clinical research facility
EDINBURGH

May 2010

Delivering excellence in clinical research

Introduction

The Wellcome Trust Clinical Research Facility (WTCRF) is firmly established at the heart of clinical research infrastructure in Edinburgh. It is almost 10 years since our building was officially opened by HM Queen Elizabeth II and we are delighted to welcome our key stakeholders to the facility for an evaluation visit. We have taken this opportunity to reflect upon pivotal achievements to date, focussing particularly on the last 5 years which have marked a number of significant advances in our research services. Key milestones in our development are detailed on page 1 with selected metrics illustrated in Figures 1-7 on pages 2-3.

From the initiation of the WTCRF on a single hospital base in 2001, Edinburgh's CRF now operates across three sites: the Western General Hospital (WGH), the Royal Infirmary of Edinburgh (RIE) and the Royal Hospital for Sick Children (RHSC). The expanded CRF facilitates high quality research across a broad range of specialities and professional groups. All three sites share a highly successful management model that has been extended to embrace other local research units including the SFC Brain Imaging Research Centre (SBIRC) and the new Clinical Research Imaging Centre (CRIC). This operational management model has also been replicated in other CRFs across the UK.

The foundation stone of our success has been the long-standing close and well-developed partnership between NHS Lothian and the University of Edinburgh. The strong track record of collaborative working continues to flourish through recent strategic developments. These include the new Clinical Research Imaging Centre (CRIC) in the Queen's Medical Research Institute (QMRI) and the larger Children's Clinical Research Facility (CCRF) that is being designed for the future children's hospital at Little France. Research undertaken through our facilities has contributed to several successful applications to form specialist centres including the third UK Tommy's Research Centre, the British Heart Foundation Centre for Research Excellence and the MRC Centre in Cognitive Ageing and Cognitive Epidemiology.

Collaborative working is central to our achievements and we are a key stakeholder in Edinburgh's Academic and Clinical Central Office for Research and Development (ACCORD). ACCORD brings together research management staff from NHS Lothian and the University of Edinburgh to facilitate collaborative clinical research of the highest quality. ACCORD supports researchers by streamlining local governance systems and providing clear and easy access to expert advice. At a national level, Edinburgh has had a leading role in the development of the Scottish CRF Network, a platform that supports the coordinated adoption of multicentre studies in Scotland. At a UK level, Fiona McArdle our Clinical Research Manager is a founder member of the UKCRF Network and she continues to sit on its Strategic Planning Team. Edinburgh has contributed significantly towards both of these networks providing particular input to IT developments, quality assurance initiatives and national research training programmes.

In 2008, Edinburgh joined Aberdeen, Dundee and Glasgow in a collaboration of four health boards and four universities to form the Scottish Academic Health Sciences Collaboration (SAHSC). The collaboration has been developed with funding from the Chief Scientist Office (CSO) to establish a world-leading platform of coordinated research infrastructure in Scotland, and the CRF has a key role in delivering Edinburgh's contributions. Recent major developments such as the aforementioned Children's Clinical Research Facility (CCRF) and the consolidation of our partnership with the Clinical Research Imaging Centre (CRIC) will support the realisation of SAHSC objectives.

In order to underpin our growing body of work and support our researchers in meeting regulatory requirements, we have invested significant time and effort in the development of our quality management systems. Key to the success of this work has been the appointment of a Quality Assurance Manager in 2007, enabling us to make significant advances in our quality systems. These advances include the implementation of new standards to meet MHRA criteria for Phase I Accreditation. Our Phase I capability has already drawn interest from colleagues in industry and we anticipate that MHRA accreditation will encourage further collaboration with parties in the commercial sector who wish to conduct early phase clinical trials in Scotland.

In conclusion, we hope that this brochure will provide supporting detail for the site evaluation visit, illustrating the hard work and commitment that we have invested in providing world class facilities for clinical researchers in Edinburgh and the UK. Each year the number of high impact publications arising from CRF studies continues to grow and these demonstrate the close and productive relationships that we have fostered with our clinical and academic colleagues. As we work together to drive up the quality of clinical research, we have chosen to showcase selected publications from the past five years and these are highlighted on pages 14-16.




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

- **1997** Edinburgh awarded Millennial Funding to develop WTCRF
- **1998** Pilot Facility opened in Western General Hospital
- **1998** Satellite Facility opened in Royal Infirmary of Edinburgh
- **2001** Official Opening of WTCRF by HM Queen Elizabeth II
- **2003** Launch of WTCRF Education Programme
- **2003** Sister Facility Opened in New Royal Infirmary of Edinburgh
- **2005** Scottish CRF Network Inaugural Meeting
- **2005** Edinburgh Experimental Cancer Medicine Centre integrates with WTCRF
- **2006** Launch of Edinburgh Clinical Trials Collaboration & accreditation of Edinburgh Clinical Trials Unit with the UKCRC
- **2006** SFC Brain Imaging Research Centre (SBIRC) enters partnership with WTCRF to form Imaging Core
- **2006** Paediatric CRF Service launched with appointment of ScotMCN Research Nurse.
- **2006** NHS Education Scotland (NES) funds Nationalisation of WTCRF Education Programme
- **2006** Clinical Research Infrastructure Award granted to develop Clinical Research Imaging Centre (CRIC)
- **2006** Translational Medicine Research Collaboration (TMRC) with Wyeth Pharmaceutical Co.
- **2007** Community Research Nurse Service initiated
- **2007** Scottish Imaging Network a Platform for Scientific Excellence (SINAPSE)
- **2007** Clinical Research Infrastructure Award granted for CRIC
- **2008** UKCRF Network officially launched.
- **2008** Edinburgh hosts the 4th Annual UK Clinical Research Facilities' Conference
- **2008** Business Case submitted for Children's CRF in New Sick Children's Hospital (opening 2013)
- **2008** Professor Sir John Savill is appointed Chief Scientist
- **2008** WTCRF Director Professor Newby is appointed Director of R&D for NHS Lothian.
- **2009** 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** Application submitted to the MHRA For Phase I Accreditation

Selected metrics 2005 - 2009

Fig 1: Edinburgh CRF Studies

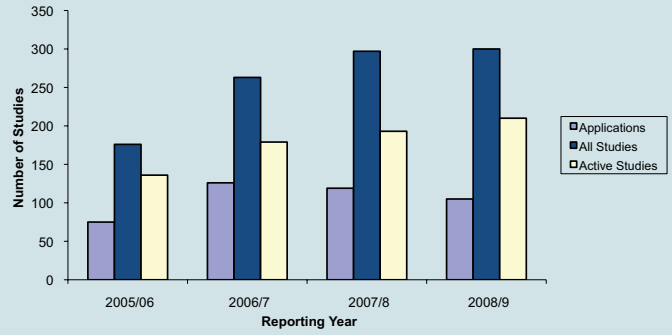


Fig 2: Range of Studies Undertaken in CRF

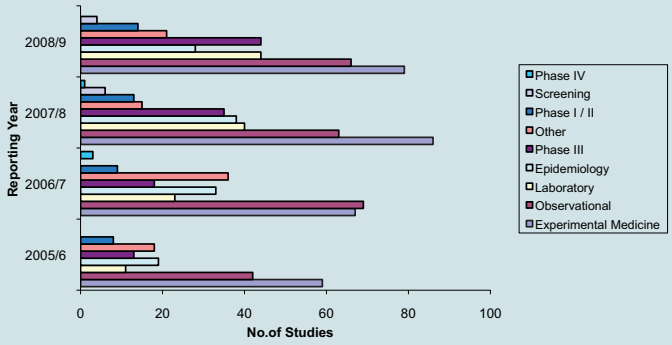


Fig 3: Top 10 Clinical Specialities

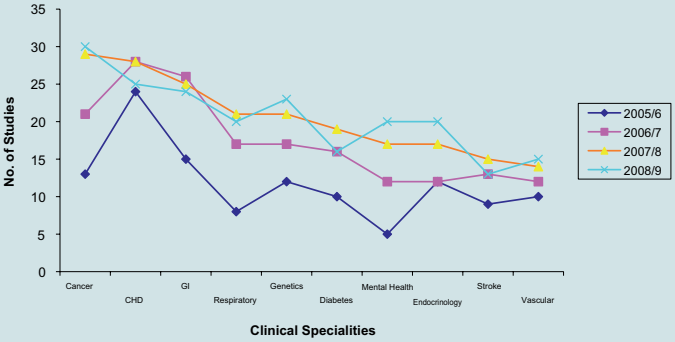
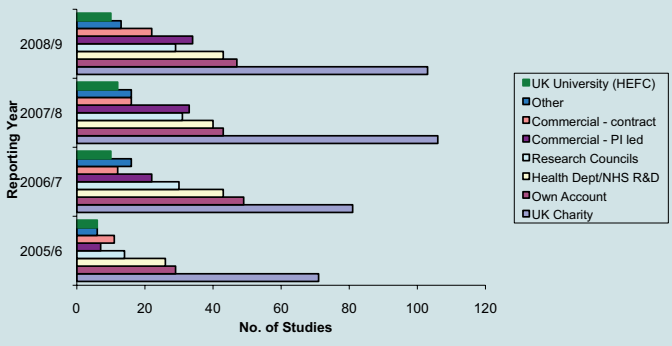
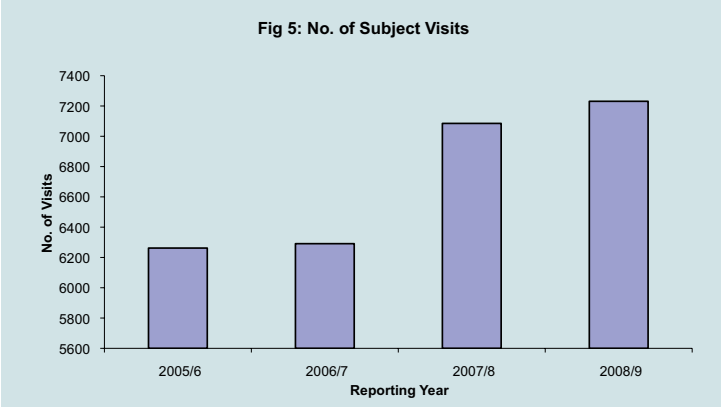
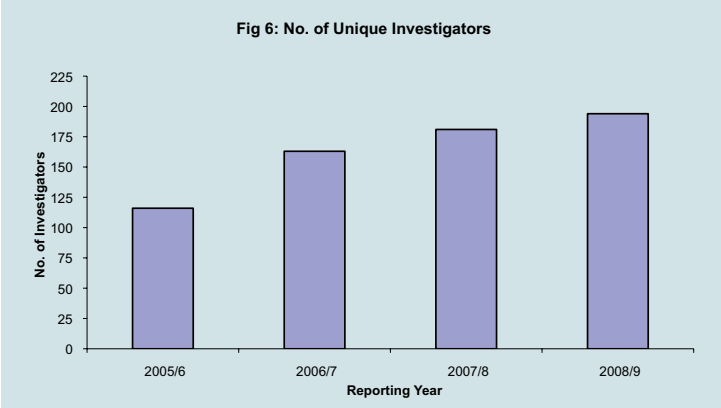
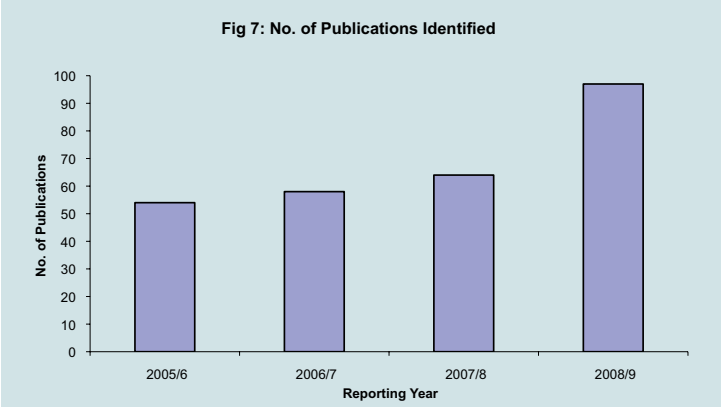


Fig 4: Funding Sources for CRF Sudies









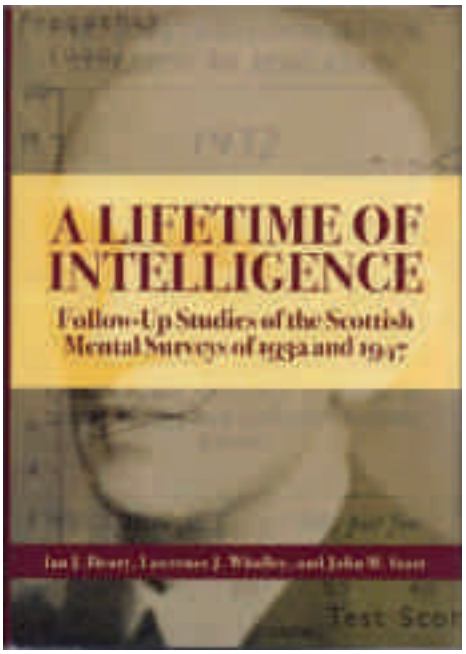
Figures 1-7 show activity data from 2005/6 to 2008/9. These illustrate the size and diversity of our research portfolio as it has developed over recent years.

Key projects and initiatives from Edinburgh's Clinical Research Facilities

The Lothian Birth Cohorts of 1921 and 1936

2011 will be our thirteenth year at the Wellcome Trust Clinical Research Facility (WTCRF) at the Western General Hospital, and we hope it will be yet another lucky one. To date, the Lothian Birth Cohort 1921 and 1936 studies have produced well over 2,500 visits to the WTCRF. During 2011, and continuing until early 2013, the Lothian Birth Cohort 1936 will be back again, at age 76. Also during 2011, the Lothian Birth Cohort 1921 will be back, at age 90!

Back in 1998, when John Starr and I were first thinking about how and where we should test the 550 people of the Lothian Birth Cohort 1921 we knew we had a problem. The then 79-year-olds needed a thorough cognitive test battery, which my psychologists were well trained to perform. But they also required several medical and physiological tests, and blood to be drawn for a number of biomarkers and genetic analysis. I had been involved with the application for the WTCRF and we knew that it would be ideal for our study. Things that would be a headache to achieve in a Psychology Department setting were what the WTCRF was set up to do. It was important to get things right. These were special people. In childhood, they had taken IQ-type tests in the nationwide Scottish Mental Surveys of 1932 and 1947, and we had a unique opportunity to study the reasons that people differ in how their mental abilities change across almost the whole lifecourse.



The Lothian Birth Cohort 1921 has now undergone three waves of testing, at ages 79, 83, and 86. The Lothian Birth Cohort 1936 has had two waves of testing, at ages 70 and 73.

The WTCRF has proven to be the perfect host for our longitudinal studies of healthy cognitive and physical ageing, and we got far more than we originally bargained for. Sure, we got very professional and well-standardised medical testing and phlebotomy services but over time, both we and the WTCRF grew. Our medical testing grew more ambitious, and the nurses at the WTCRF took on the new tasks. Our genetic ambitions grew, and the Genetics Core performed genome-wide scanning on the Lothian Birth Cohorts, and other related cohorts. When we obtained funding for brain imaging the Lothian Birth Cohort 1936, the Imaging Core took on the massive task of seeing the best part of our 800 people for an hour-long MRI scan. When we decided to analyse retinal photographs, the Image Analysis Core provided expertise and help with that. It's been a good and growing relationship.

In addition to the purely practical aspects of getting the testing and analysis done - with which the WTCRF has been essential for my team's studies - there is a lot more that the facility provides. The Lothian Birth Cohorts comprise relatively healthy individuals, providing their help because of altruism. It helps a lot that they see from the start that we are set up in a highly professional environment, with respect to the physical and personnel aspects. It helps to achieve the high retention over the waves of the studies.

What matters most is the scientific output. It's been better than we could have imagined. Each year when I send the WTCRF the list of peer-reviewed studies that have been done as a result of the Lothian Birth Cohorts visiting the Facility, it grows substantially. The studies have contributed several dozens of journal reports on the determinants of cognitive and bodily ageing - all the way from genetic to social causes - and last year our book appeared on the first ten years of the studies (Deary, Whalley, & Starr, 2009). It is on the back of this successful scientific output that we were able successfully to bid for a Research Council-funded Centre for Cognitive Ageing and Cognitive Epidemiology, which started in 2008. At the Centre's core is the Lothian Birth Cohort Studies, who were there at the start of the WTCRF, and who will be back next year, and again after that.

Ian J. Deary
Professor of Differential Psychology
Director, Centre for Cognitive Ageing and Cognitive Epidemiology

Deary, I. J., Whalley, L. J., & Starr, J. M. (2009). A Lifetime of Intelligence: Follow-up Studies of the Scottish Mental Surveys of 1932v and 1947. Washington, DC: American Psychological Association.

Generation Scotland

Formally launched in February 2006, Generation Scotland (GS) has been made possible through a unique partnership between the Scottish people, the NHS in Scotland and the Scottish University Medical Schools. This stable population, supportive of the biomedical sciences, provides an ideal platform for genetic research and development.

The aim of Generation Scotland is to create an ethically sound, family and population-based cohort and associated infrastructure through which to identify the genetic basis of common complex diseases. It was designed to have a broad phenotypic focus so that it can act as a platform resource for research. The quality of the mental health and cognitive function phenotypes is exceptional and is a major strength.

Operating as a Research Tissue Bank, to the highest ethical standards, GS provides consented access to a range of biological samples, genotype and phenotype information from over 21,000 Scots. There is also the opportunity to enhance the phenotype information through NHS medical record linkage and additional sample/data collection through the network of Scottish Clinical Research Facilities. Such additional phenotypes could include prescribing data, valuable for pharmacogenetic studies.

Edinburgh's WTCRF Genetics Core has a key role in the initiative, having extracted and characterised DNA from more than 21,000 participants so far. The biological material and associated data are now in increasing demand from clinical researchers across Scotland. The resource was recently used in a large multi-centre replication study identifying genes involved in lung function that has helped indicate potential targets for interventions to alleviate respiratory disease (1).

GS has recruited over 21,000 participants into three main collections of DNA, other samples and data:

- GS:SFHS (Scottish Family Health Study)
- GS:21CGH (Genetic Health in the 21st Century)
- GS:3D (Donor DNA Databank)

Detailed descriptions of the resources, including Participant Information Leaflets & Consent Forms, are available at **www.generationscotland.org/resources.htm**.

Generation Scotland uses a customised Laboratory Information Management System (LIMS) that was developed by StarLIMS after competitive tender. The LIMS is currently functioning in laboratories in Aberdeen, Dundee, Edinburgh (the WTCRF Genetics Core) and Glasgow, where client PCs are linked securely via JANET (the joint academic network) to the main database located on the LIMS server in Edinburgh. All GS sites book samples into the same system and all labs can view sample data in real time. The LIMS also manages the shipping of blood tubes in batches from the recruitment centres across Scotland to the WTCRF in Edinburgh where DNA is extracted, and tracks the distribution of plates containing DNA across the four GS laboratories.

Advances in gene analytic technologies have started to make a significant impact, but much of the empirically known genetic variance remains unexplained and undiscovered. The unique features of Generation Scotland - high-fidelity phenotyping of cognitive, personality and mental health, plus heart, metabolic and inflammatory disease measures, conducted in families and linked to comprehensive medical records - creates a unique capacity for novel quantitative trait gene discovery and for validation of findings arising from other single disease-focussed studies. This will create an internationally competitive and high value resource for downstream genomic resequencing, proteomic, metabolomic, epigenetic, pharmacogenetic, biomarker and drug target discovery projects.

(1) Repapi, E. et al (2010) Nature Genetics 42 : 36–44

Key projects and initiatives from Edinburgh's Clinical Research Facilities

Iron nanoparticles in clinical MRI scanning

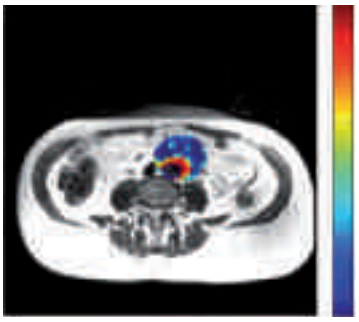
A key challenge in the management of abdominal aortic aneurysm (AAA) disease is predicting which patients are at risk of rupture and therefore require intervention. Current guidelines are based on a 55mm diameter threshold, above which intervention is recommended since it is known from surveillance data that the risk of rupture is increased. However, up to 20 per cent of ruptured AAA are less than 55mm and an improved method of assessing rupture-risk is desirable.

We have used Magnetic Resonance Imaging (MRI) with the novel contrast agent Sinerem, which contains 20nm ultrasmall superparamagnetic particles of iron oxide (USPIO), to detect hotspots of inflammation within AAA. Multi-echo, gradient echo T2*-weighted axial images of the aorta were acquired before and after administration of Sinerem.

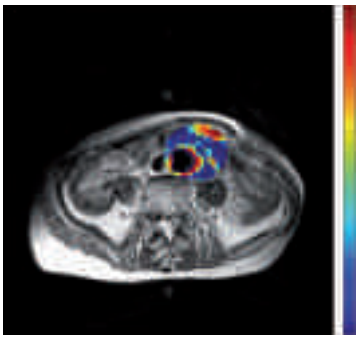
Images were registered and mean per cent change in T2* value was calculated on a multi-voxel grid. A change in T2* value in the peri-luminal thrombus was seen in the majority of patients. In addition, some patients had focal areas of USPIO uptake elsewhere within the AAA, consistent with inflammatory hotspots and aneurysm instability (see figure). Based on encouraging early results it is hoped that MRI scanning with USPIO might form the basis of an improved method of assessing AAA patients for risk of rupture in the future.

In another study we have developed a GMP-compliant, clinical-scale protocol for magnetic labelling of cells ex vivo with the SPIO agent Endorem (80-150nm). Having demonstrated in vitro that cells retain normal viability and function following labelling, we have undertaken a series of healthy volunteer pilot studies demonstrating a) that local and systemic administration of SPIO-labelled cells is safe, and b) that cells can be imaged at a target site at clinically relevant field strengths. Current studies investigate trafficking of SPIO-labelled mononuclear cells in clinical models of inflammation. If successful, this technique would lead to exciting opportunities for in vivo cell tracking in humans with both research and clinical applications which might include monitoring stem cell therapy and inflammatory cell trafficking.

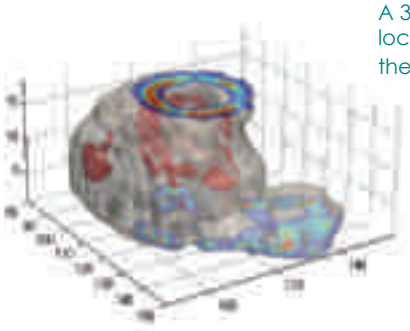
Accumulation of USPIO causes a reduction in the T2* value (red on colour scale).



An apparently stable AAA with periluminal USPIO accumulation only



A potentially unstable AAA with a focal hotspot of inflammation



A 3D representation of location of hotspots within the AAA.

The conduct of these studies was facilitated by the provision of nursing assistance and sample-processing by the WTCRF. Both of these studies have also benefited from the state of the art facilities available in the Clinical Research Imaging Centre (CRIC), including 3T MRI scanning and comprehensive physics and image analysis support.

Phase I Accreditation

Edinburgh's Clinical Research Facilities support the conduct of a broad range of clinical research studies including early phase clinical trials & First in Human (FIH) studies.

In 2007 The Medicines and Healthcare products Regulatory Agency (MHRA) introduced a voluntary accreditation scheme for units conducting Phase I clinical trials. Units within the scheme must meet satisfactory standards for avoiding harm to trial subjects and for handling medical emergencies should they arise.

This initiative followed in the wake of the widely publicised incident in 2006 when six healthy volunteers at a contract research organization were enrolled in the first Phase I clinical trial of TGN1412, a novel anti-CD28 monoclonal antibody. Within 12 to 16 hours of receiving the Investigational Medicinal Product (IMP), the subjects were critically ill and required treatment in intensive care.

A subsequent inquiry into the incident issued a set of recommendations to support the safe conduct of Phase I trials and the MHRA accreditation scheme developed from these.

In Edinburgh, we adopted the standards of the new accreditation scheme from an early stage, introducing new systems and procedures to enable us to apply for formal accreditation in March this year. A considerable amount of work has gone into the development of a local Phase I / First in Human Review Committee whose purpose is to assess proposed early phase trials and advise on their adoption by the CRF.

The committee is instrumental in recommending additional safety measures, investigator training and contingency plans that must be in place before the trial can proceed.

A large body of related Standard Operating Procedures (SOPs) have been developed to underpin the conduct of these trials in the CRF. As the lead for the UKCRF Network Quality Assurance Work stream, we have shared our Phase I work with other CRFs across the UK and we have engaged the MHRA in very useful discussions about the contributions that CRFs make towards early phase trials. These discussions have been mutually beneficial, not only informing CRF led endeavours in this area but also improving MHRA understanding of the capacity and capability of facilities such as ours.

Our determination to achieve Phase I accreditation has been driven by our longstanding commitment to providing the highest standard of research practice for our subjects, investigators and sponsors. Clinical safety and research quality are our highest priorities and our strong track record in delivering high quality research has been recognised through our contributions to industry collaborations such as Scotland's Translational Medicine Research Collaboration (TMRC) with Wyeth Pharmaceuticals. The latest initiative with Wyeth is effecting the creation of Early Clinical Development Centres (ECDCs) linking translational scientists in Wyeth with expert clinicians in Scottish centres. Our Phase I capability supports the delivery of Edinburgh's contributions to this endeavour.

Sir Gordon Duff, Chair of Commission on Human Medicines presenting "The TGN1412 enquiry: recommendations and implementation" at the 4th Annual UK CRF Conference in Edinburgh 2008

Key projects and initiatives from Edinburgh's Clinical Research Facilities

Clinical Research Training Scotland

Background. In the present highly regulated research management environment the design and conduct of clinical research projects has to be performed to the highest standards. This can only be achieved if all staff receive appropriate and adequate training for their roles. 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.
In acknowledgement of the clear and recognised need for a more co-ordinated strategy and for greater collaboration between the NHS and academic centres, the Clinical Research Training for Scotland (CRTS) working group was formed. This group aims to deliver a cross-Scotland educational response, build on individual respective strengths, and avoid duplication of effort and cost. The group has representation from all of Scotland's CRFs and input from the National Institute for Health Research (NIHR), the UK Clinical Research Network (UKCRN), the Medical Research Council (MRC), Scottish Higher Education Institutions, and the Scottish Diabetic and Cancer Research Networks. The national approach taken on by the CRTS has the potential to be adopted through the CRFs across the UK to deliver specific core elements of research education.

Evaluation. Our first step was to analyse the current educational landscape in Scotland and this was facilitated by the Medicines and Healthcare products Regulatory Agency (MHRA) who awarded the CRTS working group a grant to carry out "An evaluation of the opinions and perceptions of academic trialists regarding the legislative framework for Clinical Trials of Investigational Medicinal Products (CTIMPs)". Phase 1 of this study included identifying professionals to target a structured questionnaire. From these responses, key individuals were identified for the 2nd phase which was to follow-up the questionnaire responses with telephone, face to face structured interviews and/or focus groups. This was a pilot study in Scotland and due to the initial success, the MHRA anticipate rolling this out to England and Wales. This project was carried out by the CRTS working group and is an ideal working model for future collaborative projects.

Defining a national education strategy. Based on the results of the evaluation above, the CRTS working group drafted a blueprint document setting out a co-ordinated and national strategy for research education and training in Scotland for the next two years. If Scotland is to hold its position as a leading clinical research centre it must address these regulatory challenges with robust, co-ordinated and national educational solutions. The strategy aims to harness existing resources and personnel and offers a leadership and co-ordination plan to define the educational and training needs across the healthcare spectrum and to implement educational initiatives and infrastructural changes. These will ensure not only the maintenance of the status quo, but, through capacity building, the further development of future clinical research activity in Scotland. The document has been made widely available for consultation and has been endorsed by the Scottish R&D Directors their respective managers and the Chief Scientist Office.

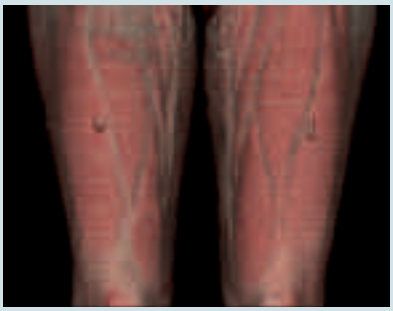
Future. The CRTS Working Group now has as its remit the streamlining of research education in Scotland and the sharing of best practice, and it is this that makes it an ideal vehicle for the delivery of much of the new educational strategy adopted by the NHS Research and Development departments across Scotland. Cross border collaboration is also a high priority for the CRTS working group and as an example of this we have developed close professional links with the NIHR Good Clinical Practice (GCP) training group in Leeds. The NIHR GCP training co-ordinator Paul Maher has now joined our group and two of our members have trained as NIHR GCP facilitators. We plan to maintain and develop such national collaborations in the future.

Specialist research services in Edinburgh's Clinical Research Facilities

Image Analysis Core

Modern imaging techniques have revolutionized many aspects of medicine and clinical research by providing more accurate diagnosis, guidance of surgical procedures, and greater understanding of disease processes. Digital images are generated by diverse techniques such as X-ray, computerized tomography (CT), magnetic resonance (MR), ultrasound, and radionuclide imaging. Optical microscopes, lasers, and endoscopes are also sources of images. Post-processing, i.e. the manipulation of digital images, following an examination can yield a vast amount additional information.

The Image Analysis Core is equipped with computer workstations and specialised software packages, and staffed by personnel with expertise in the field. We provide help, advice and support with the handling, archiving and analysis of medical image data. Staff are available to train researchers in the use of computational techniques, participate in the scientific work of research projects, and develop new cutting-edge image processing and analysis methods including retinal imaging, volumetric studies of muscle and liver volume using MR and CT techniques, visualisation of the coronary arteries and structures in the brain using MR and X-ray quantification of bone thickness.

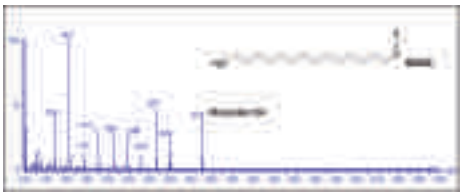


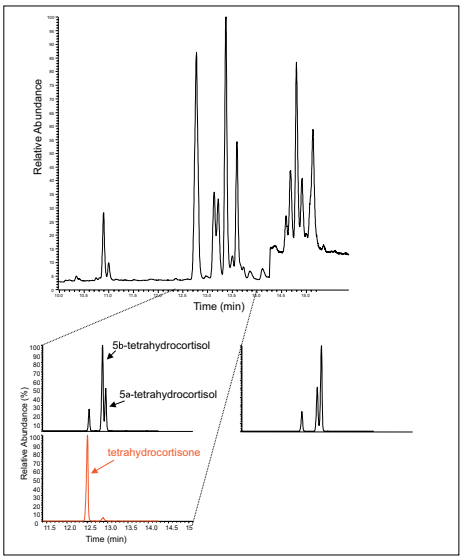
3D visualization of the quadriceps muscle group created from MR scan

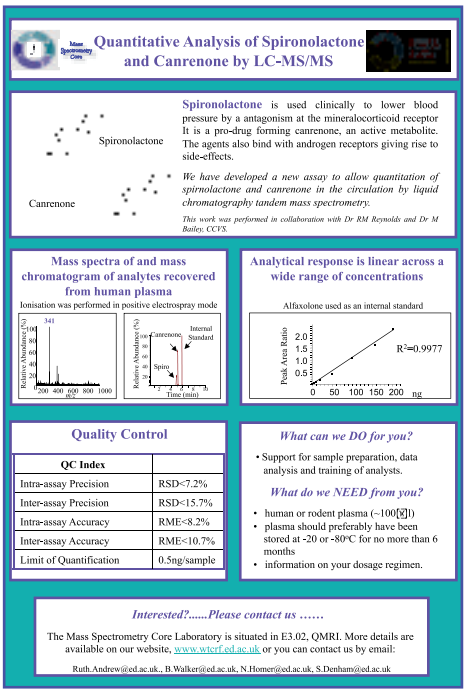
Mass Spectrometry Core

The Mass Spectrometry Core promotes the application of highly sensitive analytical chemical tools to clinical research, in particular dynamic profiling of biochemical pathways using stable isotope labelled tracers and characterising pharmacokinetics of zenobiotics. In the last year the Core has sustained its productivity in investigations of steroid hormone action and also provided key support to Drug Development programmes based at Little France.

We have recently been awarded an equipment grant (£1.2M) from the Wellcome Trust to upgrade our facilities, which will greatly enhance the scope for research using these techniques, providing two new state-of-the art mass spectrometers to supplement our existing systems and a new post-doctoral scientist to lead innovation, along with our existing team. The Core has also been facilitating metabolomic studies through the Scottish Metabolomics Facility, led by the Scottish University Life Sciences Alliance (SULSA) initiative.







Specialist research services in Edinburgh's Clinical Research Facilities

The Nursing Team

Since the outset of the CRF, we have developed a large group of highly trained research nurses to support our growing portfolio. Responding to national strategic developments and local needs, we have expanded our general nursing team to include paediatric, community and topic specific research nurses. We have provided significant support to the new research networks by recruiting, training and managing their specialist nurses within our team.

CRF nurses provide expert research skills across a broad range of complex studies and their work is underpinned by robust quality management systems. Aside from mandatory regulatory training, our nurses undertake project specific training as needed e.g. Doppler scanning of leg veins (Edinburgh Vein Study).

Our team has particular expertise in supporting forearm plethysmography, a technique that has been widely used in cardiovascular studies in Edinburgh. CRF nurses have had a key role in teaching this technique to colleagues from a collaborating site in Sweden. Training has taken place in both Edinburgh and Umea.

A significant number of studies are supported on an outreach basis for researchers who cannot bring their subjects into the facility e.g. critical care studies. Our outreach service ensures that investigators in such settings still have access to the research governance infrastructure that the CRF provides. In recent years, our nurses have supported projects involving patients with Subarachnoid Haemorrhage (SAH) & intensive care needs.

Olympian cyclist Sir Chris Hoy opened our existing Children's CRF in April 2009. An expanded purpose-built paediatric facility will open in the new Sick Children's Hospital at Little France in 2013.

Epidemiology and Statistics Core

Since its launch in May 2001 the aim of the Epidemiology and Statistics Core has been to improve the methodological quality of studies through the provision of expert statistical input. The Core can be involved in studies at all stages depending on investigator requirements from initial design through to analysis and dissemination. By encouraging investigators to approach the Core at an early stage we aim to support the development of the highest quality study designs for submission to regulators, ethics committees and grant awarding bodies. By supporting academic, NHS and independent researchers from across Lothian, Scotland and further afield we also provide an invaluable educational resource.

The Core is closely associated with the recently accredited Edinburgh Clinical Trials Unit and, through the work of its Associate Director, Dr Steff Lewis, the Edinburgh MRC Clinical Trials Methodology Hub.
The Core has contributed to a substantial list of publications enhancing the profile of the WTCRF beyond the local setting. Some highlights of recent work of the Core statisticians include:

- Clots in Legs Or sTockings after Stroke [CLOTS], a family of three multi-centre trials. CLOTS 1 had a simultaneous European Stroke Conference presentation with its Lancet publication and led to changing clinical practice. Clots 2 is submitted for publication and CLOTS 3 is actively recruiting patients.
- Continuing involvement with the Specialist Virology Centre resulting in ongoing collaborations and numerous journal publications and conference presentations.
- Involvement with group examining MRSA and other hospital infections supporting junior medics in their early research careers.

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

Genetics Core

The WTCRF Genetics Core was established in anticipation of the increasing role of genomics analysis in clinical research.

The laboratory provides a technically sophisticated biobanking and genetic analysis service and since inception has assisted 101 investigators on 170 projects, contributing directly to important discoveries and high-impact research papers.

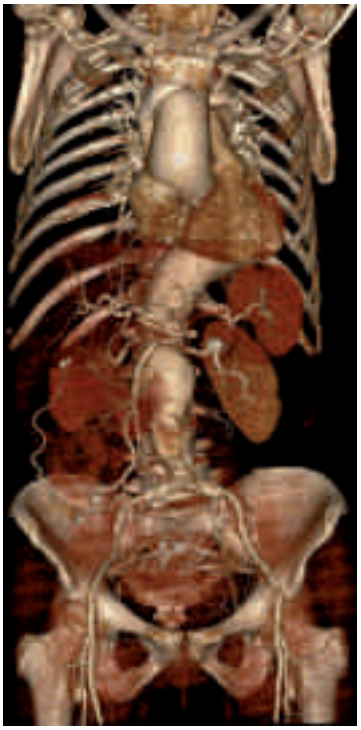
The Genetics Core provides a secure, audited and quality-assured system for receipt and processing of biological samples from clinical research programmes. Standard operating procedures and a Laboratory Information Management System ensure accuracy and facilitate the long-term utilization of the biological materials gathered.

Over 82,000 samples are held within a secure suite of freezers. Many of these projects are large collections of samples of national importance, such as ORCADES (McQuillan *et al* (2008) Am J Hum Gen 83:359), LBC1936 (Deary *et al* (2007) BMC Geriatrics 7:28), Inflammatory Bowel Disease (Lees *et al* (2008) Plos Med 5:e239) and Generation Scotland (Smith *et al* (2006) BMC Med Genet 2:74).

High-throughput genotyping and gene expression analysis is provided through three different platforms – Applied Biosystems 7900HT, Applied Biosystems OpenArray and Illumina Beadstation. Investment in robotics has allowed the automation of many of the liquid handling procedures enabling the systems to run 24 hours a day.
This has allowed the efficient and reliable delivery of high-quality, high-throughput genetic and microarray analyses from thousands of samples.

By providing a core service, delivered by specialist staff, clinical researchers have been able to gain access to transformational genetic technology.

Clinical Research Imaging Centre



The Clinical Research Imaging Centre (CRIC), located within the Queen's Medical Research Institute, is a multidisciplinary and multimodality facility aimed at bringing together academics from all walks of life, where advanced medical imaging is required. At the heart of the facility is state-of-the-art equipment, including 3T MRI (Siemens Verio) with multinuclear capability, 320-MDCT (Toshiba Aquilion ONE) and 128-PET-CT (Siemens mCT-PET), with cyclotron (GE PETtrace 8) and radiochemistry facility. In addition, there is an advanced image analysis and postprocessing laboratory.

The facility was funded through partnerships involving both the public and private sectors, and forms a unique bridge between NHS Lothian and the University of Edinburgh, allowing for the advanced imaging (both clinically and for research purposes) of human subjects.

The mission of CRIC is to advance medical imaging, translate new techniques into clinical applications, and use imaging for improving the understanding as well as the quantification of diseases through collaborative partnerships, including the Centre for Inflammation Research, the Centre for Cardiovascular Science, the Centre for Reproductive Biology, the Centre for Regenerative Medicine and the Department of Psychiatry of the University of Edinburgh. In addition, CRIC is willing to apply imaging to non-medical applications and to enhance teaching, and is actively involved with the Department of Music, the Department of Anatomy and public entities such as the National Museums of Scotland.

Specialist research services in Edinburgh's Clinical Research Facilities

Education Programme

Courses

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 also utilise videoconferencing and web streaming technologies.

Our training includes:

- Audit & Monitoring
- Consent
- Data management
- Ethics
- Evidence-Based Healthcare
- Literature Searching
- Patient & Public Involvement
- Personal Development
- Qualitative Methods
- Questionnaire Design
- Regulatory Training
- Statistics
- Use of Human Tissue In Clinical Research
- Writing & Publication Strategy

Extended Service

The Education team now offers its expertise in course and conference planning and administration to other organisations. This work brings in funding for the WTCRF Education Programme and raises our profile in Scotland.

Printed material supports the wide range of courses run by the Education Programme

Nationalisation

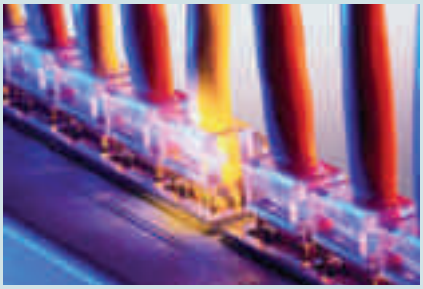
As part of our effort to co-ordinate education across Scotland, the Clinical Research Training Scotland (CRTS) working group was set up in 2008. This group has representation from all Scottish CRFs and is involved in various projects to implement educational initiatives and infrastructural changes that will ensure the further development of clinical research activity in Scotland.

These include:

- The CRTS website – highlighting research training opportunities across Scotland
- A project for the MHRA entitled "An evaluation of the opinions and perceptions of academic trialists regarding the legislative framework for Clinical Trials of Investigational Medicinal Products (CTIMPs)".
- A Blueprint for a National Education and Training Strategy for Clinical Researchers in Scotland

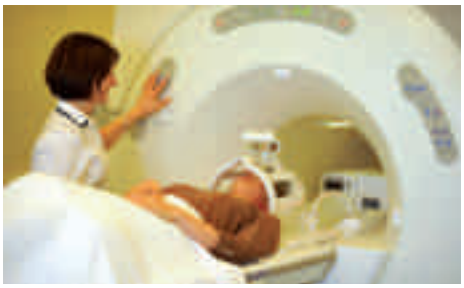
IT Programme

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 Facilities (CRFs), 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. CRF Manager has been shared with colleagues across the UK and it is now installed in six other CRF sites. One more installation is planned in May this year and seven 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 2 years, Edinburgh CRF's IT team coordinated the IT for the Clinical Research Imaging Centre (CRIC) and we continue to support the CRIC staff with their complex IT needs. This year we are working on the development of an eCRF system, which we have already used to collect data for studies.

WTCRF Imaging Core SFC Brain Imaging Research Centre



The SFC Brain Imaging Research Centre (SBIRC), directed by Professor Joanna Wardlaw and based in the University Of Edinburgh Division Of Clinical Neurosciences, was formed in 1998, funded by the MRC and Scottish Funding Council. It currently supports a portfolio of imaging research projects worth over £30 million, primarily in stroke, ageing, dementia, mental health, neuro-oncology, and psychology, and has scanned over 16000 subjects in many research studies.

SBIRC's mission:

- to enable high quality research using Magnetic Resonance (MR) imaging to improve understanding of the causes, pathophysiology and treatment of common neurological disorders
- to foster more widespread use of high quality MR imaging in research, eg in other organ systems.

Timeline of success:

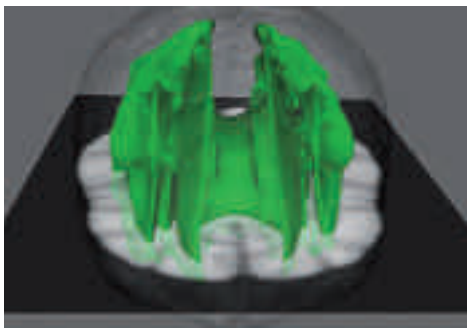
- The Centre was originally accessed by researchers from all over the northern UK.
- The success of those imaging studies was key to securing funding for new research scanners, primarily for neuroimaging in Aberdeen, Glasgow and Newcastle, and most recently for the 3T MR scanner and PET body imaging facility at the Queen's Medical Research Institute in Edinburgh.
- The model of SBIRC imaging research – collaborative, high quality, building imaging infrastructure capacity, and ultimately performing research that aimed at improving outcome of common neurological diseases – was the kernel for the Scottish Imaging Network, A Platform for Scientific Excellence (SINAPSE) Collaboration, a £42 million investment by the Scottish Funding Council, the Chief Scientist Office and six Scottish Universities.
  This has attracted 8 new chairs, 17 new midlevel posts and 36 new studentships in neuroimaging in Scotland in the last 2.5 years.

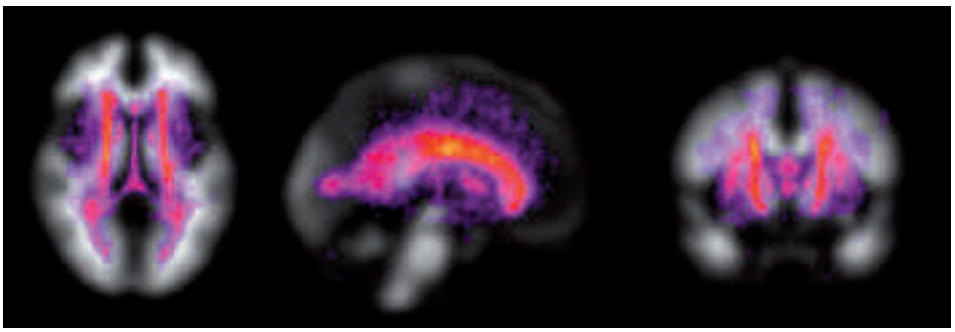
Currently our main projects include scanning up to 1000 subjects from the Lothian Birth Cohort 1936 with tractography and structural imaging to define the role of white matter damage in cognitive ageing; 350 subjects with small vessel stroke to further define the role of blood brain barrier failure in age-related small vessel brain damage; and patients with brain tumours to evaluate the role of fMRI and tractography in preoperative planning, as well as various other studies in mental health and of normal brain function.

Research highlights from SBIRC include:

- How to use brain imaging cost effectively in stroke – now in UK, European, North American and Australasian stroke guidelines.
- Up to 25% of all strokes and most age-related white matter lesions (which cause cognitive decline and much dementia) may be caused by blood brain barrier failure which can be measured using imaging.
- Anatomical and connectivity abnormalities in the hippocampus and frontal lobes predate and predict onset of psychosis in at-risk individuals and are associated with specific genetic polymorphisms.
- Brain mineralisation is associated with early and late life cognitive ability.
- Much of the cognitive status of older subjects and the appearance of their brain on imaging can be explained by their cognitive ability in early life, indicating the importance of not assuming that all findings in later life are a consequence just of late life events.
- In ischaemic stroke, temperature is elevated in tissue at risk (penumbra) more than infarct core and the high temperature may be a by-product of a protective mechanism.

SBIRC merged its imaging project management with the WTCRF project management in 2006-07, providing a model for administration of the new Clinical Research Imaging Centre. Through SINAPSE, SBIRC initiated meetings to encourage radiologists to undertake research training and to encourage better management of ethical aspects of research imaging in the UK, both to be held at the Wellcome Trust in London, in April and July respectively.





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

Scottish Aortic Stenosis and Lipid Lowering Trial, Impact on Regression (SALTIRE)

Cowell SJ, Newby DE, Prescott R, Bloomfield P, Reid JR, Northridge DB, Boon NA for the (SALTIRE) Investigators (2005) Scottish Aortic Stenosis and Lipid Lowering Trial, Impact on Regression A randomized controlled trial of intensive lipid lowering therapy in patients with calcific aortic stenosis. New England Journal of Medicine, 352 (23): 2389 –2397.

Calcific aortic stenosis has many characteristics in common with atherosclerosis, including hypercholesterolemia. The SALTIRE investigators hypothesized that intensive lipid-lowering therapy would halt the progression of calcific aortic stenosis or induce its regression. In this double-blind, placebo-controlled trial, seventy seven patients with calcific aortic stenosis were randomly assigned to receive either 80 mg of atorvastatin daily or a matched placebo. Aortic-valve stenosis and calcification were assessed with the use of Doppler echocardiography and helical computed tomography, respectively. The primary end points were change in aortic-jet velocity and aortic-valve calcium score.
The trial demonstrated that intensive lipid-lowering therapy does not halt the progression of calcific aortic stenosis or induce its regression.
The study cannot exclude a small reduction in the rate of disease progression or a significant reduction in major clinical end points. Long-term, large-scale, randomized, controlled trials are needed to establish the role of statin therapy in patients with calcific aortic stenosis

N.B In 2008, a large scale RCT investigating intensive lipid lowering treatment in 1873 aortic stenosis patients also showed no reduction in aortic valve events: Rossebø AB et al for the SEAS Investigators (2008) Intensive Lipid Lowering with Simvastatin and Ezetimibe in Aortic Stenosis. New England Journal of Medicine, 359 (13): 1343-1356.

Scottish Colorectal Cancer Study (SOCCS)

Barnetson RA, Tenesa A, Farrington SM, Nicholl ID, Cetnarskyj R, Porteous ME, Campbell H, Dunlop MG (2006) Identification and survival of carriers of mutations in DNA mismatch-repair genes in colon cancer. New England Journal of Medicine, June 29; 354 (26): 2751-2763.

The identification of mutations in germ-line DNA mismatch-repair genes at the time of diagnosis of colorectal cancer is important in the management of the disease. The investigators on the Scottish Colorectal Cancer Study (SOCCS) recruited 870 patients under the age of 55 years soon after they received a diagnosis of colorectal cancer. These patients were studied for germ-line mutations in the DNA mismatch-repair genes MLH1, MSH2 & MSH6. The investigators developed a new genetic test to identify bowel cancer patients who have an inherited form of the disease. The test could also be used to detect people at high risk of developing the disease, before any symptoms appear. The findings suggest that around four per cent of bowel cancer patients have hereditary nonpolyposis colon cancer (HNPCC) - a higher figure than previously estimated. People who inherit HNPCC are at increased risk of developing colon cancer as well as womb and other cancers
The study has allowed the investigators to develop a new means to identify patient groups who are likely to carry genetic defects responsible for their bowel cancer. The researchers have developed an online resource for clinicians, to assess which patients need a genetic test (**http://www1.hgu.mrc.ac.uk/Softdata/MMRpredict.php**). In the long term, this approach could be used to offer tests to the relatives of these patients, before they develop the disease.
Study participants attended the WTCRF in Edinburgh where the research nurses administered risk factor questionnaires, conducted physical assessments, took genetic family histories and undertook blood sampling for genetic analysis. The WTCRF Genetics Core provided DNA extraction and DNA Quality Control services for the study in addition to support with genotyping.

> ***"I am writing to thank you and the team of research nurses who have helped with the SOCCS study over the last 4 years. We have now assembled a truly world class resource for colorectal cancer research and this is just beginning to bear fruits with a recent discovery of a new genetic variant which has scientific as well as clinical importance. Please extend our gratitude to all concerned. We would not have been able to do the work without your help."***

Professor Harry Campbell, Scottish Colorectal Cancer Study (SOCCS) Principal Investigator (May 2005)

CHARISMA

Bhatt DL, Fox KA, Hacke W *et al* (2006) Clopidogrel and Aspirin versus Aspirin Alone for the Prevention of Atherothrombotic Events. New England Journal of Medicine, Volume 354 (16):1706-1717

This multi-centre study was supported in the Edinburgh CRF. The investigators randomly assigned 15,603 patients with either clinically evident cardiovascular disease or multiple risk factors to receive clopidogrel (75 mg per day) plus low-dose aspirin (75 to 162 mg per day) or placebo plus low-dose aspirin and followed them for a median of 28 months.

The primary efficacy end point was a composite of myocardial infarction, stroke, or death from cardiovascular causes.

In this trial, there was a suggestion of benefit with clopidogrel treatment in patients with symptomatic atherothrombosis and a suggestion of harm in patients with multiple risk factors.

Overall, clopidogrel plus aspirin was not significantly more effective than aspirin alone in reducing the rate of myocardial infarction, stroke, or death from cardiovascular causes.

Study Of Public place Intervention on Tobacco exposure (STOPIT)

Pell JP *et al* (2008) Smoke-free legislation and hospitalizations for acute coronary syndrome. New England Journal of Medicine, Jul 31; 359(5): 482-91

We provided extensive support for the STOPIT Study (Study Of Public place Intervention on Tobacco exposure) published in the New England Journal of Medicine in 2008. Rated the top research advance of 2008 by the American Heart Association / American Stroke Association, this study demonstrated that the number of hospital admissions for acute coronary syndrome decreased after the implementation of the Smoking, Health & Social Care (Scotland) Bill. Edinburgh's CRF nurses recruited the most patients out of all the centres (n1076), and our laboratory staff coordinated the receipt and storage of thousands of blood samples from all 9 study sites.

"A 2008 study makes a strong case for smoke-free legislative initiatives. In Scotland, after smoke-free legislation covering all enclosed places was implemented, hospital admissions for acute coronary syndrome decreased 17 percent, compared with only a 4 percent decrease in England, where there was no such legislation. The decrease in Scotland was highest in never-smokers, but there was also a smaller decrease in former smokers. Smokers had the lowest decrease, but saw a 14 percent decline. Of the decrease in hospital admissions, 67 percent were non-smokers, supporting the argument that protection for these individuals is an important benefit of this legislation, and it should be extended more broadly."

(American Heart Association / American Stroke Association Top Research Advance 2008)

Genetic Risk of Schizophrenia

International Schizophrenia Consortium (2008) Rare chromosomal deletions and duplications increase risk of schizophrenia. Nature, Sep 11; 455(7210):237-41.
Stefansson H *et al* (2008) Large recurrent micro deletions associated with schizophrenia. Nature, Sep 11; 455(7210):232-6.

Professor Douglas Blackwood and Dr Walter Muir from Edinburgh are members of an international team that discovered four mutated gene regions that increase the risk of schizophrenia. It is hoped that these findings could lead to earlier diagnosis of the disorder and the development of new drug treatments. In two studies published in Nature, the scientists scanned the genes of 10 000 schizophrenia patients and healthy volunteers, to identify the genetic differences associated with the illness. Our Genetics Core provided DNA extraction, peripheral blood lymphocyte isolation and genotyping services to support the significant Scottish contributions to these internationally recognised studies.

Dr Walter Muir died suddenly in September 2009. We are grateful for his support over many years.

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

Orkney Complex Disease Study (ORCADES)

Vitart V *et al* (2008) SLC2A9 is a newly identified urate transporter influencing serum urate concentration, urate excretion and gout. Nature Genetics, Apr; 40(4): 437-42).

The Orkney Complex Disease Study (ORCADES) is a genetic epidemiology study in rural isolates in Orkney. The research team have collected DNA for genetic analysis as well as data on health behaviours and risk factors for disease.

An early finding published in Nature Genetics, is the discovery of a gene that influences levels of serum uric acid and the risk of gout. The gene is the strongest known uric acid transporter and will be a good target for drug therapy.

Edinburgh WTCRF has provided significant support for the ORCADES project. CRF staff traveled to Orkney to recruit local research nurses and to assist with study set up. The study nurses spent time in Edinburgh WTCRF undergoing training in research techniques including pulse wave analysis, digital retinal photography and anthropometry. They also completed GCP training through our Education Programme. CRF staff advised on the specifications for the ORCADES research equipment, as well as coordinating its procurement and delivery. Our Genetics Core provides the DNA extraction service for the project.

Aspirin for Asymptomatic Atherosclerosis (AAA Trial)

Fowkes FG, Price JF, Stewart MC, Butcher I, Leng GC, Pell AC, Sandercock PA, Fox KA, Lowe GD, Murray GD; Aspirin for Asymptomatic Atherosclerosis Trialists (2010) Aspirin for prevention of cardiovascular events in a general population screened for a low ankle brachial index: a randomized controlled trial. JAMA, 303 (9): 841-8

The routine use of aspirin for the primary prevention of vascular events in people with asymptomatic disease cannot be supported, according to results from the Aspirin for Asymptomatic Atherosclerosis (AAA) study.

The study is the first placebo-controlled randomised trial designed to determine the effect of aspirin in asymptomatic atherosclerosis as reflected by a low ankle brachial index (ABI). Results found no statistically significant difference in primary endpoint events between those subjects allocated to aspirin or placebo (HR 1•03, 95% CI 0•84-1•27). A low ankle brachial index (ABI) indicates atherosclerosis and an increased risk of cardiovascular and cerebrovascular events. Screening for a low ABI can identify an asymptomatic higher risk group potentially amenable to preventive treatments.

The objective of this study was to determine the effectiveness of aspirin in preventing events in people with a low ABI identified on screening the general population.

The study recruited 28,980 men and women aged 50 to 75 years who were free of clinically evident cardiovascular disease in central Scotland. All were given an ABI screening test. Those with a low ABI (3350 subjects, ≤0•95 ABI) were entered into the trial and randomised to once daily 100 mg aspirin or placebo.

Participants were followed up for a mean of 8•2 years and outcomes ascertained by annual contact, general practitioner records, linkage to discharges from Scottish hospitals, and death notification.

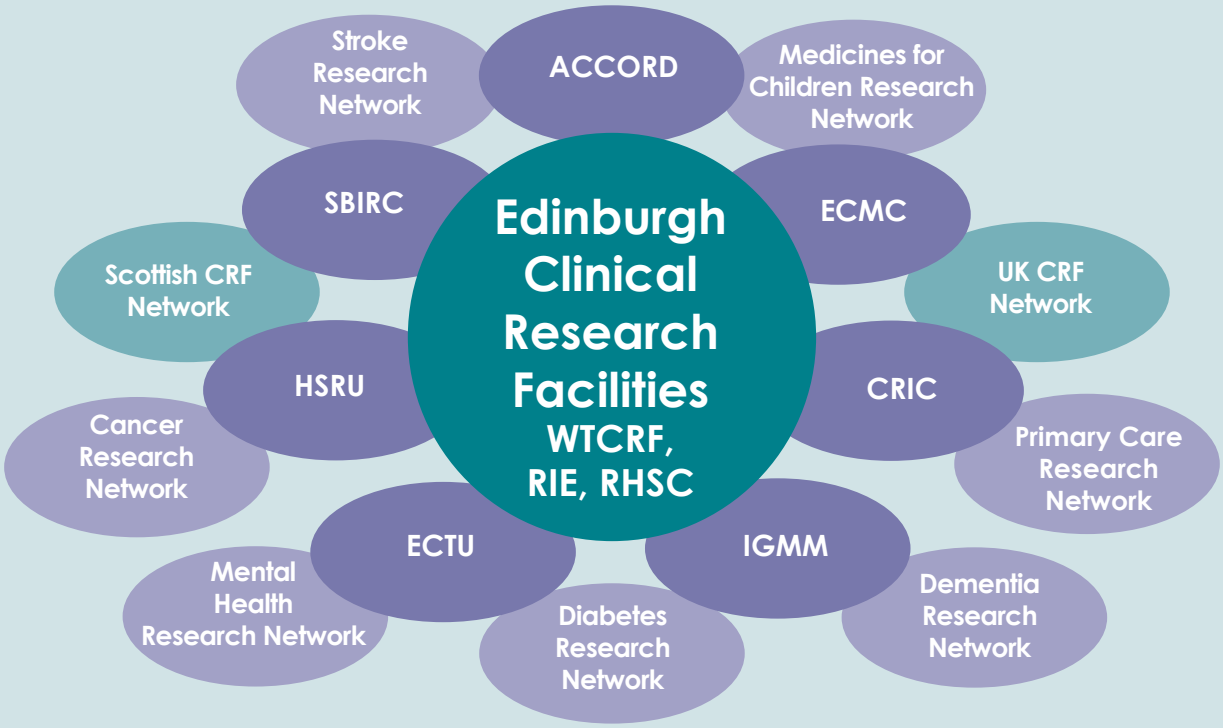
The trial demonstrated that the administration of aspirin compared with placebo did not result in a significant reduction in vascular events among participants with low ABI and no clinical cardiovascular disease.
Commenting on the results (and on the use of ABI as a screening method), joint first author Professor Gerry Fowkes said:

> ***"It is possible that in the general population, aspirin could produce a smaller reduction in vascular events than this trial was designed to detect, but it is questionable whether such an effect, together with aspirin related morbidity, would justify the additional resources and health care requirements of an ABI screening programme."***

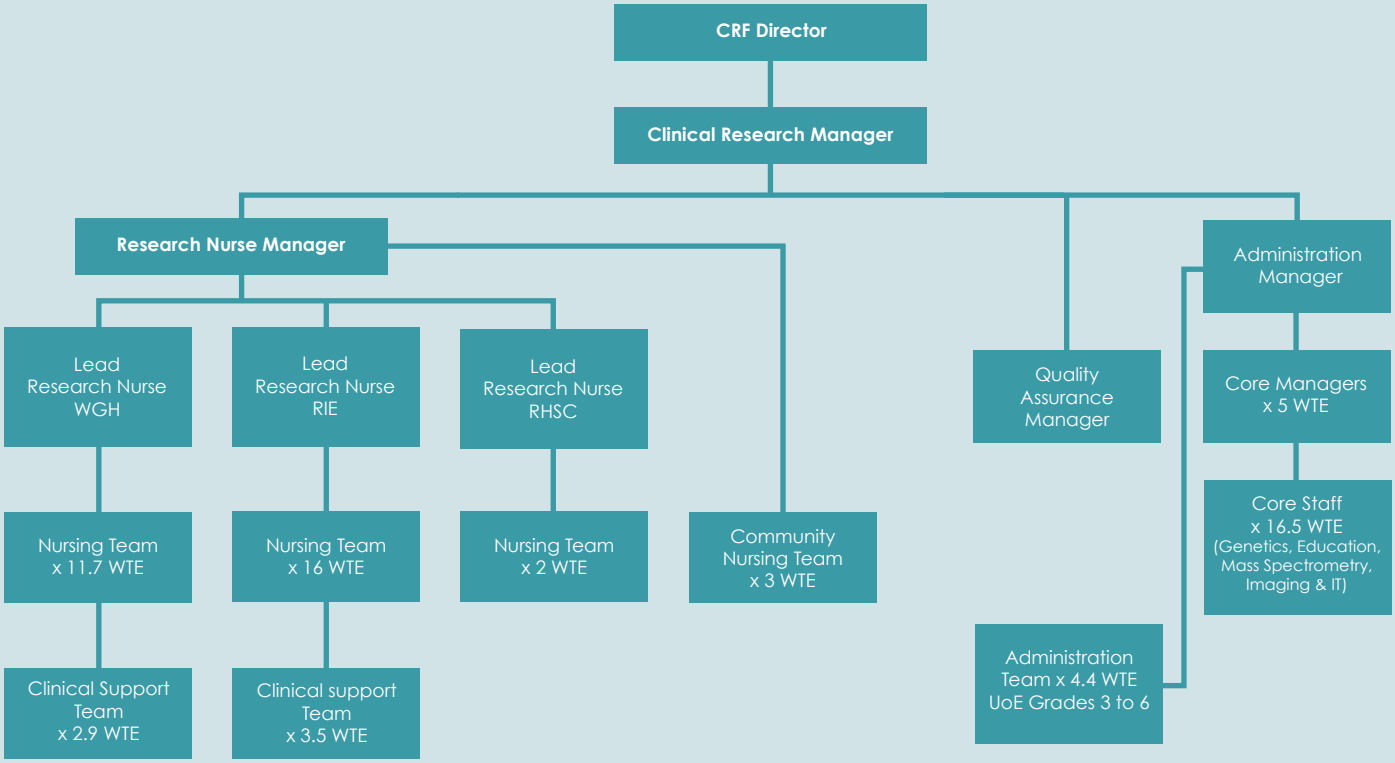
> ***"Although the AAA trial was not of screening per se, the results would suggest that using the ABI as a tool to screen individuals free of cardiovascular disease in the community is unlikely to be beneficial if aspirin is the intervention to be used in those found to be at higher risk. Other more potent antiplatelets might be considered, but only if increased effectiveness in avoiding ischaemic events is not matched by increased bleeding."***

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

Outward focus



Internal structure



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CHIEF SCIENTIST OFFICE

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clinical research training for scotland

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