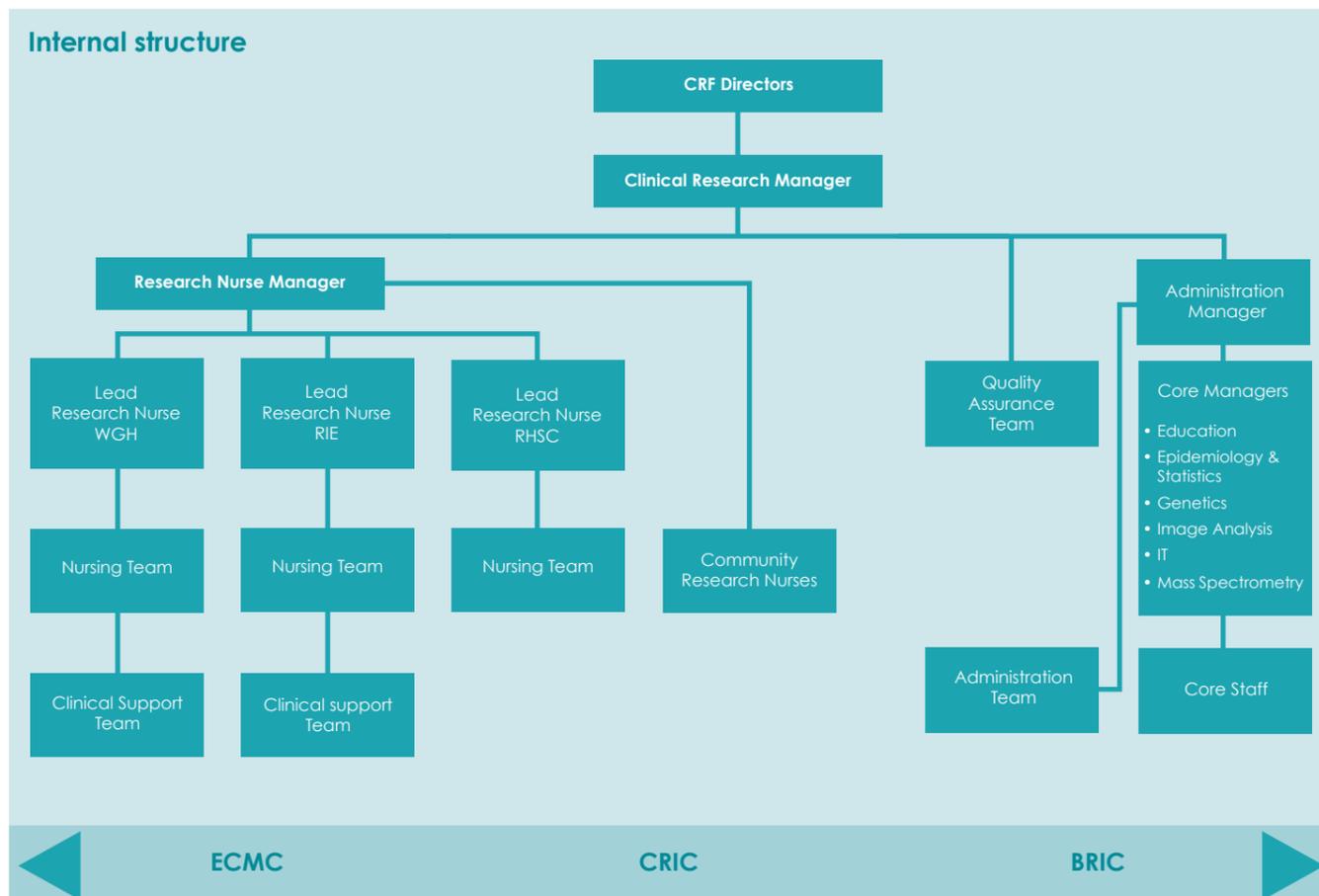
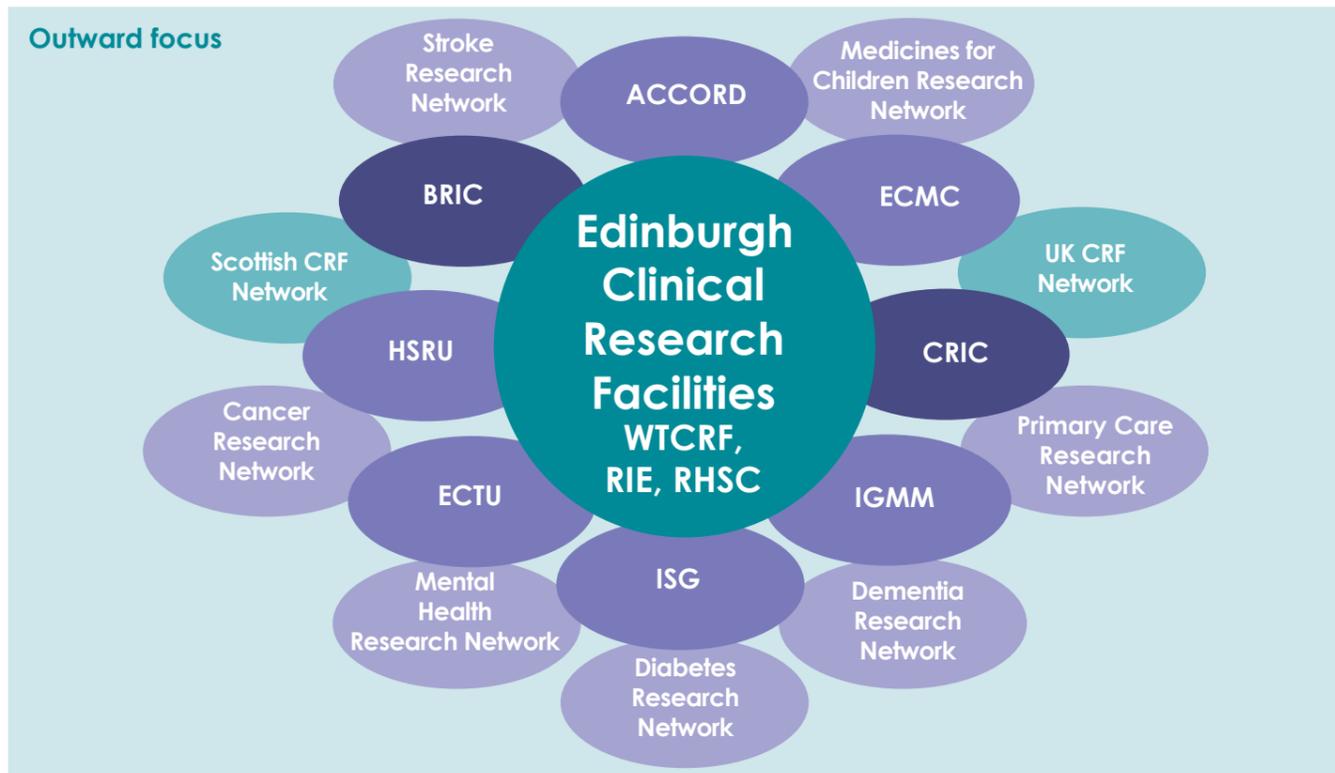


'Ring of Fire' courtesy of Dr Marc Dweck

New papers

1. Wardlaw JM, Bastin ME, Valdes Hernandez M, Munoz Maniega S, Royle NA, Morris Z, Clayden JD, Sandeman EM, Eadie E, Murray C, Starr JM, Deary IJ. **Brain aging, cognition in youth and old age and vascular disease in the Lothian Birth Cohort 1936: rationale, design and methodology of the imaging protocol.** Int J Stroke 2011; 6:547-559.
2. Dickie DA, Job DE, Poole I, Ahearn TS, Staff RT, Murray AD, Wardlaw JM. **Do brain image databanks support understanding of normal ageing brain structure? A systematic review.** European Radiology 2012; 22(7):1385-1394.
3. Rousselet GA, Pernet CR. **Improving standards in brain-behavior correlation analyses.** Frontiers in Human Neuroscience 2012; 6:119
4. Valdes Hernandez MdelC, Royle NA, Jackson MR, Munoz Maniega S, Penke L, Bastin ME, Deary IJ, Wardlaw JM. **Color fusion of magnetic resonance images improves intracranial volume measurement in studies of aging.** Open Journal of Radiology 2012; 2:1-9

Top projects - SPIRIT (PhD projects with industrial collaboration and co-supervision), Mild Stroke Study 2, Brain Tumour fMRI study (CRUK funded study allowing pre-operative planning of tumour surgery based on minimising damage to eloquent brain tissue).



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THE SICK KIDS



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