clinical research facility
EDINBURGH

June 2011

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 Edinburgh Clinical Trials Collaboration & accreditation of Edinburgh Clinical Trials Unit (ECTU) with the UKCRC
- **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 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 Conference
- **2008** Business case submitted for Children's CRF in new Sick Children's Hospital
- **2008** WTCRF 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** Scottish Academic Health Sciences Collaboration (SAHSC) launched
- **2009** Clinical Research Imaging Centre (CRIC) opens
- **2010** CRF Mass Spectrometry Core receives £750,000 Wellcome Trust equipment award for major new investment
- **2010** Wellcome Trust Director Sir Mark Walport and other key stakeholders visit the Edinburgh CRFs
- **2010** Professor Sir John Savill (Head of College of Medicine and Veterinary Medicine) appointed Chief Executive of the MRC
- **2010** Official opening of the CRIC by HRH Prince Phillip, Chancellor of the University of Edinburgh
- **2010** Edinburgh CRF is the first non-commercial unit to be inspected for accreditation under the MHRA Phase 1 scheme
- **2011** Plans are agreed for reconfiguration of space in WTCRF to support trial of gene therapy for cystic fibrosis

Introduction

The past 12 months have been both busy and rewarding for Edinburgh CRF. We received over 150 new applications to use our facilities and we supported over 350 projects between April 2010 and March 2011. The scope of our research portfolio continues to expand and this brochure contains features on some of our challenging studies in cystic fibrosis, reproductive health and acute lung injury.

Over the course of the past year, a number of significant events took place including an evaluation visit by senior representatives from the Chief Scientist Office and the Wellcome Trust. The visit took place on the 4th of May 2010, six years after we last welcomed these key stakeholders into the CRF. We were delighted to showcase our expanded facilities and extensive research portfolio and the visit ran very successfully. It provided an excellent opportunity to demonstrate the major developments and scientific outputs that we have delivered since inception.

Other notable events last year included the official opening of the Clinical Research Imaging Centre (CRIC) at Little France. The CRIC welcomed its first patients into the facility in October 2009 but it wasn't until the 29th of October 2010, that the CRIC was officially opened by HRH Prince Philip the Duke of Edinburgh. Under the central structure of the CRF Imaging Core, the CRIC, Brain Research Imaging Centre (BRIC) and CRF Image Analysis Core collectively provide access to a comprehensive research imaging service that is underpinned by sophisticated IT infrastructure and robust quality management systems.

November 2010 marked another milestone when the CRF underwent a Phase I Inspection by the Medicines and Healthcare products Regulatory Agency (MHRA).

Edinburgh CRF is the first non-commercial clinical research centre in the UK to apply for Phase I Accreditation and we are delighted to offer exemplar Phase I facilities for our academic and commercial users. Over the course of the inspection process, we worked closely with the MHRA to present an alternative accreditation model for non-commercial, hospital-based clinical research facilities. This model now forms the basis of a proposal to revise the current accreditation criteria for the academic sector.

We hope that our brochure illustrates the hard work and commitment that we have invested in order to keep pace with the national clinical research agenda. Throughout this busy year, our staff have worked with tireless enthusiasm and dedication to advance the range and quality of services that we offer. This annual brochure provides additional detail about our specialist research services, world class facilities and the flagship projects that Edinburgh CRF is leading. We have also included details of selected key publications arising from projects supported by the CRF.

We hope that you enjoy it!

CHIEF SCIENTIST OFFICE

wellcome trust

NHS Lothian

THE UNIVERSITY of EDINBURGH

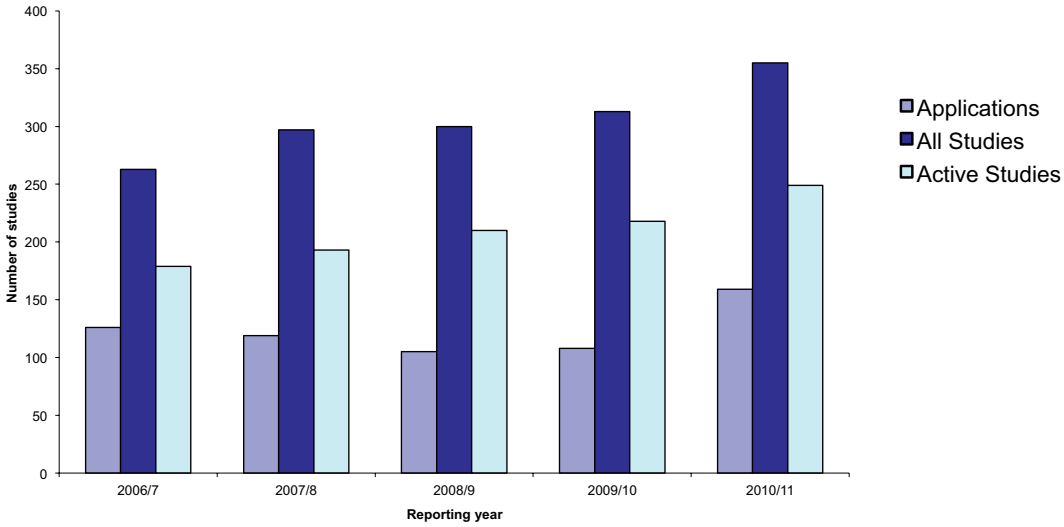
UKCRF NETWORK
UK Clinical Research Facility Network

clinical research facility EDINBURGH

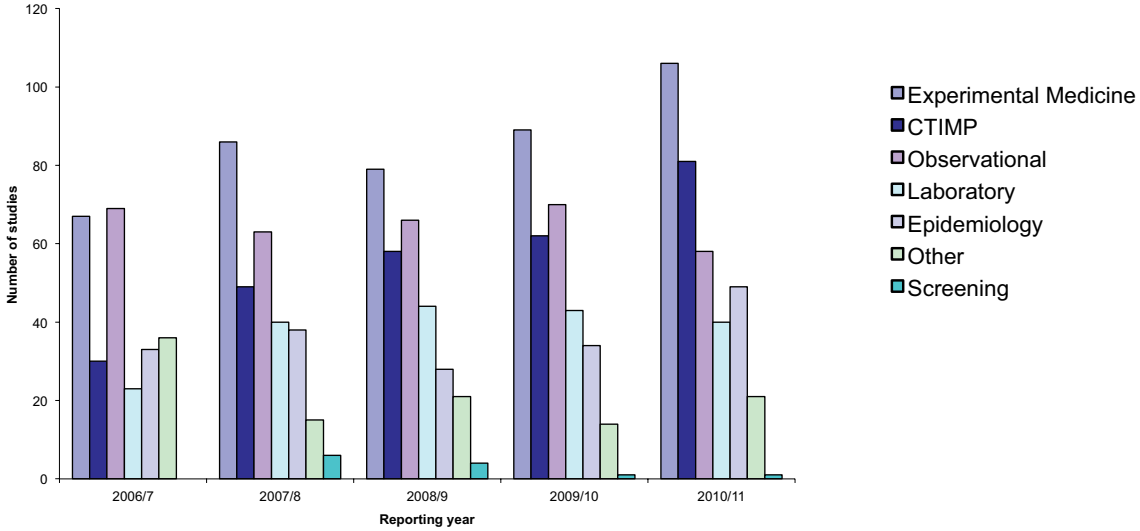


Selected CRF metrics 2006/7 - 2010/11

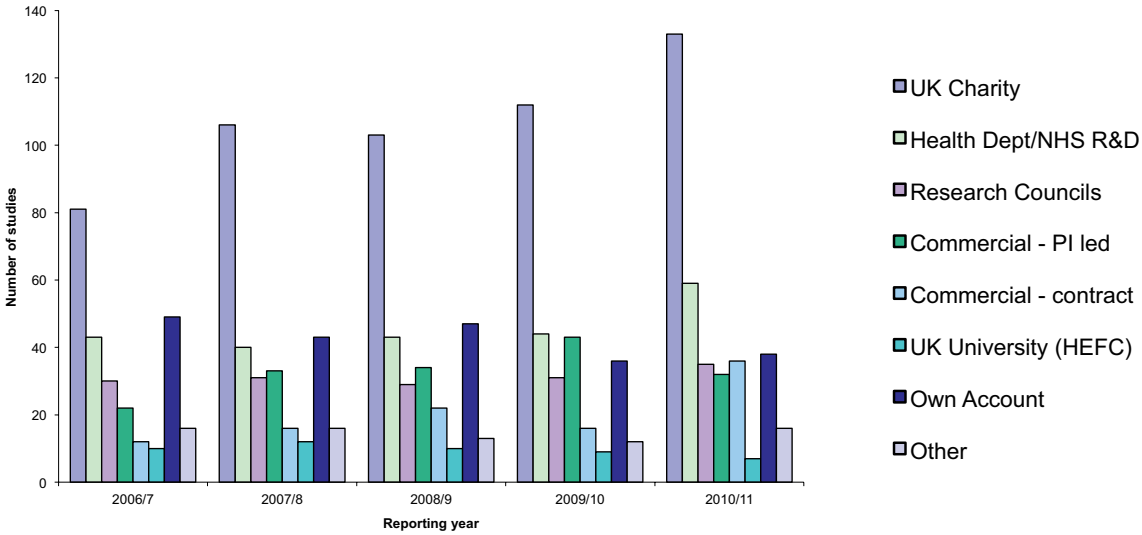
Edinburgh CRF studies



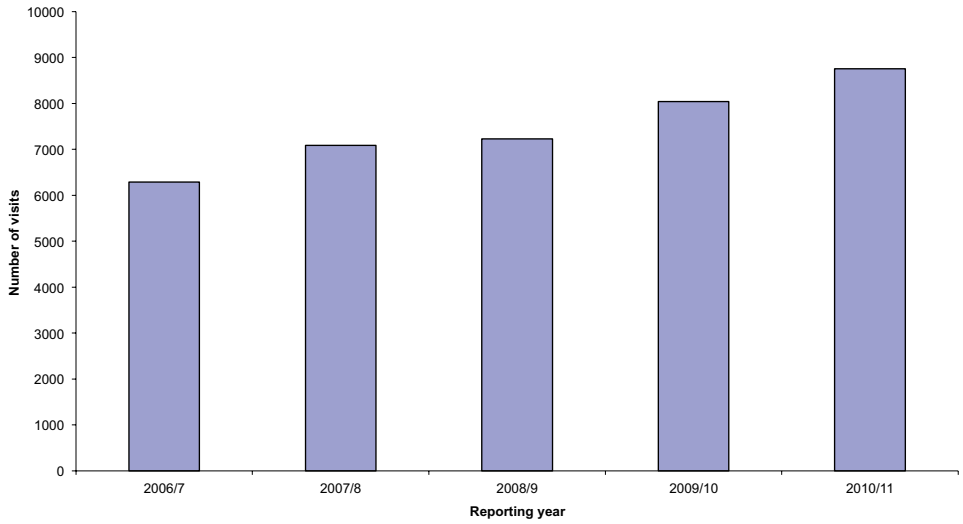
Range of CRF study types



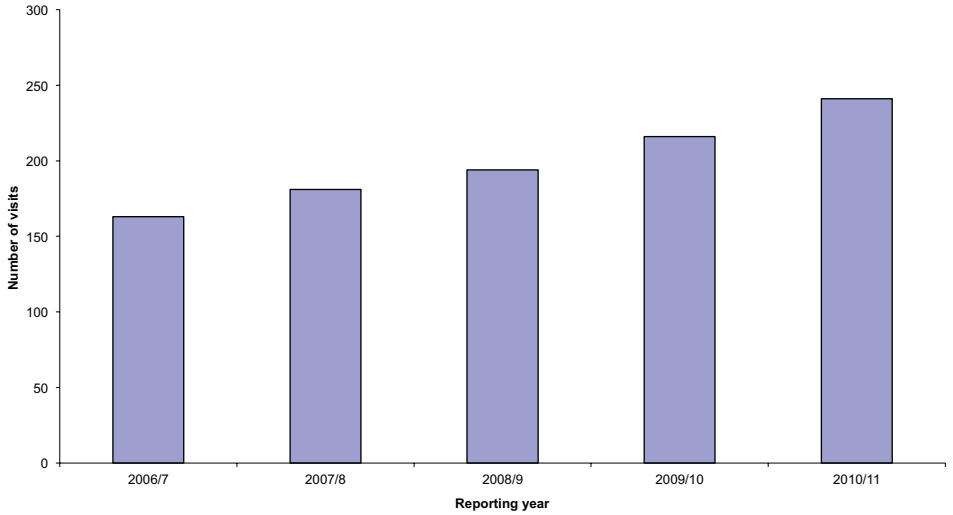
Funding sources for CRF studies



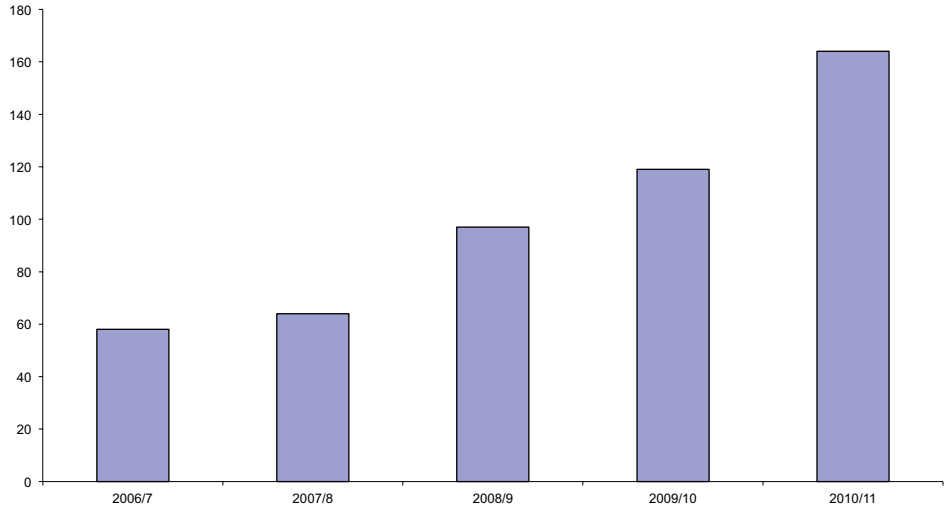
Number of participant visits to the CRF



Number of unique investigatiors using the CRF



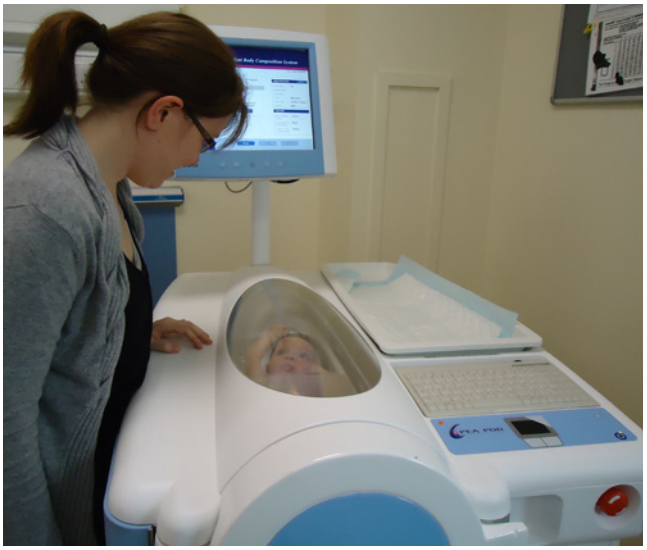
Number of publications linked to CRF studies



Key projects and initiatives from Edinburgh's Clinical Research Facilities

Research into the health of women in pregnancy and their babies

The Edinburgh Tommy's Centre for Maternal and Fetal Health was set up in 2008. With the enthusiastic help of pregnant women in Lothian, and with support from the charity Tommy's (1), from the University of Edinburgh and from NHS Lothian we are trying to understand why obese pregnant women have adverse outcomes in pregnancy, and why their babies are at increased risk of obesity in later life. The Edinburgh CRF has been hugely helpful and we have a number of exciting studies ongoing.

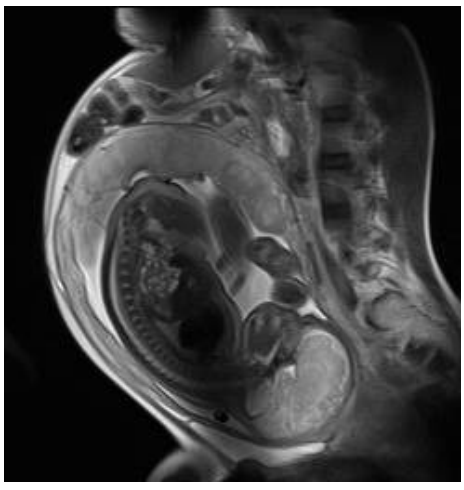


A baby enjoys the view from inside the PeaPod body fat measurement machine

- Our first study has been an observational study to quantify body fat changes in pregnancy using a "BodPoD". This is the gold standard technique for body fat measurement – essentially it's a capsule that women sit in and which uses the Archimedes principal (air displacement plethysmography) to measure body volume, and hence calculate body fat percentage. We've also been using the Edinburgh CRF "PeaPoD" which makes similar measurements in babies. Babies of obese pregnant women are more likely to grow up themselves to be obese. The percentage of fat mass at birth seems to be an important surrogate marker for future life obesity: we hope our studies will show which factors in pregnancy (including maternal fat mass) can predict this.

- Our second study aims to investigate hormonal factors which might be important in the link between obesity and adverse pregnancy outcome. Again with kind volunteers from our metabolic clinic, we have been measuring glucose disposal in obese and lean pregnant women at three time points during pregnancy. This will be the first study to accurately quantify central and peripheral insulin resistance in obese and lean pregnant women. The hyperglycaemic euglycaemic clamps are conducted whilst women rest in the Edinburgh CRF, and blood is subsequently analysed in the Mass Spectrometry Core. We think that we will show that obese pregnant women have greater insulin resistance and higher blood glucose than lean pregnant women, although we are not sure whether central or peripheral insulin resistance will be the main driver to this.

- Our third study involves trying to improve pregnancy outcome in obesity. Assuming that elevated glucose and insulin resistance contributes to adverse pregnancy outcome, it seems likely that treating this will improve outcome. A drug called metformin does just this, and it is safe to use in pregnancy. In an NIHR funded, EME managed study called "EMPOWaR" we will compare pregnancy outcomes in a group of obese pregnant women treated with metformin, and another group treated with placebo. We will again use the Bodpod and Peapod - we think that metformin will reduce percentage body fat in both Mum and baby.



A baby in utero in the third trimester, scanned in CRIC using the 3T Magnetic Resonance Imaging scanner

- Lastly, we are collaborating with colleagues in CRIC to use MR scanning to investigate the health of the baby in utero. MR scanning is safe to use in pregnancy. The 3T scan machine in the CRIC allows us to get very detailed images of the baby whilst in utero, and we hope to be able to investigate the effects of maternal obesity on fat distribution in the baby's abdomen and liver. In the future we hope that we will be able to develop MR techniques to identify babies who are "at risk" in utero, and who would benefit from early delivery.

1. http://www.tommys.org/Page.aspx?pid=367

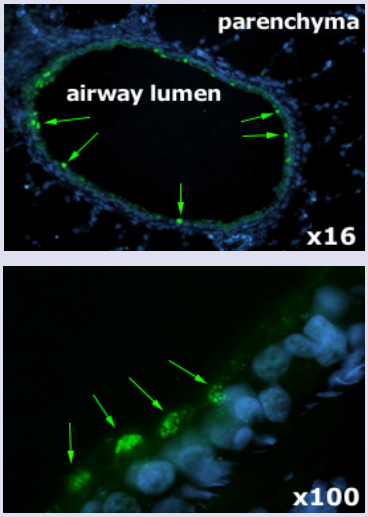
Professor Jane Norman, Professor of Maternal and Fetal Health, University of Edinburgh

Research into the use of gene therapy in Cystic Fibrosis

The Edinburgh CRF will be hosting an important intervention trial of gene therapy in people with Cystic Fibrosis. Starting in June 2011, bedroom 4 in the WTCRF will be converted into a gene therapy delivery suite comprising two cubicles and a clean preparation area. Infection control is paramount, due both to the nature of the intervention and the particular infection risk in this group of patients. The clinical activity will be contained within the dosing cubicles by means of a negative air pressure system. NHS Lothian R&D and the CRF management team have supported the project as a demonstration of their belief in the importance of this trial in particular and their intention to be able to support gene therapy research in the future.

Cystic fibrosis (CF) remains the commonest lethal genetic disease in caucasian populations, affecting over 8000 patients in the UK alone. Although median life expectancy has risen to 38 and adults now outnumber children with CF, the burden of disease and treatment remains high. The most important feature is chronic destructive infection of the conducting airways in the lung.

The desire of the CF community in the UK for a more effective treatment targeting the basic molecular defect has resulted in the formation of the UK CF Gene Therapy Consortium **www.cfgenetherapy.org.uk**. This is a collaboration of clinicians and scientists from Oxford, London and Edinburgh. The goal is to develop a gene-based treatment to the point of performing an ambitious clinical trial of the efficacy of inhaled CF gene therapy in the treatment of CF lung disease.



Immunological detection of lung cells expressing CF protein (green flourescence) after gene therapy. Cell nuclei are stained blue.

Run-in study

Beginning in February 2008 around 200 CF patients in Edinburgh and London were enrolled into an observational programme recording pre-treatment baseline measurements with the aim of defining the level of CF disease activity in individual patients so that the team were able to select the most effective methods of measuring changes in the lung. There are 47 adults and 34 children still actively taking part in the run-in in Edinburgh, with adult patients being seen in the WTCRF and children in the Children's CRF in the Royal Hospital for Sick Children. The Edinburgh CRF has been crucial in enabling the run-in trial visits to proceed in a timely and efficient fashion.

Intervention trial

Patients who have completed four run-in visits and are found to be eligible according to the trial entry criteria will have the opportunity to participate in the planned gene therapy trial. At least 100 patients (split between London and Edinburgh) will be recruited to this double-blind trial - half will receive gene therapy and half a placebo.
The two-site intervention trial will likely consist of twelve doses of non-viral liposome-based gene therapy medicine being delivered by nebuliser to the lungs of patients at monthly intervals. Outcome measures of efficacy will be based on statistical analysis of the results of the run-in study. Because of the schedule staggering necessary to accommodate the number of patients involved, the trial will take at least 18 months overall. The involvement of the Edinburgh CRF will continue to play a major role in the success of the Consortium clinical trial programme, and the introduction of tailor-made cubicles for the dosing of patients is just one example of how close co-operation between scientists, clinicians, pharmacists, administrators and Edinburgh CRF staff can result in the cost-effective translation of basic research to clinical trial assessment.

gtx UK CYSTIC FIBROSIS GENE THERAPY CONSORTIUM

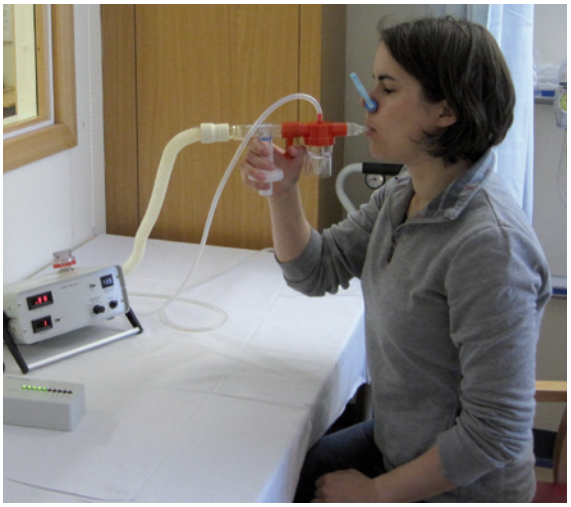
CI: Prof Eric Alton, Professor of Gene Therapy and Respiratory Medicine, Imperial College London
PI: Alistair Innes, Consultant and Honorary Reader in Respiratory Medicine, University of Edinburgh
CF Gene Therapy Group Leader: Chris Boyd, Senior Research Fellow, Medical Genetics Section, Molecular Medicine Centre

Key projects and initiatives from Edinburgh's Clinical Research Facilities

Research into mechanisms of Acute Respiratory Distress Syndrome

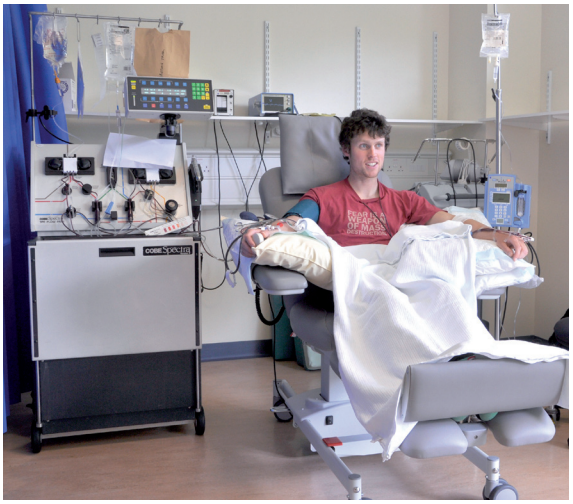
Patients with serious illnesses (eg infections, major trauma or pancreatitis) occasionally develop a complication whereby the lungs become inappropriately 'leaky'. Fluid which is normally excluded from the lung seeps into lung tissue, and respiratory failure ensues. This condition, acute respiratory distress syndrome (ARDS), is associated with mortality rates of around 30%, and no drug treatments have significantly and consistently altered this depressing statistic. The leakiness seems to be caused by neutrophils (white blood cells) being recruited to the lung and damaging the lung's thin membranes en route. Why and how neutrophils enter lung tissue in ARDS remains poorly understood, but treatments capable of reducing this process are urgently required.

Data generated in Edinburgh and elsewhere have suggested that another circulating white blood cell, the monocyte, may play a pivotal role in neutrophil recruitment to the lung in animals. Testing the relevance of the monocyte to human neutrophil recruitment is fraught with practical difficulties. However the relatively unique, cooperative clinical research environment in Edinburgh has allowed us to make inroads into this process.



Inhalation of a small dose of bacteria via a nebuliser induces a short term inflammatory response

Our work is based on healthy volunteers using the RIE CRF as a base unit, from which four key elements can be readily accessed. Firstly, volunteers inhale a small dose of a bacterial product which reproducibly induces a low-grade and transient recruitment of neutrophils to the lung, effectively mimicking very early stages of the process intrinsic to ARDS and related conditions. Secondly, shortly after the bacterial product has been inhaled, we can selectively remove monocytes from the volunteer's blood stream, using a procedure (leukapheresis) carried out in the Scottish National Blood Transfusion Service at RIE. Thirdly, we can assess whether this intervention has influenced the number and type of cells in the lung by directly inspecting and washing a small portion of the lung, using a routine technique called bronchoscopy, available in the Endoscopy Unit at RIE. Finally, we can make a more global assessment of neutrophil recruitment using sophisticated imaging equipment (PET scanning) available in the Clinical Research Imaging Centre (CRIC). Coordination and organisation of the study is supported by the CRF and the Edinburgh Clinical Trials Unit.



A volunteer undergoes leukapheresis to allow removal of monocytes from the bloodstream

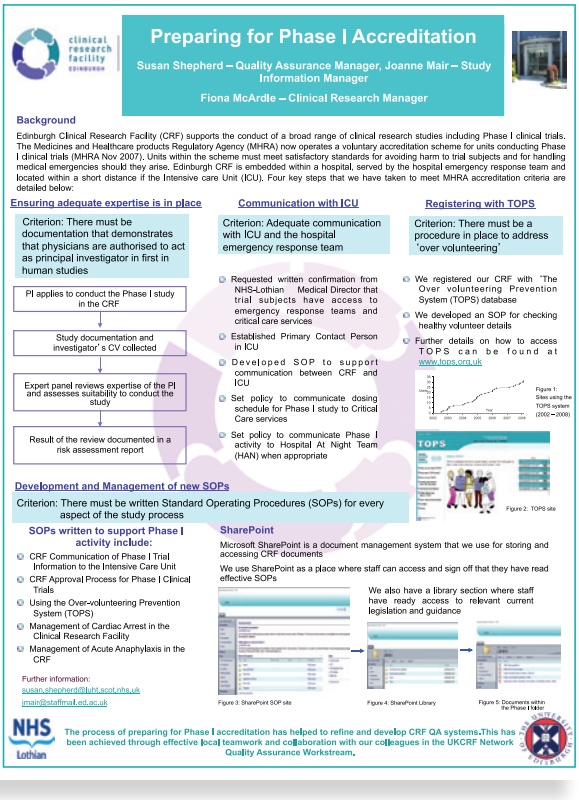
This inter-departmental, collaborative infrastructure has enabled a double-blind randomised controlled trial in which volunteers inhaling bacterial product are randomly assigned to have either monocyte depletion or 'sham' monocyte depletion. The aim is to determine whether removal of monocytes can interrupt the movement of neutrophils towards, and into, the lungs. At the time of writing the study is well under way, recruiting to target, and satisfying rigorous safety requirements. The study is expected to end in late September/early October. To our knowledge this is the first study of its kind in man. The study is guaranteed at least to provide novel insights into the biology of neutrophil recruitment to the human lung. More importantly, if neutrophil behaviour is beneficially influenced by our intervention, we intend to take the technique forward for rigorous exploration in patients at high risk of ARDS.

Professor John Simpson, Professor of Respiratory Medicine, Newcastle University

MHRA pilots non-commercial Phase 1 Accreditation Scheme in Edinburgh CRF

In November 2007, the Medicines and Healthcare products Regulatory Agency (MHRA), introduced a voluntary accreditation scheme for units conducting Phase I clinical trials of investigational medicinal products (1). Accredited units must meet stringent standards for avoiding harm to trial subjects and for handling medical emergencies should they arise. Integrated within NHS hospitals that offer immediate access to critical care facilities, CRFs provide an optimal environment in which to undertake Phase I clinical trials.

In March 2010, Edinburgh CRF submitted the first application for accreditation from a non-commercial clinical research facility (CRF) in the UK. The MHRA accepted our application and were keen to pilot the scheme within the non-commercial setting.



The existing accreditation criteria are tailored towards commercial research units, and under the current scheme Principal Investigators (PIs) for Phase I trials must have particular qualifications in clinical pharmacology. This poses a challenge for non-commercial CRFs, which unlike commercial units do not employ permanent medical staff to support their studies. Edinburgh CRF is embedded within an acute teaching hospital and our PIs are predominantly doctors who also work in local clinical departments. Many of them do not possess the clinical pharmacology qualifications that are stipulated in the MHRA accreditation scheme.

Our solution has been to develop a Phase I Study Review Committee (PISRC) comprising clinical pharmacologists, pharmacists, statisticians, experienced researchers, senior research nurses and quality management staff. The committee provides expert scientific review, risk assessment and mentorship to young investigators; all delivered under a comprehensive framework of guidelines and Standard Operating Procedures (SOPs). The model provides a robust structure for mitigating risk in early phase clinical trials and it enables PIs without the specified clinical pharmacology qualifications to undertake such studies under strictly controlled conditions. To complement the support provided by the PISRC, our Education Programme is developing an MSc module for Phase I clinical trials. This will be delivered as part of the Scottish Translational Medicine and Therapeutics Initiative (STMTI) directed by Professor David Webb.

Our PISRC model was greeted very favourably by the MHRA and it forms the basis of a proposal to revise the current accreditation criteria for the academic sector. The MHRA is coordinating a stakeholder consultation with key figures from academia and industry and we anticipate that the stakeholder group will reach a decision on the proposal this summer. Regarding our own accreditation status, we underwent a full GCP / Phase I inspection in November 2010 and while waiting for the outcome of the stakeholder consultation exercise, we have requested that our application be considered against the existing criteria. We expect to receive a decision regarding our acceptance into the Phase I Accreditation scheme very soon.

1. MHRA Phase I Accreditation Scheme (November 2007)

Specialist research services in Edinburgh's Clinical Research Facilities

Nursing and 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.

Operating across three hospitals sites, the research nurses 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 Royal Hospital for Sick Children (RHSC). Outreach and community research nurse support is also provided in the wider hospital and primary care setting.

Our research nurses are supported by an experienced team of Clinical Support Workers, Clinical Measurement Technicians, reception staff and a ward clerk. All work undertaken in the CRF is underpinned by robust quality management systems and monitored by our Quality Assurance Manager to ensure that we remain compliant with the regulatory requirements for clinical research. All CRF staff receive regular ICH Good Clinical Practice (GCP) updates according to our strict training policy.

The past year has been dominated by preparation for our Phase I accreditation inspection by the Medicines and Healthcare products Regulatory Agency (MHRA). The clinical team has worked exceptionally hard to meet the standards required for formal accreditation and this has paved the way for other non-commercial clinical research facilities across the UK. In addition to this intensive Phase I preparation, our nurses have supported an extensive range of studies, many involving the acquisition of new knowledge and skills. Examples include endoscopy studies and body composition investigations using our PeaPod and BodPod kits.

Two significant projects that reached completion last year were the Airwave Health Monitoring Study (AHMS) and the MRC National Survey of Health and Development (NSHD). Both of these projects were intensive, large scale and multicentre in nature. Our clinical team worked efficiently and effectively to overcome the many logistical challenges that these studies posed. Both projects were delivered to time and budget with healthy recruitment figures. More information can be found at the following websites:

http://www.police-health.org.uk/ http://www.nshd.mrc.ac.uk/

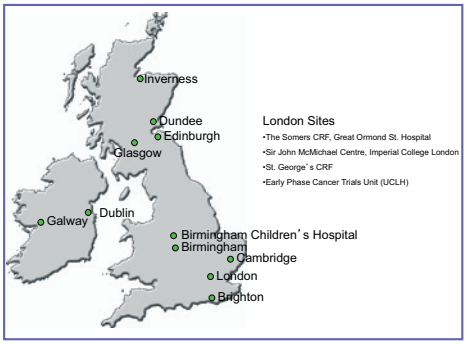
Research Nurse Manager: Sharon Cameron - sharon.cameron@luht.scot.nhs.uk - 0131 242 7185

Information Techology

Information technology pervades 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. We source, install and maintain hardware and software solutions and we provide guidance for computer systems validation, an important quality assurance function.

Key software developments to date include **CRF Manager**, which manages studies and resource bookings and **Course Manager**, which manages courses and seminars from registration to payment. This year we are working on the development of **Forms Manager**, an eCRF system which we have already used to collect data for several studies.



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

CRF Manager has been shared with colleagues across the UK and Ireland and it is now installed in thirteen other 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 **CRF Manager** as a common IT system for new facilities. The system has also been used to support non-CRF groups such as local research networks for study data input (forms) and resource scheduling.

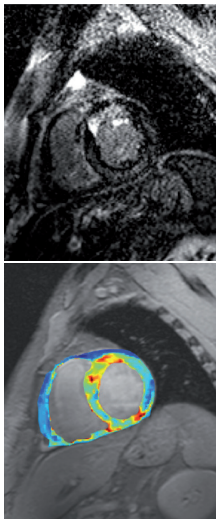
Course Manager has contributed to the success of our Education Programme, and the connected Clinical Research Training Scotland (CRTS) website is used across Scotland to publicise clinical research related courses and events.

Over the past 3 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

Image Analysis Core

The Image Analysis Core is now embedded within the Clinical Research Imaging Centre (CRIC) while still maintaining several workstations at the WTCRF. Over the past 12 months the Core has participated in a range of research activity featuring images from the scanners in CRIC (i.e. MRI, CT, PET-CT) as well as, amongst others, MR data from the Brain Research Imaging Centre (BRIC), images of the retina, and photographs of patients in hospital beds!



The Image Analysis Core is one of the leading partners in VAMPIRE which is an international collaboration developing a software platform for the analysis of retinal images. The software has already been used to analyse data from several studies that use the WTCRF including ORCADES and LBC1936.

The Core has been involved in processing and analysing MR scans acquired in CRIC. Change in T2* value derived from T2*-weighted MR imaging is used to detect accumulation of ultrasmall superparamagnetic particles of iron oxide (USPIO) within tissues inside the body. Uptake of USPIO is thought to identify areas of cellular inflammation. Regions of interest have so far included aortic aneurysms and myocardial infarctions.

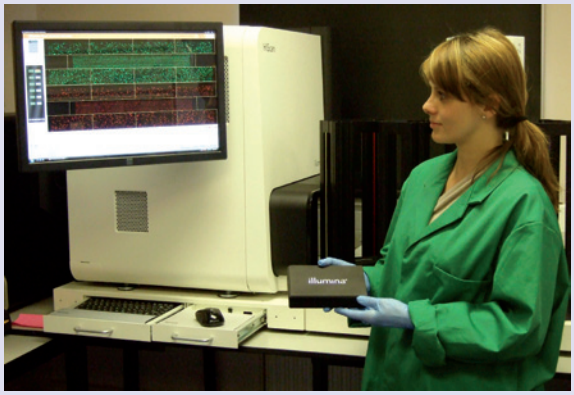
Currently, the Image Analysis Core is working with clinicians from the intensive care unit in Edinburgh on the analysis of photographs of patients lying in hospital beds. Post-processing a photograph returns a measurement of surface area which is then related to the patient's height and weight and used to determine drug dosage levels.

Core Manager: Tom MacGillivray - t.j.macgillivray@ed.ac.uk - 0131 242 7756; 0131 537 3351

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 and gene expression analysis is provided through three different platforms – Applied Biosystems 7900HT, Applied Biosystems OpenArray and Illumina HiScan.

The Genetics Core has been running an Illumina microarray platform for the past 5 years to investigate genetic variation, gene expression levels and methylation levels. The laboratory has upgraded the platform to become the first in Scotland to utilise the Illumina HiScan. This platform is able to process the new generation of high density genotyping arrays utilising data from the 1,000 genomes project. This investment in new technology will ensure that researchers continue to get access to these top-of the-range genetic platforms for their clinical research.



The Illumina HiScan provides high throughput genotyping coupled with the ability to run inexpensive gene expression and methylation assays

The Genetics Core has contributed work towards more than 300 publications, many in high-impact journals such as Molecular Psychiatry [27], Nature Genetics [26], Human Molecular Genetics [11], Nature [7], American Journal of Human Genetics [6], New England Journal of Medicine [4], PNAS [2], JAMA [1] and The Lancet [1].

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

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.

Investigators (Dr Fiona Denison and Dr Jackie Price) with Lead Statistician Catriona Graham presenting results on "Risk factors for post-dates pregnancy" to HRH Princess Anne

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:

Sensitive troponin assay: Although troponin assays have become increasingly more sensitive, it is unclear whether further reductions in the threshold of detection for plasma troponin concentrations will improve clinical outcomes in patients with suspected Acute Coronary Syndrome (ACS). As a result of this work we concluded that in patients with suspected ACS, implementation of a sensitive troponin assay increased the diagnosis of Myocardial Infarction (MI) and identified patients at high risk of recurrent MI and death. Lowering the diagnostic threshold of plasma troponin was associated with major reductions in morbidity and mortality.

Clots in Legs Or sTockings after Stroke (CLOTS): A suite of three trials investigating Deep Vein Thrombosis (DVT) prevention in patients following strokes. With the second trial (comparing thigh-length stockings to knee-length stockings) completed recently we were able to establish that proximal DVT occurs more often in immobile patients with stroke who wear below-knee stockings than in those who wear thigh-length stockings. Combining these data with the results from Trial 1 (ie. comparing thigh-length stockings to none) we hoped to determine if there were factors to allow us distinguish between immobile stroke patients at high and low risk of developing DVTs.

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

Mass Spectrometry Core

The Mass Spectrometry Core has had a productive year, supporting a range of projects in research fields of metabolism, reproduction, drug discovery and toxicology. The last year has seen major expansion with the introduction of 4 new instruments, purchased through a Wellcome Trust Equipment bid. The installation of the equipment is taking place in Q1 and Q2 of 2011 and the new facilities will offer a greater range of possibilities to scientists and clinicians.

The main area of improvement will be in the sensitivity of analysis permitting analysis of smaller volumes of samples and low abundance analytes. Other advances are the ability to analyse volatile compounds using Headspace analysis by GC-MS and lastly to permit on-line and automated sample preparation, benefiting high-throughput screening.

Finally the Core has introduced a synthetic chemistry service and has a dedicated post-doctoral scientist available to help synthesise novel analytes and metabolites. This opportunity has already been successful in supporting drug discovery and toxicology. We have enjoyed lively interactions with a number of post-graduate and post-doctoral scientists who have trained in our lab and the coming year will see the first PhD studentship embedded within our Core.

Dr Gregorio Naredo, synthetic chemist, recently joined the Mass Spectrometry Core team

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

Education Programme

Courses & Seminars

The Education Programme continues to run over 50 research training courses and seminars per year to meet the changing needs of clinical researchers locally and across Scotland. In addition to face-to-face teaching, we utilise online learning, web streaming and videoconferencing technologies, to reach a wider audience. An important new project for the team is the development of an MSc module for Phase I Clinical Trials as part of the Scottish Translational Medicine and Therapeutics Initiative led by our Programme Director Professor David Webb.

clinical research training for scotland

Event Planning

The Education team now offers its expertise in event planning (courses/seminars/conferences/open days) to other organisations. Among the events organised by the team were:

- Scottish Research Nurse & Co-ordinator's Network 4th Annual Conference 'Ethics & Governance in Clinical Research'
- The 'VITAmins TO Prevent Stroke (VITATOPS)' trial participants meeting
- WTCRF Public Open Day

Public Open Day May 2011

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 all 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 Scotland (CRTS) was set up in 2008 with a view to co-ordinating the provision of clinical research education and training across Scotland. Its remit is to implement educational initiatives and infrastructural changes to ensure the further development of clinical research activity in Scotland.

CRTS projects include:

- The CRTS website **www.crts.org.uk** – highlighting research training opportunities across Scotland
- An MHRA commissioned survey "*An evaluation of the opinions and perceptions of academic trialists regarding the legislative framework for Clinical Trials of Investigational Medicinal Products (CTIMPs)*". This resulted in the introduction of a risk based approach to the regulation of non-commercial CTIMPs in the UK.
- A Blueprint for a National Education and Training Strategy for Clinical Researchers in Scotland

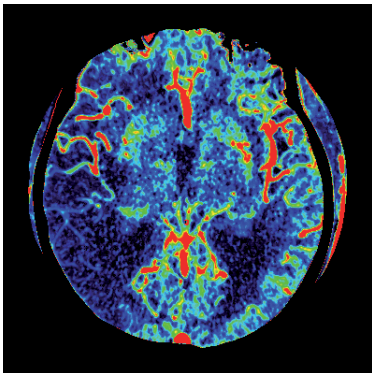
Edinburgh CRF Education Programme provides a wide variety of training and courses

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

Programme Manager: Michelle Evans - 0131 537 3326 – michelle.evans@ed.ac.uk

Specialist research services in Edinburgh's Clinical Research Facilities

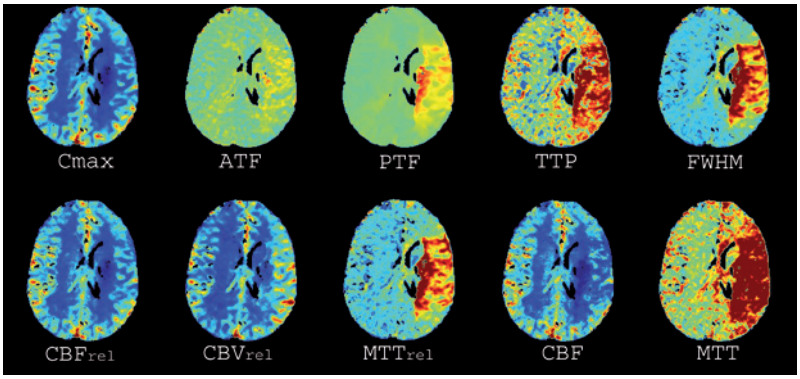
Brain Research Imaging Centre



The Brain Research Imaging Centre (formerly SBIRC) is a key component of the WTCRF Imaging core. BRIC is home to multi-disciplinary 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 experience of the staff and the dedicated research MRI scanner at the heart of the Centre allow BRIC to achieve 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 is embedded within clinical space in the Department of Neuroradiology and Clinical Neurosciences (DCN) at the Western General Hospital (WGH). The relationship of this University of Edinburgh research facility within an NHS department is mutually beneficial, enabling BRIC to carry out research work on critically ill subjects, as appropriate emergency clinical support is on hand.



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.

BRIC is a leader in excellence in neuroimaging and disseminating knowledge through teaching and research seminars and provision of an MSc and Continuing Professional Development (CPD) online. The Centre supports staff development in maintaining a portfolio of transferable skills. The Centre website makes available downloadable software tools for qualitative and quantitative image analysis.
Ethical management of research imaging is a key focus of the Centre. In July 2010 BRIC led a UK wide seminar hosted at the Wellcome Trust, London, for all research imaging centres, professional organisations, ethicists and lay groups to produce a UK model on managing incidental findings in research images. The Centre also set up "Imaging in Society" workshops, the results of which were presented to the Scottish Parliament.

Professor Joanna Wardlaw, Chair of Applied Neuroimaging

Top papers

1. Penke L, Muñoz Maniega S, Murray C, Gow AJ, Hernández MC, Clayden JD, Starr JM, Wardlaw JM, Bastin ME, Deary IJ. **A general factor of brain white matter integrity predicts information processing speed in healthy older people**. Journal of Neuroscience 2010;30(22):7569-74.
2. Sprooten E, Sussmann JE, Moorhead TW, Whalley HC, Ffrench-Constant C, Blumberg HP, Bastin ME, Hall J, Lawrie SM, McIntosh AM. **Association of white matter integrity with genetic variation in an exonic DISC1 SNP**. Molecular Psychiatry 2011; In press
3. Walter T, Shattuck DW, Baldock R, Bastin ME, Carpenter AE, Duce S, Ellenberg J, Fraser A, Hamilton N, Pieper S, Ragan MA, Schneider JE, Tomancak P, Hériché JK. **Visualization of image data from cells to organisms**. Nature Methods 2010;7(3 Suppl):S26-41.
4. Bastin ME, Muñoz Maniega S, Ferguson KJ, Brown LJ, Wardlaw JM, MacLullich AM, Clayden JD. **Quantifying the effects of normal ageing on white matter structure using unsupervised tract shape modelling**. NeuroImage 2010;51(1):1-10.

Top projects - SPIRIT (industrial collaboration), Mild Stroke Study 2, LBC wave 2 scanning

Clinical Research Imaging Centre

The Clinical Research Imaging Centre (CRIC) was formally opened by HRH the Duke of Edinburgh in the Queen's Medical Research Institute on October 29th 2010, and is rapidly developing into one of the flagship research centres within the University of Edinburgh.

CRIC is a partnership between the University and NHS Lothian, offering state-of-the-art imaging facilities for patient care, clinical research purposes and more general public engagement.

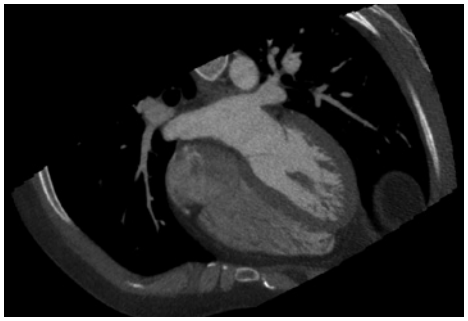
CRIC is staffed by a multidisciplinary group of imaging scientists, including radiologists, physicists, image-analysis specialists and radiochemists, facilitated by a team of support staff.

The group is further strengthened by close collaboration with clinicians who have a need for image-based tools in their research, including cardiologists, obstetricians, psychiatrists, oncologists, hepatologists and allied scientists in the health sciences domain.

As well as hosting the 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 CRF Manager system developed by the 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.

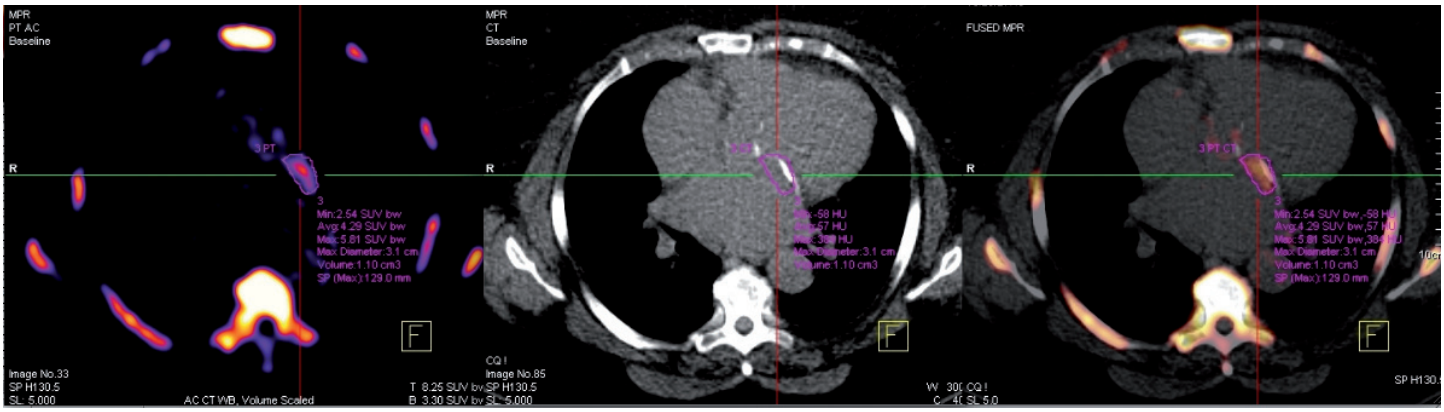
The facility currently houses a 3T Verio MRI system, a 128-MDCT mCT-PET system and a 320-MDCT Aquilion ONE system with supporting image-analysis facilities, as well as a GE cyclotron and radiochemistry suites to allow the full range of imaging-based research to be developed.

CRIC developments over the past 18 months include: installation of a multinuclear functioning high-field strength magnet capable of probing bodily functions in the brain and other organs; development of unique supporting structures to provide fMRI and MR elastography; establishment of research using all modalities and in a wide range of clinical specialities and provision of public support to schools and the National Museums of Scotland.



We welcome anybody with imaging needs interested in discussing potential collaboration and we 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



CRIC's partnership with Cardiovascular Sciences has resulted in novel ways to assess aortic valve stenosis. This image demonstrates the calcification process using Na-18-F as a tracer using PET-CT imaging.

Selected key publications from Edinburgh's Clinical Research Facilities 2005 - 2010

Translational Promise of the Apelin-APJ system

Jaap AG, Cruden NL, Barnes G, van Gemeren N, Matthews J, Adamson J, Johnston NR, Denvir MA, Megson IL, Flapan AD, Newby DE (2010)
Acute cardiovascular effects of apelin in humans: potential role in patients with chronic heart failure.
Circulation, Apr 27; 121(16): 1818-27.

Apelin, the endogenous ligand for the novel G protein-coupled receptor APJ, has major cardiovascular effects in preclinical models. In a series of randomised, double-blind, placebo-controlled studies, investigators in Edinburgh set out to establish the effects of acute apelin administration on peripheral, cardiac, and systemic hemodynamic variables in healthy volunteers and patients with heart failure.

Measurements of forearm blood flow, coronary blood flow, left ventricular pressure, and cardiac output were made by venous occlusion plethysmography, Doppler flow wire and quantitative coronary angiography, pressure wire, and thoracic bioimpedance, respectively. Intrabrachial infusions of (Pyr(1)) apelin-13, acetylcholine, and sodium nitroprusside caused forearm vasodilatation in patients and control subjects (all P<0.0001). Vasodilatation to acetylcholine (P=0.01) but not apelin (P=0.3) or sodium nitroprusside (P=0.9) was attenuated in patients with heart failure. Intracoronary bolus of apelin-36 increased coronary blood flow and the maximum rate of rise in left ventricular pressure and reduced peak and end-diastolic left ventricular pressures (all P<0.05). Systemic infusions of (Pyr(1))apelin-13 (30 to 300 nmol/min) increased cardiac index and lowered mean arterial pressure and peripheral vascular resistance in patients and healthy control subjects (all P<0.01) but increased heart rate only in control subjects (P<0.01).

The investigators demonstrated that acute apelin administration in humans causes peripheral and coronary vasodilatation and increases cardiac output. APJ agonism represents a novel potential therapeutic target for patients with heart failure. The CRF clinical team provided nursing and sample processing support for these studies.

ESPAC 3 trial results

European Study Group for Pancreatic Cancer (2010)
Adjuvant chemotherapy with fluorouracil plus folinic acid vs gemcitabine following pancreatic cancer resection: a randomised controlled trial.
JAMA, 304(10): 1073-81.

Adjuvant chemotherapy for pancreatic cancer has been shown to improve survival following resection, with a preference for Gemcitabine as drug of choice among American clinicians compared with Fluorouracil in Europe and other regions.
Third in a series of trials conducted by the European Study Group for Pancreatic Cancer, ESPAC-3 is the largest adjuvant trial conducted in pancreatic cancer to date. It aimed to compare the effectiveness of gemcitabine versus fluorouracil plus folinic acid in the treatment of pancreatic ductal adenocarcinoma following R0/R1 resection. Scottish patients in the CRF were among the 1088 patients recruited worldwide into this important Clinical Trial.
Patients with resected pancreatic cancer treated with fluorouracil plus folinic acid had a median survival of 23.0 months, compared with 23.6 months for those treated with gemcitabine. Progression-free survival was 14.1 and 14.3 months, respectively.
In addition to similar overall and progression-free survival, the authors found that there were no significant differences between treatment groups in global quality-of-life scores. However, more toxic effects were reported by patients receiving fluorouracil plus folinic acid. A total of 77 patients (14%) in that group reported 97 treatment-related serious adverse events, whereas 40 patients (7.5%) in the gemcitabine group reported 52 events (P < .001).
These results contribute to the better understanding of therapy options in pancreatic cancer allowing clinicians to offer a clearly validated alternative treatment where patients are unable to tolerate either regime.
CRF nurses were trained in the administration of chemotherapy in order to support this trial and the ESPAC team returned to the CRF for an extension sample collection phase.

Profiling epigenetic changes in breast cancer

Sproul D, Nestor C, Culley J, Dickson JH, Dixon JM, Harrison DJ, Meehan RR, Sima AH, Ramsahoye BH (2011)
Transcriptionally repressed genes become aberrantly methylated and distinguish tumors of different lineages in breast cancer.
Proceedings of the National Academy of Sciences 108 (11): 4364-4369.

Epigenetics is the study of heritable changes in gene function that occur without a change in the DNA sequence and is mediated by a number of different systems in cells. One example is the mark of DNA methylation which usually indicates genes that are inactive. In cancer, many genes become aberrantly marked by DNA methylation. This is generally thought to represent a means by which tumours can inactivate genes safeguarding the cell.
This view was challenged by a recent study by researchers at the IGMM funded by Breakthrough Breast Cancer. Sproul and colleagues combined DNA methylation and gene expression profiling on arrays run on the Illumina HiScan at the CRF Genetics Core, finding that the majority of genes which are aberrantly methylated in breast cancer are already off in the normal cells from which tumours develop. DNA methylation also marked different genes in tumours derived from different cell types and may be able to be used by doctors to distinguish different types of breast cancer and thus better match patients to treatments.

Lowering the Troponin 1 assay diagnostic threshold improves outcomes in Acute Coronary Syndrome

Mills NL, Churchhouse AM, Lee KK, Anand A, Gamble D, Shah AS, Paterson E, MacLeod M, Graham C, Walker S, Denvir MA, Fox KA, Newby DE (2011)
Implementation of a sensitive troponin I assay and risk of recurrent myocardial infarction and death in patients with suspected acute coronary syndrome.
JAMA 2011 Mar 23;305(12):1210-6.

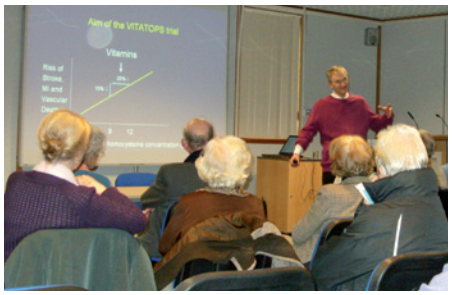
Edinburgh investigators aimed to determine whether lowering the diagnostic threshold for myocardial infarction (MI) with a sensitive troponin assay could improve clinical outcomes. A total of 2092 patients with suspected Acute Coronary Syndrome were enrolled into this two phase study. During the validation phase, only concentrations above the original diagnostic threshold of 0.20 ng/mL were reported to clinicians. During the implementation phase, lowering the diagnostic threshold to 0.05 ng/mL was associated with a lower risk of death and recurrent MI (from 39% to 21%) in patients with troponin concentrations of 0.05 to 0.19 ng/mL (odds ratio, 0.42; 95% confidence interval, 0.24-0.84; P = .01).
The main outcome measure was event-free survival (recurrent MI and death) at 1 year in patients grouped by plasma troponin concentrations. In patients with suspected ACS, implementation of a sensitive troponin assay increased the diagnosis of MI and identified patients at high risk of recurrent MI and death. Lowering the diagnostic threshold of plasma troponin was associated with major reductions in morbidity and mortality
Statistical support for the review, analysis and presentation of data from this large important clinical audit was provided by the CRF statistician Cat Graham, with specific expert advice on logistic regression and survival analysis.

B vitamins in Secondary Stroke prevention – VITATOPS trial shows no benefit

VITATOPS Study Group (2010)
B vitamins in patients with recent transient ischaemic attack or stroke in the VITAmins TO Prevent Stroke (VITATOPS) trial: a randomised, double-blind, parallel, placebo-controlled trial.
Lancet Neurology, 2010 Sep; 9(9): 855-65

Participants in one of the largest stroke trials to date were seen in the Edinburgh CRF. A total of 8164 participants from 123 centres worldwide were recruited into this study supported by the Medical Research Councils of the UK, Australia and Singapore. Results published in Lancet Neurology in September 2010 confirmed the findings from previous studies that administration of Vitamin B was safe but did not reduce the risk of major vascular events in patients with a previous stroke or TIA.

This complex multi-centre international randomised placebo control trial lasted for 12 years and produced complete follow up on 91% of participants. It represents a major contribution to the understanding of the treatment and prevention of cerebrovascular disease.



CRF nurses carried out the study visits for VITATOPS and the Education Programme organised the Trial Participant Meeting led by Prof Martin Dennis.

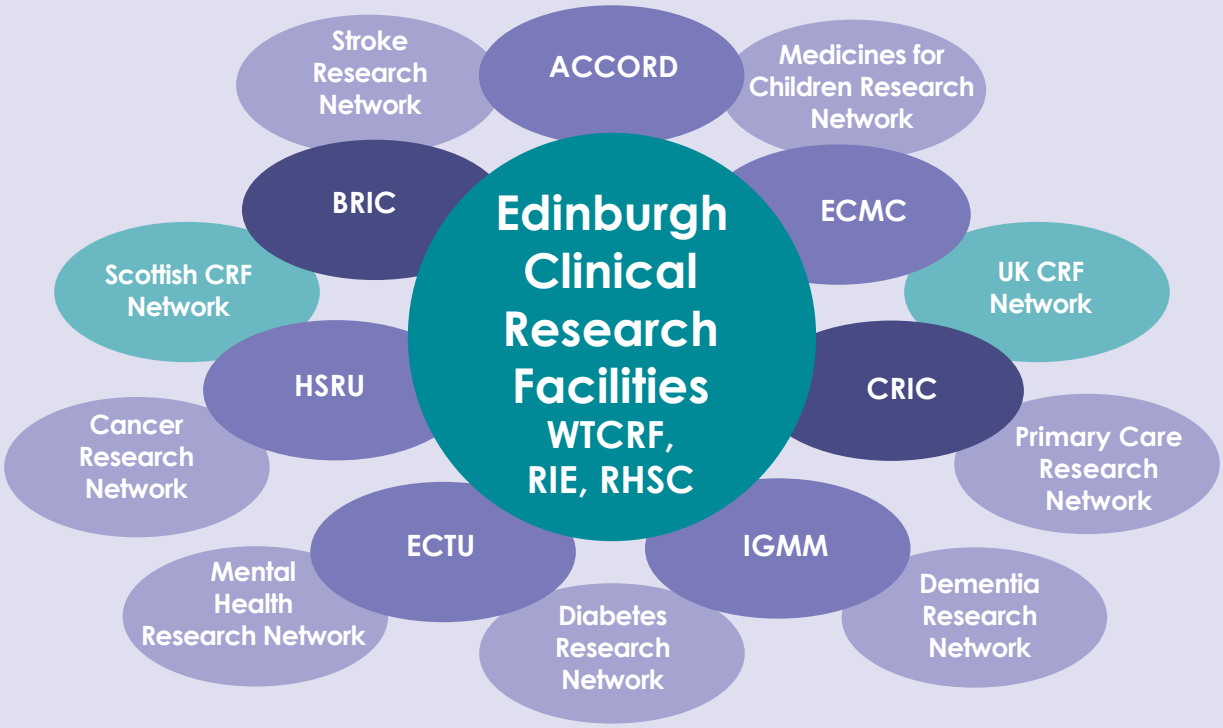
Novel imaging techniques improve prediction of outcomes in Abdominal Aortic Aneurysm

Jennifer M.J. Richards; Scott I. Semple; Thomas J. MacGillivray; Calum Gray; Jeremy P. Langrish; Michelle Williams; Marc Dweck; William Wallace; Graham McKillop; Roderick T.A. Chalmers; O. James Garden; David E. Newby (2011)
Abdominal Aortic Aneurysm Growth Predicted by Uptake of Ultrasmall Superparamagnetic Particles of Iron Oxide A Pilot Study
Circulation Cardiovascular Imaging 2011;4;274-281

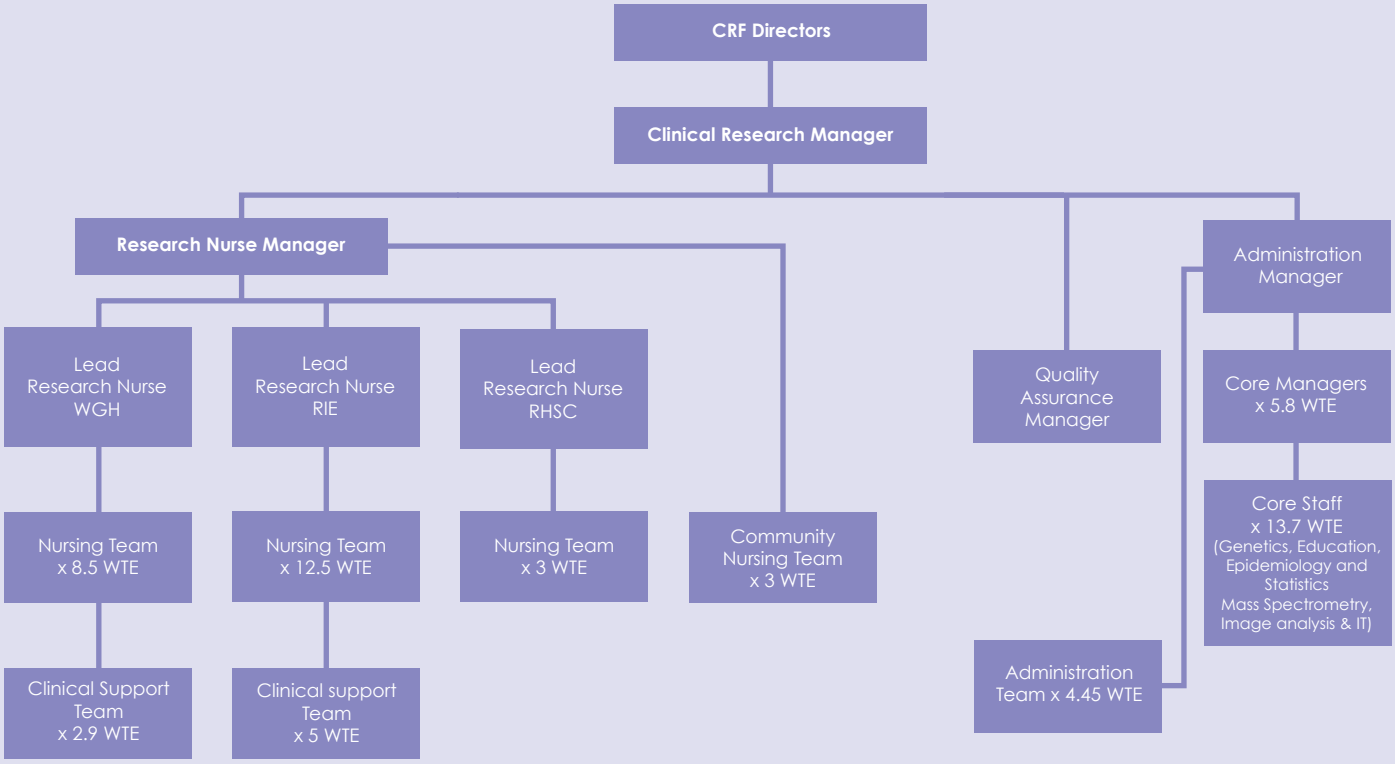
Abdominal aortic aneurysms (AAA) are a major cause of death. Current screening and surveillance data indicate that 50% of small aneurysms (<5.5cm in diameter) will not progress to further expansion and rupture. AAA screening is being introduced in many countries worldwide and there is a need for more sophisticated techniques for predicting clinical outcomes. This will enable targeted screening, surveillance and intervention at high risk patients, reducing morbidity and mortality and the overall economic cost.
Ultrasmall superparamagnetic particles of iron oxide (USPIO) have been observed to accumulate in areas of inflammation within tissues. This study investigated the contribution of USPIO and novel imaging techniques to developing a predictive model for AAA beyond the simple anatomic measure of aneurysm diameter.
Stable patients with asymptomatic abdominal aortic aneurysms were recruited from a surveillance program and imaged using a 3-T MRI scanner before and 24 to 36 hours after administration of USPIO. The change in T2* value on T2*-weighted imaging was used to detect accumulation of USPIO within the aneurysm. Uptake of USPIO in AAA identifies cellular inflammation and appears to distinguish those patients with more rapidly progressive abdominal aortic aneurysm expansion.
The RIECRF provided nursing and sample processing support for this important pilot study which also involved the state of the art research scanning facility at CRIC and the expertise of the CRF Image Analysis core.

Edinburgh's Clinical Research Facilities - external relationships and internal organisation

Outward focus



Internal structure



ECMC CRIC BRIC

Edinburgh's Clinical Research Facilities - Key Contacts

Directors
Professor David Newby
Professor Peter Hayes

Clinical Research Manager
Fiona McArdle
fiona.mcardle@luht.scot.nhs.uk
0131 537 3358

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

QA Manager
Susan Shepherd
susan.shepherd@luht.scot.nhs.uk
0131 537 3328

Study Information Manager
Jayne Blanshard
Jayne.blanshard@ed.ac.uk
0131 537 3359

Administration Manager
Elspeth Currie
e.currie@ed.ac.uk
0131 537 3357

Wellcome Trust CRF
Western General Hospital
Crewe Road South
EdinburghEH4 2XU
Scotland
Reception: 0131 537 2591
Fax: 0131 537 3361

Lead Research Nurse
Gerry Cummings
geraldine.cummings@luht.scot.nhs.uk
0131 537 3388

RIE CRF
51 Little France Crescent
Edinburgh
EH16 4SA
Reception: 0131 242 7183
Fax: 0131 242 7184

Lead Research Nurse
Finny Paterson
finny.paterson@luht.scot.nhs.uk
0131 242 7186

Children's CRF
Royal Hospital for Sick Children
Sciennes Road
Edinburgh EH9 1LF

Lead Research Nurse
Kay Riding
kay.riding@luht.scot.nhs.uk
0131 536 0808 Fax: 0131 536 0817

Education Programme
Director: Professor David Webb
Manager: Michelle Evans
michelle.evans@ed.ac.uk
0131 537 3326

IT Programme
Manager: Elizabeth McDowell
elizabeth.mcdowell@ed.ac.uk
0131 537 3353

CORES
Epidemiology and Statistics
Director: Sarah Wild
Associate Director: Steff Lewis
Manager: Cat Graham
c.graham@ed.ac.uk
0131 537 3350

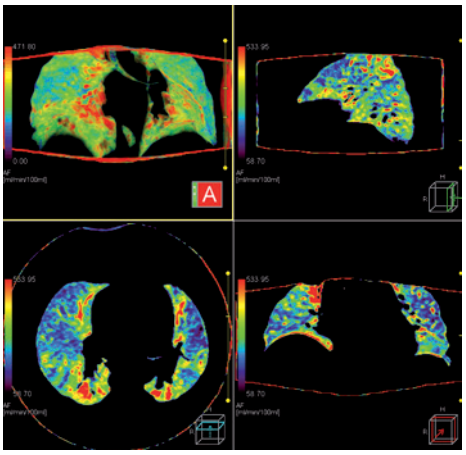
Genetics
Director: Professor David Porteous
Associate Director: Shona Kerr
Manager: Lee Murphy
lee.murphy@ed.ac.uk
0131 537 3370

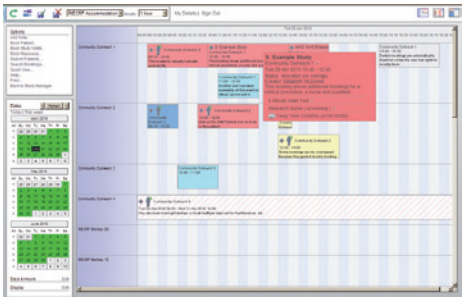
Image Analysis
Director: Professor Ian Marshall
Manager: Tom MacGillivray
t.j.macgillivray@ed.ac.uk
0131 537 3351 0131 242-7756

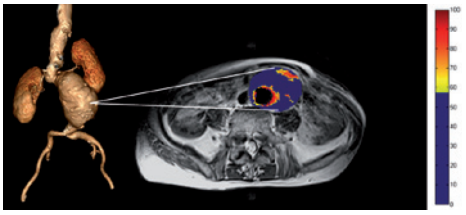
Mass Spectrometry
Director: Dr Ruth Andrew
Associate Director:
Professor Brian Walker
Manager: Natalie Homer
nhomer@staffmail.ed.ac.uk
0131 242 9333

Research Imaging Centres
Brain Research Imaging Centre (BRIC)
Division of Clinical Neurosciences
Western General Hospital
Crewe Road
Edinburgh
EH4 2XU UK
Director: Professor Joanna Wardlaw
Scientific Business Manager:
Duncan Martin
dmartin2@staffmail.ed.ac.uk
0131 537 2664 Fax 0131 537 2661

Clinical Research Imaging Centre (CRIC)
Queen's Medical Research Institute,
47 Little France Crescent, Edinburgh,
EH16 4TJ
Director: Professor Edwin van Beek
Co-Director: Professor David Newby
Manager: Stuart Docherty
stuart.docherty@ed.ac.uk
0131 242 7767 Fax 0131 242 7773







clinical research facility EDINBURGH

Wellcome Trust Clinical Research Facility
North Corridor
Western General Hospital
Crewe Road South
Edinburgh
EH4 2XU

Tel: 0131 537 2591
Fax: 0131 537 3361

RIE Clinical Research Facility
Royal Infirmary of Edinburgh
51 Little France Crescent
Edinburgh
EH16 4SA

Tel: 0131 242 7183
Fax: 0131 242 7184

Children's Clinical Research Facility
Royal Hospital for Sick Children
Sciennes Road
Edinburgh
EH9 1LF

Tel: 0131 536 0808
Fax: 0131 536 0817

CHIEF SCIENTIST OFFICE

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NHS Lothian

UKCRF NETWORK
UK Clinical Research Facility Network

THE SICK KIDS

BRAIN RESEARCH IMAGING CENTRE
Edinburgh

clinical research imaging centre EDINBURGH

clinical research training for scotland

Key Contacts:

Director: Professor David Newby
Tel: 0131 242 6422
E-mail: d.e.newby@ed.ac.uk

Clinical Research Manager: Fiona McArdle
Tel: 0131 537 3358
E-mail: Fiona.McArdle@luht.scot.nhs.uk

Website:

www.wtcrf.ed.ac.uk

Designed by Graphics Lab, Learning Technology Section, The University of Edinburgh