



clinical  
research  
facility  
EDINBURGH

Annual Report 2019



Delivering excellence  
in clinical research



# Edinburgh Clinical Research Facility

## - Key Milestones

- ▶ 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 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
- ▶ 2007 Community Research Nurse Service initiated
- ▶ 2008 UK Clinical Research Facilities (UKCRF) Network officially launched
- ▶ 2009 Paediatric CRF opened in Royal Hospital for Sick Children (RHSC) by Sir Chris Hoy
- ▶ 2010 CRF Mass Spectrometry Core receives £750,000 Wellcome Trust equipment award for major new investment
- ▶ 2010 Official opening of the Clinical Research Imaging Centre (CRIC) by HRH Prince Philip, Chancellor of the University of Edinburgh
- ▶ 2011 Edinburgh CRF is the first hospital based non-commercial unit in the UK to receive accreditation under the MHRA Phase I scheme
- ▶ 2011 Edinburgh CRF celebrates its 10th Anniversary
- ▶ 2012 CRFManager® becomes a registered trademark
- ▶ 2013 Genetics Core Director Professor David Porteous receives an OBE for Services to Science
- ▶ 2013 Patient and Public Involvement (PPI) advisor is appointed in response to funders' requirements for evidence of public engagement in clinical research
- ▶ 2015 Paediatric CRF accredited along with adult facilities under the MHRA Phase I scheme
- ▶ 2015 Genetics Core awarded Wellcome Trust Institutional Strategic Support Fund funding for a Covaris E220 platform
- ▶ 2016 First 14 students on the UoE Distance Education Initiative-funded online Masters programme graduated with MSc in Clinical Trials.
- ▶ 2016 Official opening of the new Centre for Dementia Prevention CRF on the Little France campus by HRH the Princess Royal, the Chancellor of the University
- ▶ 2016 CRF welcomes two new Associate Directors – Professor Craig Ritchie (CDPCR Director) and Professor Steve Cunningham (Children's CRF Director)
- ▶ 2016 Refurbishment of Edinburgh Imaging to include a new PET-MRI scanner and hospital-embedded 3T-MRI research scanner
- ▶ 2017 Wellcome Trust CRF office and labs achieved Silver level in the University of Edinburgh Sustainability Awards
- ▶ 2018 MHRA Phase 1 inspection at WTCRF, RIECRF and CCRF led to accreditation renewal with no major findings
- ▶ 2019 CRF Director Professor David Newby appointed to the BHF Duke of Edinburgh Chair of Cardiology in recognition of his outstanding research and his wider influence in the field.

# Introduction

**It is now 22 years since Edinburgh was awarded Wellcome Trust Millennial funding to establish the first Clinical Research Facility in Scotland as one of the first five Wellcome Trust CRFs funded in the UK. That commenced with three members of staff working in one section of a clinical ward and has now grown to over 150 staff employed across ten core areas within four Clinical Research Facilities at three separate hospital sites in Edinburgh. In the intervening 22 years, Edinburgh CRF has firmly established itself as a go-to place for innovation and best practice. Contributing to the clinical research landscape in the UK, influencing the development and acting as a blueprint for the CRFs that have followed and sharing the experience, study documentation and educational outputs, its influence and impact reaches well beyond the boundaries of NHS Lothian and the University of Edinburgh. This brochure highlights some of the achievements in 2018/19 and outlines the capabilities of the various elements and people within the Edinburgh CRF cores.**

Edinburgh CRF continues to build on its reputation for innovation and best practice in delivering clinical research activity. This year the Genetics Core expanded their sample processing to allow extraction of cell-free DNA (page 6). The Education Team hosted courses attended by over 1600 delegates and launched the Edinburgh Clinical Trialists Round Network to support current and aspiring Chief Investigators (page 8). Our Patient and Public Involvement and Engagement Advisor has been busy capacity-building by supporting researchers to set up and run their own PPI groups (page 9). Our Scientific Cores (Mass Spectrometry and Genetics) have led on Edinburgh University's Technician Commitment (pages 6 and 7).

The annual metrics published on pages 10 and 11 continue to show a consistent and growing number of clinical trials with an increasing emphasis, particularly within our nursing and clinical core, of supporting high intensity and early phase studies. The CRF's contribution to over 100 publications in 2018/19 again emphasises the impact that Edinburgh CRF has in supporting clinical research.

A key personal achievement was our Director, Professor David Newby, being awarded the BHF Duke of Edinburgh Chair in Cardiology.

A focus this year was on staff health and wellbeing, with 11 staff undergoing training to become Mental Health First Aiders. Other sustainability initiatives are highlighted on page 16.

Edinburgh CRF was well represented at this year's UKCRF Conference in Nottingham with 15 members of staff from most of our Cores attending to either run workshops, display posters, advertise our facilities or contribute to the two day meeting.



Edinburgh CRF staff attending annual UKCRF Network Conference in Nottingham

**Deputy Director: Dr Steve McSwiggan – 0131 537 3358 – [steve.mcswiggan@nhslothian.scot.nhs.uk](mailto:steve.mcswiggan@nhslothian.scot.nhs.uk)**



## Nursing and Clinical

The CRF Nursing and Clinical Services operate within the Wellcome Trust Clinical Research Facility at the Western General Hospital (WTCRF), the Children's Clinical Research Facility at the Royal Hospital for Sick Children (CCRF) and the Royal Infirmary of Edinburgh Clinical Research Facility (RIECRF) and the Centre for Dementia Prevention Clinical Research Facility (CDPCRF), both at Edinburgh BioQuarter. Jointly they provide a streamlined service to investigators of any discipline to conduct their clinical research efficiently and safely.

These units offer purpose-built facilities for the conduct of clinical research. Clinical facilities across sites include intensive studies rooms, inhalation cubicles suitable for gene therapy, consultation rooms, study bedrooms and day study areas. As well as offering dedicated clinical studies space, our infrastructure includes managed and calibrated research-specific equipment and capability and space for sample processing and storage.

All of the research nurses are trained in Immediate Life Support (ILS) or Paediatric Immediate Life Support (PILS) and Good Clinical Practice (GCP) as standard. They work to

basic as well as advanced clinical competencies including venepuncture, cannulation and the administration of chemotherapeutic and biological agents. Nurses can be trained in any study-specific clinical competency in order to meet the requirements of any particular studies.

Specialist Lead Research Nurses for Phase 1 and Education are dedicated to ensuring we meet the enhanced clinical, education and administrative requirements underpinning our accreditation under the MHRA Phase 1 scheme.

The team also includes a community research nurse team capable of



recruiting and seeing patients in their GP Practice or their own home.

To enable the nursing team to focus on providing the best quality of service for studies and to offer this service 24/7, they are supported by Clinical Support Workers, Clinical Measurement Technicians and a Project Support Team across all three hospital sites.

### Community Team

Edinburgh CRF is unique across the 50+ CRFs that exist in the UK in having a Community Outreach team. Three highly experienced Community Research Nurses - Catherine Beveridge, Fran Dougherty and Lynda Melvin - lead on delivering Outreach visits in participants' homes, ensuring that local investigators can run studies where home visits are planned to reduce the burden on patients attending hospital sites. They have successfully supported their colleagues in the Children's CRF to recruit and follow up over 200 babies in the largest study into RSV in Children (RESCEU study) with Professor Cunningham as Chief Investigator. Additionally, they have supported new investigators in the Lauriston Building to deliver trials in dermatology and ENT, where ACCORD have funded the redevelopment of an old lab room to a clinical research room.

### National Collaborations and Edinburgh CRF's influence on Practice

Edinburgh CRF has a number of staff contributing to UK CRF Network (UKCRFN) themes, with Deputy Director Steve McSwiggan representing Scottish CRFs on the senior management team of the UKCRFN. Research Nurse Manager Finny Paterson has for five years led on the Study Intensity Group, providing training on the practical application of this validated tool for planning workloads and determining resource requirements. In 2018/19 the Group has moved to online Webinars to increase capacity and to reduce the requirement for site visits to provide training. Finny has recently joined the Costing and Sustainability Group to provide her expertise in ensuring studies are accurately costed. Phase 1 and Education Lead Research Nurses Lesley Briody and Fiona Mitchell continue to play an active role in the Education group whilst Research Nurse Maggie Wishart has recently joined the UKCRF Research Nurse and Practitioners Group.

## Administration Team

### Introducing the WTCRF Administration Team

The Administration Team based at the Wellcome Trust CRF at WGH supports all the Cores in providing a high quality professional service to clinical researchers and other users.



WTCRF Administration Team. L-R - Ana Norrie Toch, Marie Leslie, Linda O'Neill, Joanne Douglas, Kirsty Roberts, Moira Husband

- The first point of contact for many will be our receptionist at WTCRF (Wellcome Trust CRF at WGH) - Ana Norrie Toch. She provides a friendly welcome to study participants, researchers and people attending our courses and events and will redirect any telephone or email enquiries to the best person to deal with it.
- Joanne Douglas is our Study Information Manager (SIM). She manages the central application service for all clinical research studies undertaken in Edinburgh CRF and Edinburgh Imaging. She is able to provide regulatory advice and support to clinical researchers to ensure that their study applications to use the CRF's services are fully compliant with statutory and regulatory requirements and local research policy before they are approved.
- Linda O'Neill is the CRF's Finance Officer and does the majority of the purchasing and invoicing for goods and services for the cores.
- Moira Husband, Clerical Assistant, combines two main roles. She works with the SIM on study management and also does purchasing and invoicing for goods and services for some of the cores.
- Kirsty Roberts, the CRF's Administration Assistant, liaises with the Nursing and Clinical teams and R&D on invoicing researchers for the work carried out by the nursing teams on clinical research studies.

As well as the above, the WTCRF Admin Team provides general administrative support to all cores as required in a variety of areas.

Please contact the team if you have any queries or if there is anything we can do to help you.

**Study Information enquiries:**  
CRF.StudyInfo@ed.ac.uk

**General CRF enquiries:**  
0131 537 2591  
info@edinburghcrf.ed.ac.uk

## Genetics Core

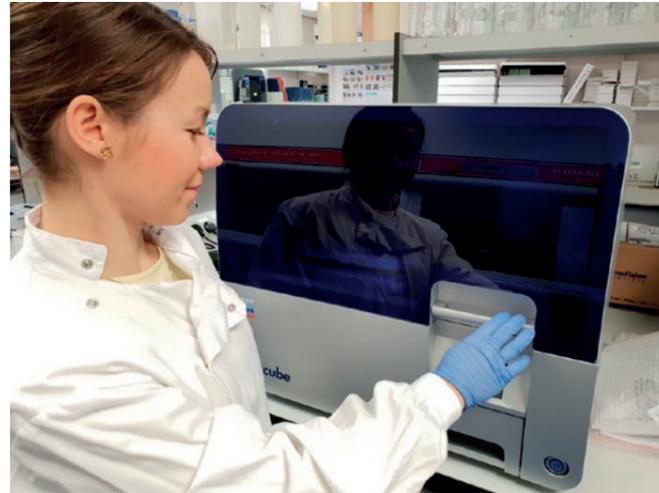
The Genetics Core specialises in providing a diversity of workflows, with the ability to take a sample from collection through processing, storage and on to analysis, all to the principles of Good Clinical Practice (GCP).

This year we expanded our sample processing to allow extraction of cell-free DNA. This can be an important biomarker in disease, such as in the analysis of circulating DNA derived from tumours in patients with cancer. To support this work we purchased a Qiagen QiaCube to help automate the cell-free DNA extractions. We also purchased a digital PCR platform (Stilla Naica) to support the analysis and detection of somatic mutations present in circulating tumour-derived DNA. By combining these two methods we are helping investigate the genetic basis of an individual's cancer, guiding therapeutic decisions by giving information on chemosensitivity and giving insights into tumour pathogenesis and evolution.

Another exciting area of development has been our work on single-cell sequencing. We have collaborated with the IGMM FACS team to provide a comprehensive workflow for single-cell gene expression and ATAC sequencing utilising the 10x Genomics Chromium system. By investigating biology at the level of the single-cell we hope to be able to better understand human disease.

Our reason for existing is to provide our researchers with the best genomics support we can for their clinical studies. We were delighted when two of our early career researchers, Dr Charlie Lees and Dr Joe Rainger, secured prestigious UKRI Future Leaders Fellowships and we look forward to continuing to support their programme of work.

In 2019 seven members of the Genetics team completed professional registration with the Science Council. This scheme provides independent recognition of the high level of knowledge and is testament to the high level of experience of the Genetics staff and commitment to professional development. Registration was funded by the University of Edinburgh to support the Technician Commitment, a national initiative to support technical careers.



The Qiagen Qiacube



The CRF Genetics Core. L-R - Nicola Wrobel, Lee Murphy, William Hawkins, Richard Clark, Audrey Duncan, Katarzyna Hafezi, Alan MacLean, Louise MacGillivray, Kirstie Morrice, Sarah McCafferty, Angie Fawkes, Tamara Gilchrist

We are always looking at ways of improving and expanding the facilities we can offer. If there are any areas that you would like to see developed please do get in touch.



## Mass Spectrometry

The Mass Spectrometry Core is a bioanalytical core with expertise in clinical sample analysis of biomarkers and drugs, using state of the art separation and mass spectrometry instrumentation. We apply FDA and European Medicines Agency (EMA) bioanalytical method validation guidelines to our analytical method development.

We offer a complete service of bioanalytical analysis. We can also mentor, train and support researchers – including MSc and PhD students - to become expert users of the analytical instruments. Our experienced Core staff use their combined expertise to carry out research, developing novel methods for biomarker analysis.

### Core instruments

- Biotage Extrahera Liquid Handling Robot for sample preparation
- ThermoFisher Quantum Ultra GC-MS/MS
- Waters Acquity-Sciex 5500 QTrap with SelexION
- Shimadzu-Sciex 6500+ QTrap with Advion Nanomate.
- Waters G2 Synapt with M-class Pump and MALDI and DESI
- Waters H-Class and Waters Xevo TQS triple quadrupole MS



Biotage Extrahera liquid handling robot for automated sample extraction. Purchased in December 2018. Extracted 8,500 samples in 2019



Imaging Mass Spectrometer Waters Synapt G2-Si Quadrupole-Time of Flight MS with Ion Mobility technology

### Ongoing and new projects in 2018/19

Steroid profiling for intensive endocrine studies with Professor Brian Walker and Professor Rebecca Reynolds' groups continues. These validated methods have been applied to other researchers; Professor Colin Duncan, Professor Roland Stimson, Dr Will Cawthorn, Dr Mark Nixon, Dr Ruth Morgan and Dr Mike Clinton (Roslin) and further afield for Dr Asma Elarbed (Nottingham University).

The Mass Spectrometry Core is a validated 25hydroxy Vitamin D laboratory, following accreditation from DEQAS, and Dr Emma Hurst – postdoctoral researcher with Professor Richard Mellanby - carries out routine analysis of Vitamin D for clinical cases.

We continue to collaborate with external researchers hosting PhD students for Professor Mandy Maclean from Strathclyde University and Dr Andre Tchernof from Quebec University for the analysis of estrogens.

We have developed a targeted metabolomic method for steroid treatment in adrenal insufficiency, in collaboration with Dr Tom Chambers. We have also developed a method for dopamine quantitation with Dr Tilo Kunath in a cell model of Alzheimer's disease, and continue to support toxicology and pharmacology research with Professor Michael Eddleston.

### Publications, conference presentations and outreach

We routinely present at local and national conferences and have published 11 methodological and clinical papers in the past year.

Natalie Homer helped organise TEAMS2019 'What Mass Spectrometry Can Do For You'; a symposium day at Roslin Institute in March 2019 attended by 100 researchers, technicians, technologists and students. Thirteen talks discussed the capabilities and research being carried out in the six mass spectrometry facilities across the University. Natalie, along with Lee Murphy (Genetics Core Manager), co-delivered a workshop with Kelly Vere and Ian Wilcox on the Technician Commitment and Core Facility careers at the CTLS Core Facility staff training school at Institut Pasteur, Paris, in November 2019.

### Next steps

A grant from the University of Edinburgh Sustainable Campus Fund awarded to Scott Denham and Natalie Homer will allow us to invest in Microflow technology to improve sensitivity of analysis, while reducing solvent use and our carbon footprint. Steroidomics remains a major focus, and development of novel methods for drugs and other small molecules will continue.

## Education Core

The Education Core facilitates and manages a range of educational courses and events to the local, national and international research community. Our aim is to provide all those involved in clinical research with the knowledge and tools to contribute to and deliver the highest standard of research practice. Courses are developed and delivered by a network of experts and constantly adapted to reflect the evolving educational requirements in accordance with best practice and legislative changes.

### Courses

#### In 2018/19:

- 76 courses run through the Education Core
- Over 1600 delegates attended our courses
- New courses added to our programme included:
  - Updated Adult Informed Consent Course
  - Reporting your research with integrity
  - A realistic introduction to R
  - Design and analysis of n of 1 trials
  - The whys and hows of applying to the PBPP for health and social care research
  - PPI in clinical trials, design, recruitment and retention
  - PPI in funding applications
  - Creating a new PPI group
- We have also collaborated with the University of Edinburgh Library Services to support the delivery of literature searching courses, management of literature and avoiding plagiarism.

Edinburgh CRF continues to use their Course Manager software to co-ordinate NRS Good Clinical Practice (GCP) training across Scotland. 10x Intro to GCP and 10x GCP Updates have been delivered in Edinburgh by x6 approved local NRS GCP trainers across the academic year.

### Edinburgh Clinician Trialist Round Network (ECTR) and Seminar Series

2019 saw the launch of the new ECTR network. Working alongside ECTU, ACCORD and motivated Chief Investigators this network has formed to support current and aspiring clinician RCT Chief Investigators across Lothian. The Education Core co-leads the co-ordination of the network and manages a monthly seminar programme. Seminar topics have included:

- Mentoring new/future trialists
- How to deal with controversial RCTs
- Complexed RCT designs: Stepped-wedge
- How to minimise loss to follow up
- PPI in clinical trial design
- Conducting global RCTs

By recording the sessions, a resource bank is being developed to provide longevity of the series, with the hope to continue to inspire and support CIs in the future. Previous seminars can be accessed here: <https://tinyurl.com/ECTRmedia>

### Events

The Education Core has been involved in the management and delivery of six different educational events over the last year. These included:

**Scottish Metabolomics Network Symposium 2018** – Event management was provided for this important network meeting of 130+ delegates in Dundee.

**Edinburgh Clinical Trials Management Course (ECTMC)** – Continuing the success of previous years

**Scottish Research Nurse and Co-ordinators Network (SRNCN) Network** – The core supported the organisation of this one-day conference, held in Dundee, celebrating clinical research nursing in Scotland.

**NHS Lothian R&D Conference 2019** – Supporting colleagues in ACCORD to organise a one-day conference showcasing excellence in research across Lothian.

**TEAMS Symposium** – A new collaborative venture highlighting the scope of different Mass Spectrometry facilities across the University of Edinburgh

**Alzheimer's disease Summer School 2019** – The Education Core are delighted to continue to collaborate with the Centre of Dementia Prevention and support the delivery of this inter-disciplinary Summer School.



Education team preparing for conference registration



Reviewing posters at NHS R&D Conference 2019

**Core Manager: Jo Merrifield - 0131 537 3326 - [Jo.Merrifield@ed.ac.uk](mailto:Jo.Merrifield@ed.ac.uk)  
[Education@EdinburghCRF.ed.ac.uk](mailto:Education@EdinburghCRF.ed.ac.uk) – Website [www.crts.org.uk](http://www.crts.org.uk) – Twitter [@WTCRF\\_Education](https://twitter.com/WTCRF_Education)**

## Patient and Public Involvement

Patient and Public Involvement (PPI) means members of the public getting involved in the research process itself – being part of the research team as colleagues rather than participants in a study.

Carol Porteous is Edinburgh CRF's Patient and Public Involvement and Engagement Advisor. She works with the CRF Patient Advisory Group (PAG) to advise and support researchers and the public to ensure patient and public involvement is helpful and meaningful for everyone involved in clinical research. This year we have recruited 20 new patients to the PAG, increasing its diversity. Funding for Patient and Public Involvement in Scotland is not universal for clinical research. Edinburgh is in a unique position in having this service funded by the Chief Scientist's Office.

The PAG's day-to-day work to support the research community includes advising on study methods, helping to write or edit lay summaries and patient information sheets, reviewing grant applications and IRAS forms, and training researchers and students for patient and public involvement. In addition, they are increasingly asked for input to larger programmes of research, particularly putting the patient view into studies regarding the ethics of big data and genomics research. An example of this is the PAG recently advising researchers at the Institute of Genetics and Molecular Medicine, who were preparing the £4.9 million grant on the next phase of Generation Scotland cohort. This study is a resource of human biological samples and data which are available for medical research, aiming to create more effective treatments based on gene knowledge for the medical, social and economic benefit of Scotland and its people.

### Recent highlights from the Patient and Public Involvement Advisory Service work for 2019 include:

#### Capacity Building to support researchers to set up their own Patient and Public Involvement groups.

New training courses have been created to support capacity building with researchers and teams across Edinburgh and the Lothians (and beyond!). These include:

- Creating and Running a PPI Group;
- PPI in Funding Applications;
- PPI in Clinical Trials;
- PPI in Fellowship Applications; and
- Bespoke training courses.

These complement the existing PPI Courses; 'A Practical Guide to Patient and Public Involvement' and 'Writing in Plain English'. Additionally, 2019 saw the running of the first PPI Summer School, with delegates from all over the UK and from as far away as China attending. This year so far we have trained over 140 people on our PPI training courses.



#### Conference and Invited speaker Presentations

Carol and members of the PAG have been invited speakers at a variety of conferences and workshops and courses and advised on this area to the Chief Scientist's Office. They have also created and delivered a very popular workshop at the UK Clinical Research Facility Conference in Nottingham, placing Scotland as visible leaders in PPI nationally.

#### PPI Champions

In Spring 2018 we appointed eight people across NHS Lothian and Edinburgh Clinical Research Facility (ECRF) as PPI Champions. All PPI Champion roles have been completed and we have five new self-sustaining PPI groups up and running

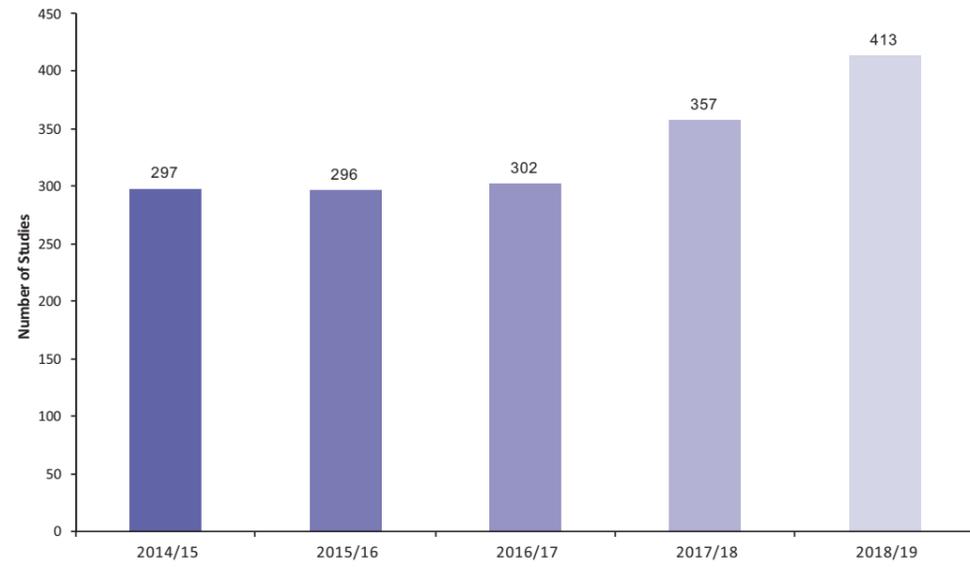
- A Children and Family group supporting clinical research in the Children's CRF;
- A PPI in Research Group in the Centre for Dementia Prevention (CDP);
- A Colorectal PPI group which is currently preparing funding applications and ethics documentation for quality of life work;
- A Cardiology Group in the Centre for Cardiovascular Sciences which has also been heavily involved in shaping research;
- The WTCRF PPI Group has completed new patient information resources which will soon be available and these will be rolled out as information resources across all ECRF sites to improve participant experiences.

#### Supporting Clinical Trials

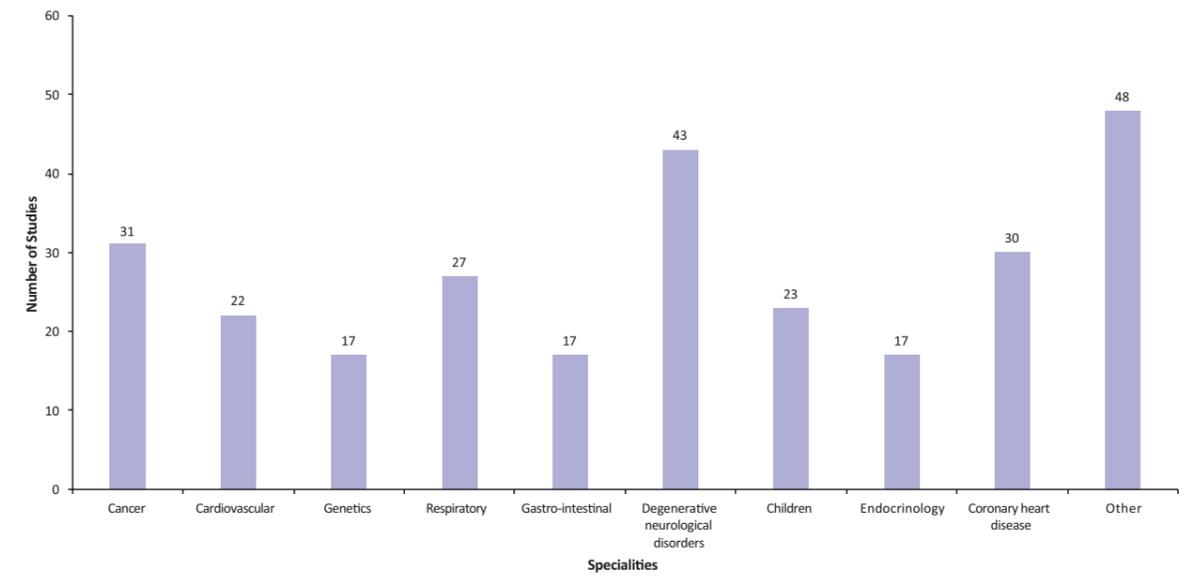
Given the importance of early involvement in Clinical Trials, we have been working closely with colleagues in Edinburgh Clinical Trials Unit to improve understanding and inclusion of PPI and supporting PPI at the earliest possible stages of trial design and development.

**PPIE Advisor: Carol Porteous - [carol.porteous@ed.ac.uk](mailto:carol.porteous@ed.ac.uk) – 0131 537 3326  
[www.ed.ac.uk/clinical-research-facility/patient-and-public-involvement](http://www.ed.ac.uk/clinical-research-facility/patient-and-public-involvement)**

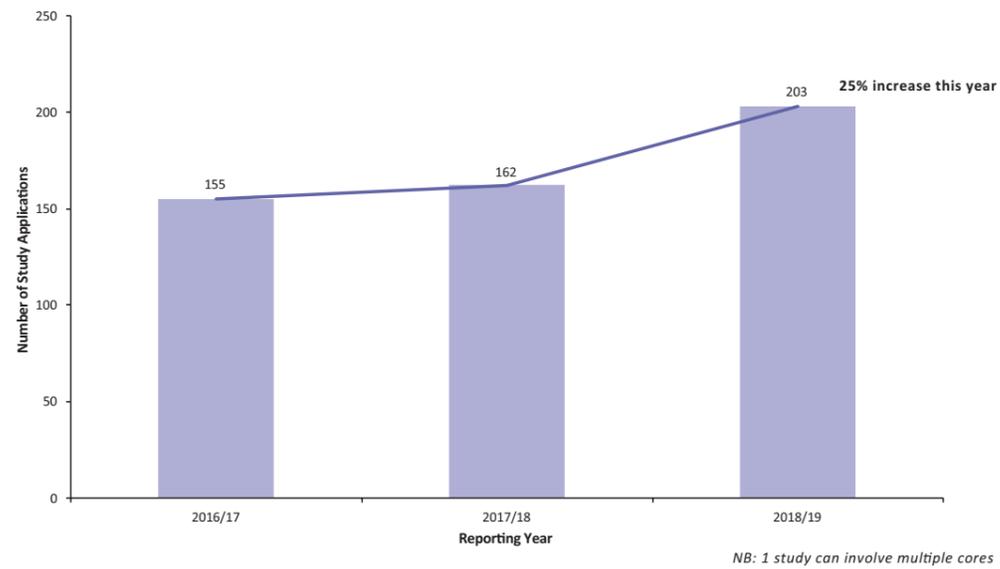
Edinburgh CRF Active Studies 2014/15 to 2018/19



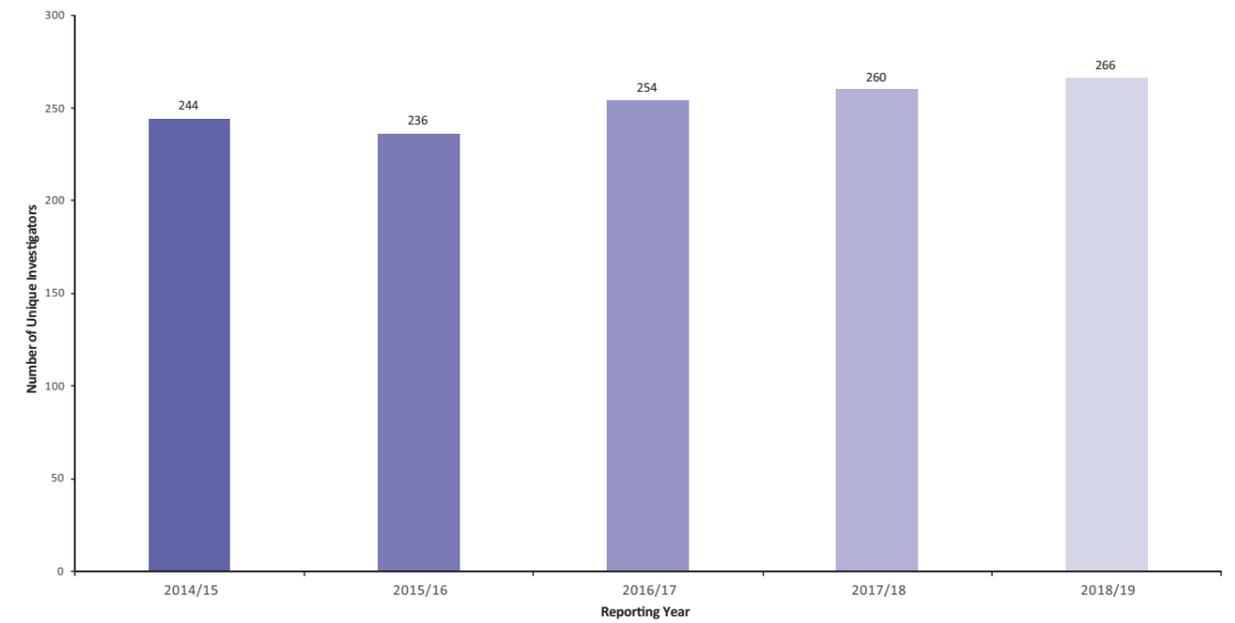
Top 10 clinical specialties using Edinburgh CRF 2018/19



Total Unique Study Applications



Unique Investigators using the Edinburgh CRF 2014/15 to 2018/19



## Image Analysis Core

Our expert team advises, guides and equips researchers with the skills necessary to perform image analysis on their own data in an appropriate and informed manner. They are also available to undertake analysis of image data acting as a central analysis facility for clinical trials or to develop state-of-the-art methodologies for new studies.

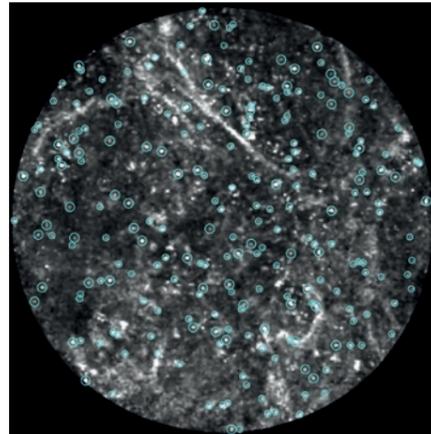
This type of environment that hubs specialist knowledge of medical physics, computer science and artificial intelligence embedded within clinically focused research infrastructure enables the Image Analysis Core to deliver innovative software solutions.

With a grant award from the Alzheimer's Drug Discovery Foundation, the Core is leading a collaboration with Duke University to quantify candidate biomarkers for the early stages of Alzheimer's disease in standard ophthalmic images of the retina. In collaboration with the Centre for

Cardiovascular Science in Edinburgh and with an award from the MRC, the Core is employing artificial intelligence to analyse images and data in the UK biobank and assess bone marrow fat associations with common conditions such as diabetes and heart disease. The Core supported the Proteus Group in the Centre of Inflammation Research in Edinburgh, providing bespoke image analysis software as they translated their novel molecular imaging technology for identifying bacteria in the lungs from the laboratory to the clinic.



*Vascular detection and analysis in images of the retina for investigation into candidate biomarkers of early Alzheimer's disease*



*Rapid in situ detection of pathogens coupled with high resolution imaging in the distal human lung has the potential to provide new insights and diagnostic utility in patients in whom pneumonia is suspected*

## Epidemiology and Statistics

The Epidemiology and Statistics Core aims to improve the methodological quality of clinical research through the provision of expert statistical input. The Core provides valuable input to studies at all stages, from the initial design through to the final analysis and dissemination of results. By encouraging investigators to approach the Core as early as possible, we support the development of the highest quality study designs ready for grant funding bodies, regulators and ethics committee reviews.

We are involved in a diverse range of projects drawn from a spectrum of clinical specialties. The Epidemiology and Statistics team has a wealth of experience in the methodology of conducting experimental medicine research.

### Highlights in 2018/19

- Working with Professor Dennis and colleagues, we provided the statistical support for the FOCUS trial, which investigates the impact of fluoxetine on long-term outcomes in patients who have suffered a stroke. The results were reported early this year with simultaneous conference presentation and Lancet publication. This was followed by an additional publication in Stroke and HTA monograph in draft. This trial found that Fluoxetine given daily for six months after acute stroke does not seem to improve functional outcomes. Although the treatment reduced the occurrence of depression, it increased the frequency of bone fractures.

These results do not support the routine use of fluoxetine either for the prevention of post-stroke depression or to promote recovery of function.

- Working with Professor Forbes and colleagues, we provide statistical support to the MATCH trial, investigating the first-in-human use of autologous monocyte-derived macrophages in participants with advanced liver cirrhosis. The first in human component was completed and recently published in Nature Medicine. We are continuing to provide support with this trial as it progresses through the Randomised Controlled Trial phase currently underway within our Nursing and Clinical core at the Royal Infirmary of Edinburgh CRF.

To find out how we can assist with your study please contact the Core Manager, Cat Graham.



### Statistics Clinic

**Need a brief session with a statistician to help answer questions on statistics and study design?**

If so we can advise on:

- Methodology and study design
- Sample size calculations
- Study data analysis

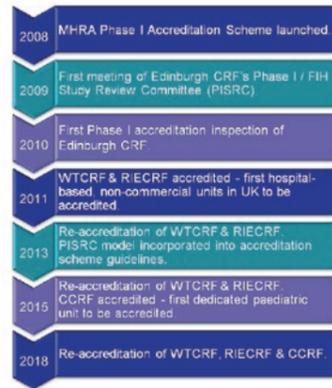
Access our Statistics Clinic by visiting: [www.ed.ac.uk/clinical-research-facility/core-services/epidemiology-and-statistics](http://www.ed.ac.uk/clinical-research-facility/core-services/epidemiology-and-statistics)

## Phase 1 / Quality Assurance

Edinburgh CRF is committed to supporting local researchers in the delivery of complex experimental medicine studies and early phase clinical trials, by providing the infrastructure, expertise and quality system to facilitate this in a manner that safeguards study participants.

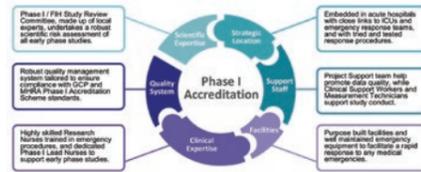
Accreditation under the Medicines and Healthcare products Regulatory Agency (MHRA) Phase I Accreditation Scheme is a key part of our strategy to realise this goal. Accredited units must demonstrate the highest standards for avoiding harm to trial participants and for handling medical emergencies.

The CRF's accredited adult (WTCRF and RIECRF) and paediatric (CCRF) facilities support both commercial and academic studies across a wide range of clinical specialities, and involving both patients and healthy volunteers. All three facilities undergo regular inspection by the MHRA, most recently in May 2018, to ensure accreditation standards are maintained. The best practice procedures that are part of our day-to-day activity are reflected in our successful inspection history, and provide assurance that Edinburgh CRF can be considered a centre of excellence for early phase research.



## Phase I Strategy

Edinburgh CRF's Phase I Accreditation is underpinned by a quality strategy covering all aspects of Phase I / FIH activity.



## Quality Assurance Team

Edinburgh CRF's quality management system is overseen by our dedicated Quality Assurance Team, who ensure we maintain regulatory compliance and uphold accreditation standards by:

- providing advice to ensure quality is built in to processes
- maintaining written procedures to direct activity
- monitoring compliance through internal audit
- advising on CAPA to drive continuous quality improvement.



CRF QA Team L-R Diane Mathers, James Gibson, Juliet Cavanagh-Anderson

The CRF's quality system extends beyond the Phase I accredited clinical facilities to include all CRF Cores. This includes a dedicated QA Manager for Edinburgh Imaging Facilities and bespoke systems within the CRF's Genetics and Mass Spectrometry laboratories which facilitate compliance in this area of increasing regulatory scrutiny.

## Beyond the CRF

By extensive engagement with regulators, other units and local and national networks, our QA Team keeps abreast of current regulatory expectations to ensure we continue to conduct research to the highest standards of safety and quality, while also supporting the wider research community.

The growing QA Team expanded further in 2019, with the appointment of a new QA Manager to support the quality system within Edinburgh Clinical Trials Unit (ECTU). This exciting development will allow ECTU to benefit from the CRF's quality management expertise, while further strengthening the ties between the two groups.

2019 also saw the QA Team involved in sharing the CRF's knowledge and experience of regulatory inspection. This included supporting preparations for an MHRA inspection of the local academic sponsors (ACCORD) by conducting mock interviews for ACCORD staff and local investigators, and also delivering inspection readiness training to staff within ECTU.

At a national level, Edinburgh CRF has had representation on the UKCRF Network QA Theme Group since its inception over a decade ago. Our current QA Lead has chaired the group since 2017, overseeing national projects including an Internal Audit Toolkit, a Phase I Accreditation Gap Analysis Tool and guidance documents on quality issues such as Data Integrity and Computer Systems Validation.

## IT Core – Software Development and Support

Our core strength lies in the design and development of custom digital services to facilitate clinical research.

We also provide training to clients across the UK and overseas with tailored support for our web-based applications. With their expert knowledge, our support team is able to provide help and advice, which consistently receives positive feedback from our product users.

### CRFManager® – www.crfmanager.com

CRFManager® is a comprehensive facility and study management tool used by over 50 research sites across the UK and overseas.

We have big plans for CRFManager®. It is currently being redeveloped as a full software suite (*think of Office365*) with multiple tools catering for different aspects of the clinical studies lifecycle.

We are hosting a user group development meeting in November 2019. We are pleased to see a lot of our users coming up to the Edinburgh CRF to take part in an all-day event to discuss some elements of the redesign and help us deliver better software.

The graphical user interface will be much improved, with features easier to find and use, therefore increasing productivity.

We've also been busy maintaining and updating other systems such as Locus, Linchpin, Brainbank and the Pharmacovigilance database.

Locus is a sample management software with workflows designed to help a team organise and track their samples. A trial version was completed and released to the Genetics Core at the Edinburgh CRF this year.

The Pharmacovigilance database was successfully inspected by the MHRA earlier this year, showing that our software met clinical regulation standards.



CRF IT team at the UKCRF Network Conference 2019 in Nottingham



## Sustainability

Edinburgh CRF is committed to working sustainably and promoting healthy working lives. The Wellcome Trust CRF site at WGH has a Sustainability Committee, with membership from both University and NHS staff employed there, and our efforts have been recognised with a Silver Sustainability Award for Offices and a Gold Award for our Genetics Lab, as part of the University Department of Social Responsibility and Sustainability's awards scheme. We are currently being assessed for a Gold Award for our offices.

To achieve an award, we need to demonstrate that we meet a range of criteria across six themes:

- Travel
- Energy
- Purchasing
- Health/Wellbeing
- Communications/Engagement
- Resource Efficiency

For the Gold Award, we also had to design and implement a unique project with a demonstrable sustainability impact, that would have a continuing legacy. We developed a project called "Zero Waist – a Health and Wellbeing Initiative".

Our central initiative for the project was a six week step count challenge in the summer. Seventy staff members (University and NHS) participated in 12 teams. Rather than just counting steps, we brought the challenge to life by creating a 'virtual' walking route along ancient walking trails, starting with the West Highland Way from Milngavie to Fort William, then continuing on the Great Glen Way to Inverness (169 miles). To reach Inverness, we had to walk an average of around 8,000 steps a day over the six week period. We also included an extension on the John O'Groats Trail, which was a total of 315 miles – an average of around 15,000 steps a day. From step-counts submitted, we calculated the average distance virtually walked within each team in the week and plotted their location along the route. We provided a weekly 'Sway' newsletter, updating everyone on where the teams were and providing photos and information on these locations, including things to see or do. At the end of the challenge, we had walked a total of 19,182 miles, with all teams reaching Inverness and some passing John O'Groats. By making the walk 'real', it increased engagement and encouraged people to get out and about. An example of our Sway reports on the challenge can be seen at <https://sway.office.com/A3pH6tqqoMwXAnRV?ref=Link>.



Other initiatives which formed part of our bid included:

- 11 members of CRF staff have been trained as Mental Health First Aiders.
- We have organised weekend walks, to encourage people to get out in the fresh air and exercise, as well as providing an opportunity for staff to get to know each other better out of the work environment.
- We encourage staff to go for lunchtime walks, and provide information on short walks that people can fit into their working day.
- We have a Sustainability Notice Board with information on cycling, walking, healthy eating and other relevant topics.
- We promote the use of the Edinburgh Community Food stall that takes place in the hospital every week. As well as selling locally-sourced fresh fruit and vegetables, they provide packs with all the ingredients you need to create healthy, meat-free meals. All proceeds go to helping people in low-income communities have an affordable, healthy diet.
- We have created a blog (<https://blogs.ed.ac.uk/sustainable-wellness>), where we post information on healthy living and sustainability.
- We promote initiatives such as World Car Free Day, National Vegetarian Week, World Beach Clean Day etc.

Our project has seen staff benefitting from improved fitness and morale, and people have made longer-term changes to their lifestyles as a result of the project. It has also encouraged cross-departmental working, as we have had participation from all parts of the CRF and also other departments with whom we work closely. We have a team that is very committed to living and working sustainably and that is proud of our achievements. We look forward to continuing to build on what we have achieved to date to do what we can to reduce our impact on the planet.



## Positive Adaptation of HPA Axis Function in Women During 44 Weeks of Infantry-Based Military Training

R M Gifford, R M Reynolds et al  
*Psychoneuroendocrinology*. 2019 Dec; 110:104432

**Background:** Basic military training (BMT) is a useful model of prolonged exposure to multiple stressors. Eight to twelve week BMT is associated with perturbations in the hypothalamic-pituitary-adrenal (HPA) axis which could predispose recruits to injury and psychological strain. However, characterisations of HPA axis adaptations during BMT have not been comprehensive and most studies included few if any women.

**Methods:** The team studied women undertaking an arduous, 44-week BMT programme in the UK. Anxiety, depression and resilience questionnaires, average hair cortisol concentration (HCC), morning and evening saliva cortisol and morning plasma cortisol were assessed at regular intervals throughout

**Results:** Fifty-three women (aged  $24 \pm 2.5$  years) completed the study. Questionnaires demonstrated increased depression and reduced resilience during training (both  $p < 0.001$ ). HCC increased from three months before training to the final three months of training ( $p = 0.003$ ). Morning saliva cortisol increased during the first seven weeks of training ( $p < 0.001$ ) and decreased thereafter, with no difference between the first and final weeks ( $p = 0.2$ ). Evening saliva cortisol did not change. Fasting cortisol decreased during training.

**Discussion:** These results suggest a normal stress response in early training was followed quickly by habituation, despite psychological and physical stress evidenced by questionnaire scores and HCC, respectively. There was no evidence of HPA axis maladaptation. These observations are reassuring for women undertaking arduous employment.

Edinburgh CRF's Nursing Core undertook the sample collection, questionnaires and data entry for this study. The Mass Spectrometry Core developed and undertook the cortisol analysis.

## Safety profile of autologous macrophage therapy for liver cirrhosis

Moroni F, Forbes S et al  
*Nature Medicine*: 2019 Oct; 1560(25):1560–1565

Globally, liver cirrhosis currently causes 1.16 million deaths every year. Patients often present with advanced liver disease and cirrhosis. No curative options bar organ transplantation, which requires major surgery and lifelong immune-suppression, exist. Donor organ availability restricts access to transplantation. Alternative therapies to treat cirrhosis are therefore being developed, including cell therapies.

In pre-clinical models of liver fibrosis, macrophages injected via a peripheral vein home to the liver, recruit host immune cells to liver scar, ameliorating liver fibrosis, stimulating liver regeneration and improving function. Circulating CD14+ monocytes can be isolated from cirrhotic patient mononuclear cell leukapheresis products with high yield and purity and can be differentiated into macrophages similar to those from healthy volunteers. These macrophages can also resolve liver fibrosis in pre-clinical models. These data prompted this first-in-human, phase 1, single-arm, dose-escalation clinical trial in people with cirrhosis, evaluating the maximum tolerated dose and the safety of peripheral infusion of ex vivo matured autologous monocyte derived macrophages.

Nine participants with compensated liver cirrhosis attended the Royal Infirmary of Edinburgh, were enrolled between August 2016 and March 2017 and had one year follow up. Each group of three participants received a single infusion of autologous macrophages at 107, 108 or 109 cells, respectively, in a dose-escalation manner.

This first-in-human trial confirmed administration of macrophages was safe, with no clinically relevant adverse reactions recorded during the infusion or in the immediate post-infusion period. Edinburgh CRF nursing staff undertook the clinical measurements, data entry and sample management on this study.

## Too Much Sunscreen? Why avoiding the sun could damage your health

Geddes, Linda  
*New Scientist*: 2019 March; 3221

It has been known for at least 50 years that blood pressure is lower in summer than winter but the reason for this has been less clear. Individuals with lower circulating vitamin D levels tend to have higher blood pressure but a growing number of clinical trials of oral vitamin D supplementation now show quite clearly that it plays no part in cardiovascular health. Dr Richard Weller ran a research project in the Edinburgh Clinical Research Facility in 2013 and 2014 with his PhD student Dr Donald Liu and support from Professor David Newby and the cardiology department. Richard was able to show a new mechanism by which ultraviolet radiation mobilises nitric oxide from stores in the skin to the circulation where it vasodilates arteries and lowers blood pressure (Liu et al 2014 doi.org/10.1038/jid.2014.27).

There is clearly more to sunlight's actions than just vitamin D and research by collaborators since then has shown that this sun-skin-NO mechanism probably plays a role in the prevention of metabolic syndrome as well as in cardiovascular health. This research is helping precipitate a rethinking of the benefits risk ratio of sunlight exposure which has previously been dominated by dermatological concerns over skin cancer. This science and the ongoing debate around it featured on the front cover article of *New Scientist* in March this year as well as a chapter of Linda Geddes book 'Chasing the Sun' (Wellcome 2019) which was presented at this year's Edinburgh Book Festival. It is satisfying to see CRF research so rapidly having an influence on international guidelines and research.

The Image Analysis Core is working with colleagues in Edinburgh at the **Centre for Cardiovascular Sciences** and Edinburgh Imaging to investigate non-invasive imaging of human coronary atherothrombosis, part of a 5 year programme of research funded by the **British Heart Foundation**. The Image Analysis Core is providing specialist expertise in image reconstruction, attenuation correction, registration, anonymisation and machine learning.



Edinburgh CRF Education team supported the **9th European Network for Oxysterol Research (ENOR) Symposium**



Edinburgh CRF Genetics and Mass Spectrometry Cores host 5th year high school pupils in the laboratory as part of the **Science Insights Programme**, to give them a real insight into research and work in the fields of genetics and mass spectrometry.



Clinical managers of the **Scottish CRF Collaboration** work proactively to support and promote clinical research in Scotland



The Genetics Core has seven members of staff who have professional registration with the **Science Council** and two members of staff in the Mass Spectrometry Core are working towards this.



A PhD student co-funded by **Optos** and the **MRC** in conjunction with the Image Analysis Core is exploring retinal imaging as a means of personalizing 3D computer modelling of vascular information in the eye as a surrogate or virtual biopsy for kidney disease.



Natalie Homer from the Mass Spectrometry Core took part in a public engagement activity 'Stress Busters' at the **Scottish Parliament International Science Festival**, including a chromatography activity for school aged children.



The Mass Spectrometry Core is part of the **Scottish Metabolomics Network** and the Education Core support the organisation of the annual conferences. The Mass Spectrometry Core is also part of **Edinburgh TEAMS** (The Edinburgh Association of Mass Spectrometrists) and the Education Core also support the organisation of TEAMS2019 at Roslin Institute.



**NRS Training Forum** – Edinburgh CRF Education team collaborates with other educators across Scotland to deliver standardised NRS GCP training and to develop research education nationally.



Edinburgh CRF is represented across all the main workstreams in the **UKCRF Network**.



The **Stratified Medicine Scotland-Innovation Centre** is funded to develop the Scottish Precision Medicine Ecosystem. The CRF Genetics Core is partnering on projects including Multiple Sclerosis and non-alcoholic fatty liver disease where they are providing expertise in sample processing, RNA extraction and sequencing.



In a project funded by the **Alzheimer's Drug Discovery Foundation**, the Image Analysis Core is collaborating with **Duke University** to identify candidate biomarkers of dementia derived from retinal imaging.



Staff within the Mass Spectrometry and Genetics Cores are contributing to the implementation of the **Technician Commitment** in the University. This is a driving force in improving the visibility, recognition, career development and sustainability of technicians in higher education.



Edinburgh CRF IT team liaises with **Edinburgh Innovations** to manage our CRFManager® contracts. Over 50 sites now use our CRF administration database. Our Genetics and Mass Spectrometry Cores also work with El on their commercial contracts.



Genetics and Mass Spectrometry Core Managers co-delivered a workshop with Kelly Vere and Ian Wilcox on the Technician Commitment and Core Facility careers at the **Core Technologies for Life Sciences** Core Facility staff training school at Institut Pasteur, Paris in November 2019.



#### Directors

Professor David Newby, Professor Peter Hayes

#### Associate Directors

Professor Craig Ritchie, Professor Steve Cunningham

#### Deputy Director

Dr Steve McSwiggan  
Steve.McSwiggan@nhslothian.scot.nhs.uk 0131 537 3358

#### Research Nurse Manager

Finny Paterson  
Finny.Paterson@nhslothian.scot.nhs.uk 0131 242 7185

#### QA Lead

James Gibson  
james.gibson@nhslothian.scot.nhs.uk 0131 537 3328

#### Administration Manager

Marie Leslie  
marie.leslie@ed.ac.uk 0131 537 3357

#### Study Information Manager/Deputy Administration Manager

Joanne Douglas  
Joanne.Douglas@ed.ac.uk 0131 537 3359

### CORES

#### NURSING AND CLINICAL

##### Wellcome Trust CRF

**Lead Research Nurse:** Gerry Cummings  
Geraldine.Cummings@nhslothian.scot.nhs.uk 0131 537 3388

##### RIE CRF

**Lead Research Nurse:** Heather Spence  
heather.spence@nhslothian.scot.nhs.uk 0131 242 7186  
**Lead Research Nurse:** Pip Howgego  
philippa.howgego@nhslothian.scot.nhs.uk 0131 242 7186

##### Children's CRF

**CRF Associate Director:** Professor Steve Cunningham  
**Lead Paediatric Research Nurse:** Debbie Miller  
debbie.miller@nhslothian.scot.nhs.uk 0131 536 0808

##### Centre for Dementia Prevention CRF

**CRF Associate Director:** Professor Craig Ritchie  
**Lead Research Nurse:** Jill Steven  
jill.steven@nhslothian.scot.nhs.uk 0131 651 7664

#### EDUCATION

**Core Director:** Dr Kenneth Simpson  
**Education Programme Manager:** Jo Merrifield  
Jo.Merrifield@ed.ac.uk 0131 537 3326

#### IT

**Software Development Manager:** Patrice Fleury  
pat.fleury@ed.ac.uk 0131 537 3353

#### EPIDEMIOLOGY AND STATISTICS

**Core Director:** Professor Chris Weir  
**Associate Core Director:** Professor Steff Lewis  
**Core Manager:** Cat Graham  
c.graham@ed.ac.uk 0131 537 3350

#### GENETICS

**Core Directors:** Professor Tim Aitman  
Professor David Porteous  
**Associate Core Director:** Dr Shona Kerr  
**Core Manager:** Lee Murphy  
lee.murphy@ed.ac.uk 0131 537 3370

#### IMAGE ANALYSIS

**Core Directors:** Dr Mark Dweck  
Dr Gerry Thompson  
**Core Manager:** Dr Tom MacGillivray  
t.j.macgillivray@ed.ac.uk 0131 465 9565 / 0131 242 7756

#### MASS SPECTROMETRY

**Core Director:** Professor Ruth Andrew  
**Core Manager:** Dr Natalie Homer  
n.z.m.homer@ed.ac.uk 0131 242 6452

#### IMAGING

**Business Manager:** Dr Duncan Martin  
duncan.martin@ed.ac.uk 0131 242 7776  
[www.edinburghimaging.ed.ac.uk](http://www.edinburghimaging.ed.ac.uk)



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**Centre for Dementia Prevention**



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Sustainability Awards  
**GOLD - LABS**



Sustainability Awards  
**GOLD - OFFICES**

**Wellcome Trust Clinical Research Facility**

North Corridor  
Western General Hospital  
Crewe Road South  
Edinburgh  
EH4 2XU

Tel: 0131 537 2591

**RIE Clinical Research Facility**

Royal Infirmary of Edinburgh  
51 Little France Crescent  
Edinburgh  
EH16 4SA

Tel: 0131 242 7183

**Children's Clinical Research Facility**

Royal Hospital for Sick Children  
Sciennes Road  
Edinburgh  
EH9 1LF

Tel: 0131 536 0808

**Centre for Dementia Prevention Clinical Research Facility**

9A Bioquarter  
9A Little France Road  
Edinburgh  
EH16 4UX

Tel: 0131 651 7828

**Key Contacts:**

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

Deputy Director: Dr Steve McSwiggan  
Tel: 0131 537 3358  
E-mail: [Steve.McSwiggan@nhslothian.scot.nhs.uk](mailto:Steve.McSwiggan@nhslothian.scot.nhs.uk)

[www.ed.ac.uk/clinical-research-facility](http://www.ed.ac.uk/clinical-research-facility)

[info@edinburghcrf.ed.ac.uk](mailto:info@edinburghcrf.ed.ac.uk)

[@EdinburghCRF](https://twitter.com/EdinburghCRF)

If you have received this publication and do not wish to receive copies in the future, please contact the Administration Manager of the CRF - Marie Leslie - [marie.leslie@ed.ac.uk](mailto:marie.leslie@ed.ac.uk).

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