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Academic and Clinical Central Office for Research and Development

NHS Lothian

NHS SCOTLAND
NHS RESEARCH SCOTLAND

Promoting clinical research excellence for the health and wealth of Lothian and Scotland

May 2022

Contents

Introduction

Professor Alasdair Gray
Director of Research & Development, NHS Lothian

Welcome to the 2021-22 brochure from the Academic and Clinical Central Office for Research and Development (ACCORD). Sitting at the centre of clinical research activity in Lothian, ACCORD combines research management staff from NHS Lothian and the University of Edinburgh. Together these staff provide a joint research office that offers central access to professional advice, expert regulatory support and clinical research infrastructure for every stage of the research pathway.

In May 2021, our last brochure detailed ACCORD's research response to Covid-19. We used the brochure to highlight a selection of talented people, projects & scientific achievements that demonstrated how Edinburgh's clinical research community tackled the pandemic. As 2020 ended, we dared to hope for a less challenging year in 2021 and with new, highly effective vaccines becoming available, we began to imagine a return to pre-pandemic life. Things did not quite turn out like that of course and we started 2021 under lockdown conditions yet again…

Predictably, 2021 turned out to be another very tough year. While maintaining delivery of key national Covid-19 studies, our research teams worked hard to restart the non-covid clinical research portfolio. Simultaneously, we were tackling a major backlog of work that had accumulated during the pandemic. The entire ACCORD team showed incredible fortitude during this difficult time, made all the harder by protracted homeworking conditions and reduced staffing levels. We owe them a significant debt of thanks for their commitment and loyalty throughout.

At the end of March 2021, we said goodbye to Professor Tim Walsh who stepped down as NHS Lothian's R&D Director after four very busy years. In his final year in the role, Tim led ACCORD through the onset of the pandemic and the first frantic 12 months of Covid-19. We are immensely grateful for Tim's steadfast guidance and support throughout his tenure as R&D Director, particularly during the uncertainty and challenges of the first Covid-19 wave.

As Tim departed, we welcomed Professor Alasdair Gray as our new R&D Director. Alasdair has been a Consultant in Emergency Medicine in Edinburgh since 2001, where he founded Lothian's thriving Emergency Medicine Research Group (EMERGE). Since then, he has led a number of prestigious clinical trials with EMERGE, including RAPID-CTCA, which is featured in this brochure.

> **"Over the summer of 2021, we were delighted when three senior investigators from Edinburgh were awarded funding through the Chief Scientist Office (CSO) Precision Medicine Alliance Scotland scheme"**

Alasdair joined ACCORD just as Scotland was emerging from a third lockdown and work was starting across the UK to support the managed recovery programme for clinical research. It is safe to say, his role as R&D Director has kept him very busy ever since! 2021 was an extremely difficult year in which to start as R&D Director, but Alasdair has grasped the nettle firmly and we are very fortunate to be working with him. He has just completed his first year in the role!

Over the summer of 2021, we were delighted when three senior investigators from Edinburgh were awarded funding through the Chief Scientist Office (CSO) Precision Medicine Alliance Scotland scheme. Professors Stuart Forbes, David Hunt and Manu Shankar-Hari were awarded almost £7M between them through this competitive national initiative. You can read more in this brochure about their research programmes in liver disease, multiple sclerosis and critical illness.

We are delighted to showcase our key operational partners and to present recent examples of Edinburgh's ongoing contribution to the Covid-19 research response

Other achievements from the past year include the renewal of our Clinical Research Facilities' MHRA Phase I Accreditation. This prestigious scheme acknowledges the stringent safety and quality standards that our CRFs meet in delivering early phase and first in human studies.

On this occasion, for the first time, the Phase I inspection included our newly built Children's Clinical Research Facility (CCRF) in the new Royal Hospital for Children and Young People (RHCYP). Thanks to the hard work and scrupulous standards of the CRF staff, both adult CRFs and our children's CRF were successfully re-accredited. It is a major achievement to maintain this gold standard.

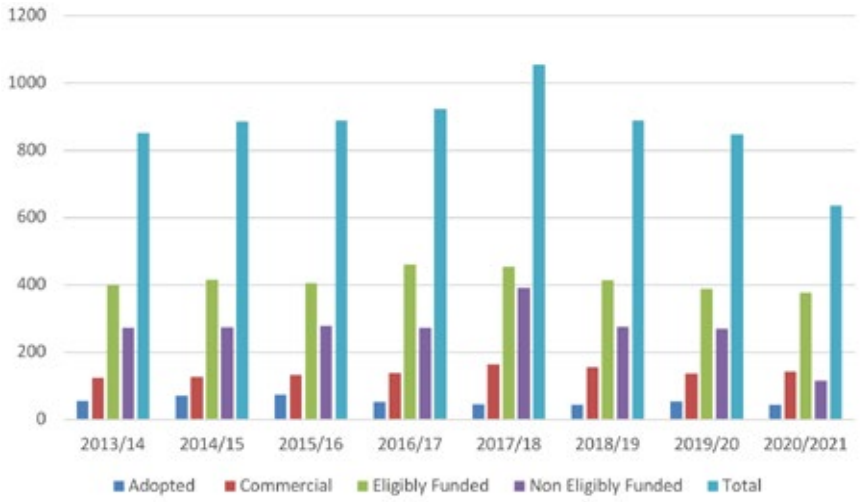
This brochure also highlights some of the significant developments, achievements and publications from the past twelve months. We are delighted to showcase our key operational partners and to present recent examples of Edinburgh's ongoing contribution to the Covid-19 research response. We know that 2022 will be another challenging year for clinical research staff throughout the UK and we are in the process of writing our new R&D strategy for the next five years. We are aligning our strategic plan with the themes set out in the four nations' report of 23 March 2021 'Saving and Improving Lives: The Future of UK Clinical Research Delivery". We look forward to sharing it with you later this year.

There is no doubt that another busy year lies ahead for all of us. For the moment, I hope everyone will pause to reflect proudly on the excellent activities, facilities and scientific outputs detailed within this report.

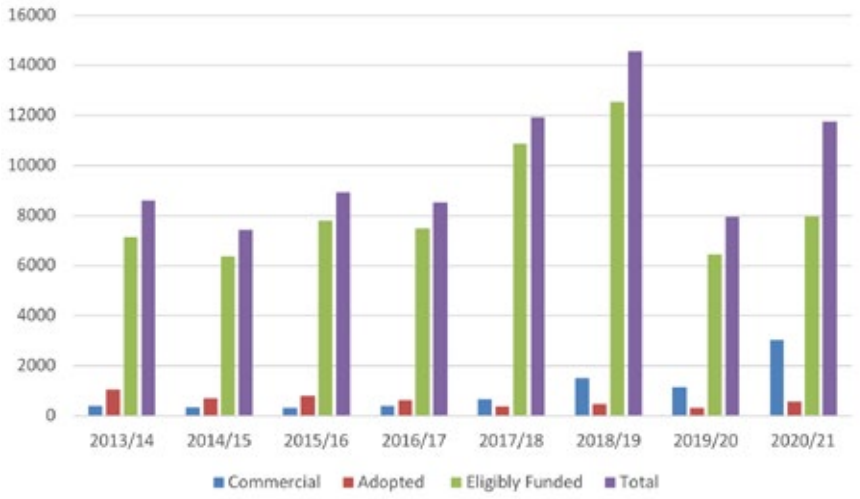
Please enjoy our brochure!

ACCORD Metrics

Number of Studies by Year

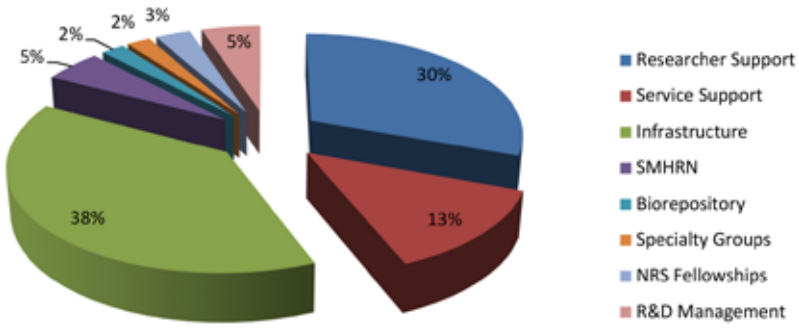


Study Recruitment by Year



ACCORD Metrics

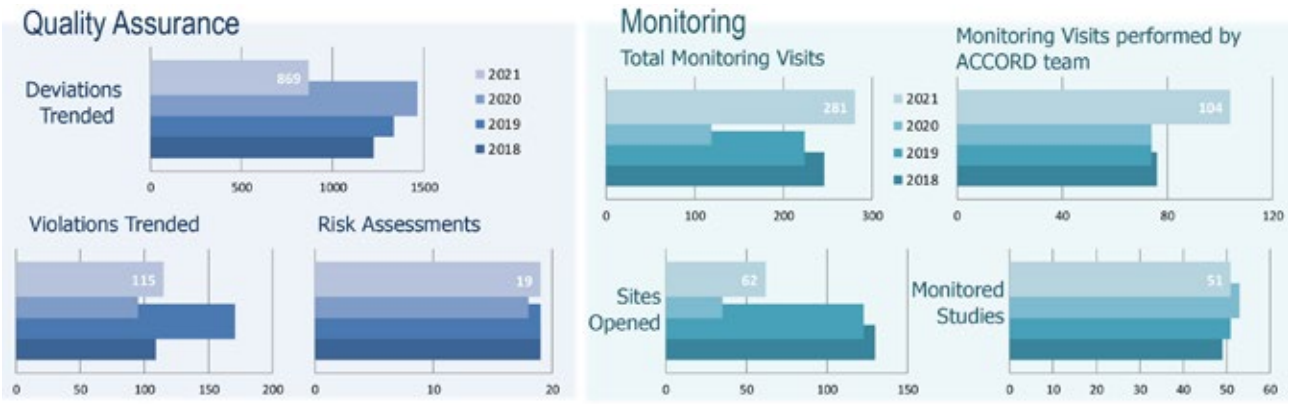
Distribution of NHS Lothian's NRS Funding Allocation 2021/22

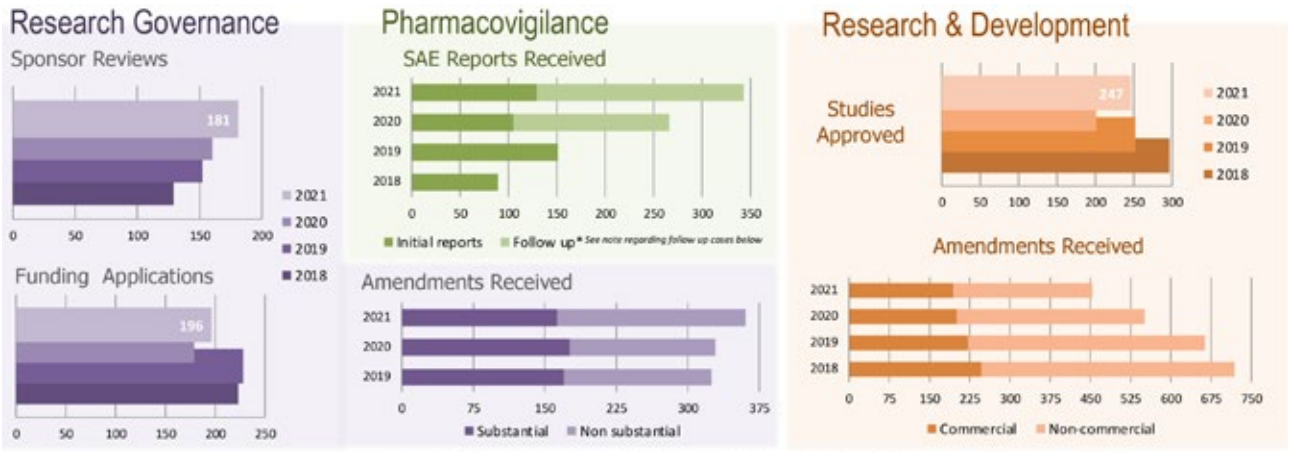


Annual NRS Allocation by Year

ACCORD Metrics

Comparison with 2020, 2019, 2018.





Metrics compiled by individual ACCORD teams for period 01 Jan – 31 Dec 2018, 2019, 2020, and 2021.
*SAE data on number of follow up reports received is only available from March 2020. 2018 and 2019 data contain initial SAE reports only, 2020 data does not contain follow up cases reported in Jan and Feb 2020, 2021 follow up case data is complete.
Monitoring visits includes SIVs . Sponsor reviews includes regulated and non-regulated studies where UoE is lead Sponsor. R&D includes hosted studies, R&D amendments received includes those assigned as Category A and B only, not Category C.

ACCORD Services

Funding Proposals

ACCORD, NHS Lothian R&D Finance Team, UoE Research Support Team

Working closely with the UoE Edinburgh Research Office and NHS Lothian Finance team, ACCORD reviews funding applications to identify important costs e.g. regulatory fees, monitoring, drug and labelling, database, archiving, NHS resources and facilities.

Sponsorship

Research Governance Team

The role of 'Sponsor' is defined in the UK policy framework for health and social care research and in the UK clinical trials regulations as an organisation responsible for ensuring arrangements to initiate, manage, finance and indemnify a study. ACCORD reviews all clinical research led from Edinburgh that involves people, their tissues or data and identifies if single or co-sponsorship by UoE and/or NHS Lothian is appropriate. Co-sponsorship by both organisations is the default sponsorship model.
A lead Sponsor Representative is assigned to review the protocol, study documents e.g. participant information sheets/consent forms and the IRAS application for ethics and R&D submissions.
The Representative provides advice and document templates to help ensure successful submissions.
Throughout the research study, the Representative is available for advice, and to review Amendments for submission as they arise.

Facilitation Team

Clinical research regulated under the clinical trials or medical device regulations or considered to be complex or high risk is assigned a Clinical Research Facilitator. Facilitators provide support with the protocol, study documents and IRAS application or Combined Review for ethics, R&D and regulatory submissions, help with sourcing investigational supplies and work closely with the ACCORD Monitoring team to hand over for trial set up. Regulated and more complex research undergoes an ACCORD risk assessment to identify any risks and ensure appropriate mitigation is in place. The risk assessment feeds into a risk based monitoring and audit plan for the ACCORD Monitoring and QA teams.

Contracts Teams

Legally binding agreements are often needed between organisations participating in clinical research to set down arrangements for e.g. collaboration, finance, insurance, publication and intellectual property, regulatory compliance, provision of drugs or equipment, human tissue transfer, data sharing etc.
Sponsor Representatives work closely with the University and NHS Lothian Legal and Contracts teams to identify the agreements required for clinical research. The Legal and Contracts teams fulfil drafting, review, negotiating and signing of these agreements.

Quality Assurance Team

The QA team provides regulatory support and resources for researchers and independent oversight of trial related activities. QA manages a library of ACCORD Standard Operating Procedures (SOPs) and policies, which are designed to provide clear written instructions to help researchers.
The team also manage an audit programme to ensure ongoing compliance of facilities and vendors involved in clinical research, and of specific research studies that may have been identified as high risk.

Monitoring Team

Monitoring of clinical trials is performed on a risk-based approach to ensure that the rights and well-being of participants are protected; reported data are accurate, complete and verifiable from source documents and the conduct of the research is in compliance with the approved protocol, amendments, SOPs, Good Clinical Practice (GCP) and regulatory requirements.
Clinical Research Monitors support researchers with trial set up and help to ensure compliance throughout the life of the trial to closure. Monitoring visits are conducted on-site or remotely in accordance with the research monitoring and source data verification plans.

Pharmacovigilance Team

ACCORD takes on Pharmacovigilance responsibilities for regulated trials, receiving reports of Serious Adverse Events (SAEs), Serious Adverse Reactions (SARs) and Suspected Unexpected Serious Adverse Reactions (SUSARs), maintaining a safety database and onward reporting all SUSARs to ethics committees

and regulatory authorities. The Pharmacovigilance team prepare SAE listings, complete MedDRA coding for annual Data Safety Update Reports (DSURs) for all regulated trials and provide safety line listing reports to Data Monitoring Committees. Pharmacovigilance also involves a regular review of the Reference Safety Information (RSI) for regulated trials to ensure participant safety and quarterly reviews of all SAEs to perform trend analysis on clinical research.

Research Data Support

ACCORD promotes the importance of research data management and transparency. The UoE Research Data Service provides tools and support to help researchers store, manage and share data responsibly. ACCORD provides advice and support to ensure clinical research is appropriately registered and results are posted within the required timeframes.

Information Governance & Information Technology Security

ACCORD works closely with UoE and NHS Lothian Information Governance (IG) and Information Technology (IT) Security teams to ensure compliance with all aspects of data protection legislation. The Sponsor review usually covers everything necessary; projects involving higher risk scenarios e.g. processing or transfer of personal data, access etc. Where required, research studies are referred to IG/IT security for the relevant input and support. This could involve an additional data protection impact assessment, IT security risk assessment and/or Caldicott Guardian approval.

R&D Management Permissions

NHS LOTHIAN RESEARCH & DEVELOPMENT (R&D) GOVERNANCE TEAM

For research involving the NHS to begin in Scotland, the relevant NHS organisation(s) must issue NHS R&D permission. Permissions are obtained in Scotland via a national R&D process. HRA approval is required for research involving the NHS in England. ACCORD Sponsor Representatives advise on R&D submissions to all NHS organisations that may be involved in the research study. They also help with other requirements such as Research Passports or Caldicott Guardian approvals. Although a research study has been reviewed by the ACCORD Research Governance team for sponsorship, review by the ACCORD NHS Lothian R&D team is also required. The R&D review involves assessing the impact of the research on the NHS and confirming local capacity and capability for NHS Lothian to take part in the research.

Training

ACCORD Governance, Facilitation, QA, Monitoring and Pharmacovigilance teams deliver training courses in many areas of clinical research and are happy to discuss research team requirements for training and refresher courses. The Wellcome Trust Clinical Research Facility Education Programme also delivers a variety of courses relevant to researchers in Edinburgh and the UoE Research Data Service run a range of workshops, online courses and tailored training on research data.

Research Transparency

More people than ever before are taking part in health and social care research; over a million people each year. This research brings better care for patients by discovering new treatments as well as new ways to detect, diagnose and reduce the chance of developing an illness.

But if the research findings are not easily available to those research participants, how are they to know the difference they have made, and why would they take part in future research?

Similarly, how are other researchers to know what research is happening, so they can avoid duplication of effort and maximise research funding? How can health professionals, policy makers and funders make informed decisions without the knowledge of research outcomes?

That's where research transparency plays a huge role. Transparency is about what research is going on and what the findings are, making that information accessible to the public and to the research community.

The Health Research Authority (HRA) developed the #MakeItPublic strategy to transform research transparency in the UK. Responding to recommendations for change made by the House of Commons Science and Technology Committee, the strategy was developed to make transparency the norm.

Four pillars of research transparency are considered – **Registering Research**, **Reporting Results**, **Informing Participants** and **Sharing Data and Tissue**. The first 3 of these pillars are described in more detail here, while work is ongoing to promote data and tissue sharing.

Across Edinburgh, clinical research is also conducted that doesn't fall under the remit of the HRA, but nonetheless should make the same considerations when it comes to research transparency.

> **Four pillars of research transparency are considered – Registering Research, Reporting Results, Informing Participants and Sharing Data and Tissue**

In order to avoid waste, information about research projects (other than those for educational purposes) is made publicly available before they start

Registering Research

Registration is a condition of a favourable ethics opinion for clinical trials and is good practice for all other research.

Making research visible in a publicly accessible database before recruitment begins reduces duplication and protects participants from unnecessary research.

Clinical Trials

Clinical trials of investigational medicinal products (CTIMPs) and combined trials of an IMP and investigational medicinal device are now automatically registered on the ISRCTN registry when the trial is submitted via the combined review service. This registration allows plain English summaries and public titles to be visible on the Be Part of Research website, where the public can search for clinical research relevant and local to them.

Automatic registration will be rolled out for other types of clinical trials in time. For now, other clinical trials should be registered on a platform acceptable to the International Committee of Medical Journal Editors (ICMJE), who will only consider clinical trials for publication if they have been registered in an appropriate registry.

The ICMJE defines a clinical trial as 'any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes' and lists www.clinicaltrials.gov and www.ISRCTN.org as acceptable registries.

Other Research

This leaves other types of research, including observational studies and questionnaires. A useful platform to support research transparency and enable collaboration is the Open Science Framework. The Health Research Authority (HRA) also publish information about studies they have approved on their research summaries website.

Reporting Results

'Other than research for educational purposes and early phase trials, the findings, whether positive or negative, should be made accessible in a timely manner after the research is finished.'

Publishing results in a peer-reviewed journal is often the main focus of researchers, and of course is important, but not always achievable or easily accessible to the public. **Results should be made available in a place they can be seen and in a way that they can be understood by the public.**

The HRA request a final report for studies they have approved, which is submitted using their Final Report Form, and which they publish on an accessible website.

They intend to measure transparency performance based on the receipt of final reports, publish transparency information about individual institutions, and take into consideration the extent to which an applicant has fulfilled previous transparency responsibilities when reviewing new studies for approval.

It's also important to maintain the registration record, uploading results to the registry or database used to make that study public.

> **Information about the findings of the research should be available in a suitable format and timely manner, to those who took part in it, unless otherwise justified**

Informing Participants
Providing research findings to participants is an important part of good public engagement, respecting the participants and acknowledging their contribution.

Researchers seeking HRA approvals must describe their dissemination plans when applying for approvals. To help researchers in this area of transparency, the HRA is drafting new guidance on how to inform participants, taking into account the types of research where this may be more of a challenge, such as research involving adults with incapacity, emergency research and research in which participants are likely to die from their existing illness.

The final report form required by the HRA includes a lay summary of study results that they publish on an accessible website and they have developed an e-learning module explaining how to write a plain language summary of research findings.

Research Transparency Highlight

The Restart or Stop Antithrombotics Randomised Trial (RESTART), led by Professor Rustam Al-Shahi Salman is an excellent example of sharing results in a variety of formats. Other good examples from the Centre for Clinical Brain Sciences are available on the University of Edinburgh website.

Over the last few years, ACCORD has been focussed on improving clinical trial reporting and upload of results into trial registries. With commitment from Investigators, Statisticians, Trial Managers, supported by our QA and Research Governance teams, we increased our EU Trials Tracker statistics for reporting into the EU Drug Regulating Authorities Database (EudraCT) from 55% in 2019 to 93.2% as of March 2022. This was no mean feat for everyone involved, given the complexity of that particular database!

Post Brexit, new clinical trials are no longer entered to EudraCT, and instead will be registered on ISRCTN (thankfully uploading results into this registry is somewhat easier). We will strive to continue to improve results reporting for all clinical trials and for other clinical research too, regardless of where they are registered.

As Sponsor or researcher, we must all aim to make transparency easy, make transparency the norm and make information public for the benefit of all.

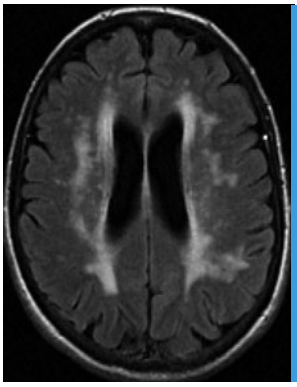
NRS Career Development

NRS Clinician: Targeting cerebral small vessel disease to reduce stroke and dementia.

Fergus Doubal is a consultant stroke physician in the Royal Infirmary of Edinburgh, honorary senior lecturer with the University of Edinburgh and Lothian Stroke MCN clinical lead. Fergus was an NRS fellow between 2015 and 2018 and NRS clinician since with research interests focusing on all aspects of cerebral small vessel disease.

The problem

The insidious onset of brain abnormalities coupled with varied clinical presentations make cerebral small vessel disease tricky to recognise and manage. Cerebral small vessel disease causes about 25% of all ischaemic strokes, 80% of all haemorrhagic strokes and even more worryingly contributes to at least 50% of all cases of dementia but the cause of cSVD is unknown.
Without a clear picture of the pathophysiology or grasp of all the clinical presentations of cSVD, it is difficult to treat or even provide reliable information to patients and their families about their condition.



cSVD changes seen here as white matter hyperintensities iaround the black ventricles develop slowly and can cause subtle symptoms as well as stroke and dementia

The University of Edinburgh Cerebral Small Vessel Disease Research Group

Working with the Edinburgh cerebral small vessel disease research group led by Joanna Wardlaw and funded by a lectureship from the Stroke Association in conjunction with NRS funding and latterly funding from the University of Edinburgh my research aims to investigate all clinical aspects of cerebral small vessel disease.

Using advanced imaging to understand the pathophysiology

Cerebral SVD is a disease defined by brain scans (typically MRI) showing SVD – including white matter hyperintensities, lacunes and microbleeds. We at the University of Edinburgh have pioneered the use of advanced imaging such as cerebrovascular reactivity imaging and dynamic contrast MRI to glean insights into the mechanisms of disease. In 2008 we developed a technique that used inhaled carbon dioxide gas (6%) to vasodilate cerebral arteries measured using blood oxygen level dependent MRI sequences.

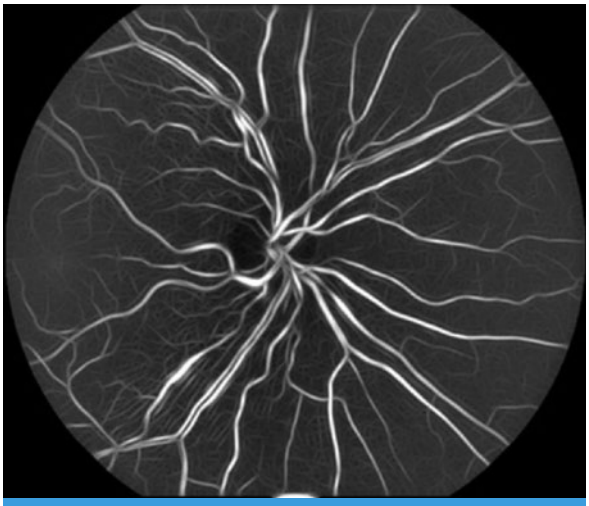
This close (and enduring) collaboration between clinicians, physicists and medical image analysts allowed development of a reliable and reproducible technique.

This collaboration led to a first study in patients and subsequently into multicentre studies where the technique was exported to other European countries. This CVR measure is also the primary outcome measure for TREAT@SVDs, a RCT assessing blood pressure agents in cerebral SVD and CADASIL, a genetic cerebral SVD.
We have shown that SVD is associated with leakier and stiffer blood vessels that do not vasodilate well, helping to understand the underlying causes.

What happens to patients?

Given the wide spectrum of changes seen on MRI it is not surprising that there are many associated syndromes beyond stroke and dementia. In the Mild Stroke Study 3 (MSS3), an ongoing longitudinal cohort study, 230 patients with minor ischaemic stroke are followed up with detailed clinical assessment including cognition, fatigue, mood, anxiety, collection of atypical neurological symptoms and regular advanced MRI brain scanning. Worryingly we have found that a high proportion of these patients develop new, incident infarcts (that are often asymptomatic) despite current best management. What are we missing? In the MSS3 we will be able to correlate any symptoms including the atypical features of SVD with baseline small vessel disease parameters from advanced MRI (and retinal scans).

Patients with stroke and cerebral small disease worry about cognition yet there is little known about trajectories of cognitive decline following stroke and studies to date have focussed on complex cognitive assessment leading to selection bias favouring patients with milder stroke. In order to map out this cognitive decline over at least two years following stroke we lead the UK wide R4VaD study which follows 2300 patients post stroke (all severities) with regular cognitive and other assessments including fatigue, anxiety.



Assessing the blood vessels in the retina sheds light on the underlying pathophysiology of the blood vessels in the brain in CSVD

Finding new treatments

There are no specific cSVD treatments but drugs used for other diseases may prove useful. We combined advanced neuroimaging (cerebrovascular reactivity) in the LACI-1 Phase II trial and the repurposed drugs cilostazol and isosorbide mononitrate to assess the feasibility and safety of recruiting 60 patients with lacunar stroke to receive these drugs. The results from this trial were encouraging leading to LACI-2 (recruitment just finished) assessing the same drugs in a larger sample with longer term clinical and radiological follow-up.

Developing SVD clinical services

Patients living with cSVD report that they feel unsupported by clinical services – a finding reinforced by data from our qualitative analysis of correspondence from patients. Patients with cSVD present to many different specialties often not designed to provide a consistent, evidence based approach to their investigation and management. A major part of our ongoing work is establishing locally and nationally agreed evidence/ consensus based protocols and an evidence base for patients with cerebral small disease to provide optimum medical management aiming to reduce stroke and dementia.

Acknowledgements:
I am fortunate to work in the productive, collegiate and supportive Edinburgh Small Vessel Disease group led by Joanna Wardlaw and the research mentioned here results from much hard work by many skilled researchers in Edinburgh and beyond and supported by funding from MRC, Wellcome Trust, Stroke Association, British Heart Foundation, Alzheimer's Society, Dementia Research Institute, Horizon 2020, Fondation Leducq, CSO. Most importantly however I would like to thank patients and their families involved in research who continue to contribute so much.

NRS Career Development

NRS Clinician: EXPRESSO (EXploring the PREvalence, Service utilisation and patient experience of Severe Obesity)

A view from the streets: community health and social care research as an NMAHP* NRS clinician
(*Nursing, Midwifery and Allied Health Professional).

Introduction

Standing weary late one evening, with another district nurse, outside the front door of a patient with severe obesity, having just undertaken another difficult catheterisation for them - the 9th one in 2 weeks, I thought to myself "There has to be a better way".
Our care didn't seem good for them, or a good use of organisational resources. That realisation prompted my current research work. People with severe obesity (PwSO) are an emerging population. Pre-1970's severe obesity (Body Mass Index (BMI) ≥40kg/m^2) was considered a rare pathological condition. Since then rates have increased faster than other BMI categories of overweight and obesity. As a District Nurse, I was caring for increasing numbers of housebound people with high BMIs, sometimes up to 100 kg/m^2, involving multiple community services including social care, podiatry, physiotherapists, occupational therapists and community equipment service. However there was little evidence base to guide practice, or documentation of costs to support the need for service development. Instead what I saw were poor outcomes of early death and reduced quality of life.

Building a case for effective policy and service development requires robust data, of which there is little around this population. The current evidence base mainly focuses on care of specific comorbidities, hospital care or weight management (including bariatric surgery) interventions for PwSO. Thus my study, EXPRESSO (EXploring the PREvalence, Service utilisation and patient experience of Severe Obesity) set out to document service usage of community health (excluding GP services) and social care services, providing a detailed micro-costing for an exemplar cohort of individuals (n=25). Its aim is to evidence this emerging population, making them visible to service planners, policy makers, and other researchers, enabling the building of a wider evidence base to inform policy and practice.

EXPRESSO design

EXPRESSO uses a retrospective, observational mixed-methods design, recruiting people directly through community staff, given the lack of robust population BMI data. Its novelty and value come from its context, in the under-evidenced community health and social care sectors, combined with an NMAHP researcher perspective. My clinical background was critical for study design, particularly in identifying and accessing community health and social care data sources.

Navigating cross-sector data governance was not straightforward, with much unanticipated learning and delay!
The upside has been writing up my experience as an illustrative case study – recently accepted for publication.
Recruitment for EXPRESSO began just before Covid hit. Again the benefits of being a clinical academic came through, as after initial delay, I was able to weave data collection in with essential operational work, making it a win-win for services and research.

EXPRESSO outcomes

EXPRESSO robustly documents individual-level service utilisation, illustrating the range and extent of services used and the type and scale of costs involved. Findings show that multiple services, particularly district nursing, community equipment service and social care (occupational therapy and formal packages of care) can be needed long term (upwards of 14 years), to enable PwSO to live safely at home. Annual total community health and social care costs vary hugely, with upper estimates of £88,870, (mean £30,726) and greatest costs being for social care. An unexpected outcome was the difficulty in taking accurate anthropometric measures in the community for PwSO, due to functional limitations associated with high BMI.

Whilst I was well prepared with specialist scales for measuring weight, alternative height measures, such as knee height or half-span, proved inaccurate due to lower leg oedema or difficulty raising heavy arms. These findings, recently accepted for publication, aptly demonstrate how care of PwSO quickly becomes complex, compared to care of lower weight individuals. Consequently, PwSO are often under documented and under served in terms of access and quality of care.

EXPRESSO also incorporated a nested qualitative study exploring people's experience of services, including around stigma, as health professionals are known to stigmatise PwSO. Current qualitative evidence focusses on experiences of people who are receiving weight management treatment, which applied to just 20% of EXPRESSO participants. Data analysis is ongoing, but early indications suggest much new learning for care professionals around how to improve service provision and quality of care for PwSO.

Future work

Given the paucity of evidence for this population group, future research work is wide open. The high resource utilisation evidenced by EXPRESSO, particularly around social care, along with the poor outcomes experienced by individuals, offers huge opportunity for optimisation of care. Current thoughts include development of care pathways, staff training and improved cross-service coordination, with a focus on maintaining functionality for individuals.

I am keen to remain a clinical academic, as there is huge strength in having a base in both practice and research.
Yet the role is demanding and funding for obesity research that is holistic in nature and not connected to a specific comorbidity, such as diabetes, is rare. As such, I am particularly grateful to Prof Tim Walsh and Prof Alasdair Gray for seeing the potential in this work and funding some of my research time. NMAHP research structures are hugely less developed than that of our medical colleagues. However in Scotland, NHS Lothian is at the forefront of progressing this valuable resource, with Andy Peters, AHP Research Facilitator and Juliet MacArthur, Chief Nurse for Research, growing a burgeoning network of committed and tenacious NMAHP researchers. My thanks to them both, and Prof Alex McMahon former Executive Director of Nursing, Midwifery and Allied Health Professionals, for their support and encouragement, particularly with Research Futures funding. Lastly, thank you to the Weight Management team, especially service lead Laurie Eyles, who has helped facilitate my growth as a researcher over many years, even when direction wasn't altogether clear.

If you are interested in any aspects of this work, please do get in touch:

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NRS Career Development

Lothian Nurses, Midwives and Allied Health Professionals (NMAHP)

Lothian NMAHPPS Research Strategy 2022-2025

Over the past couple of years Nursing, Midwifery and Allied Health Professions (NMAHP) representatives have been working in partnership with Pharmacy, Psychology and Healthcare Science colleagues in NHS Lothian to develop a wider Lothian NMAHPPS Research Strategy. A high-level group including the Directors of these services and the Deans and Heads of Schools of our academic partners at Edinburgh Napier University, Queen Margaret University, University of Edinburgh, University of Stirling and Robert Gordon University has met quarterly to shape this strategy. Several areas of strategic ambition have been agreed:

- Developing **Research Leadership**
- Building **Capacity and Capability**
- Expanding **Clinical Academic Career Pathways** opportunities
- Widening **Clinical and Academic Homes** arrangements
- Identification of **Key Programmes of Research**
- A focus on **Dissemination and Impact**.

At present these ambitions are being translated into a concrete Action Plan for the next three years.

Lothian Clinical Academic Pathways Partnership

The multi-professional and multi-agency strategic partnership described above has a vision of offering funded clinical academic training opportunities for NMAHPPS across the range of career development levels. For a number of years funded doctoral opportunities have been available to NMAHP staff in NHS Lothian but over the coming months, several other opportunities will be made available under our 'Gateways' scheme funded by Edinburgh and Lothians Health Foundation.

Doctoral opportunities and awards

NHS Lothian continues to fund doctoral awards through its partnership with the University of Stirling. In response to the highest number of applications received since the partnership was set up in 2017, four NMAHPs were awarded fees scholarships in 2021 to undertake their Clinical Doctorate:

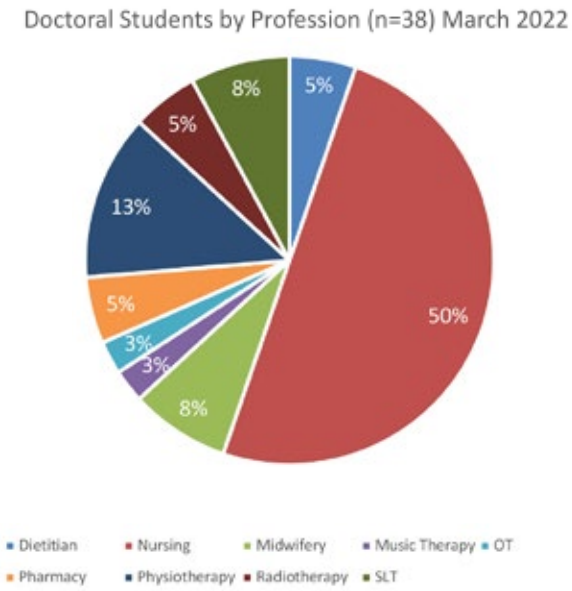
- Zoe Johnstone, Clinical Specialist Respiratory Physiotherapist, Royal Hospital for Children & Young People
- Joanna Macutkiewicz, Sexual Health Practitioner (Midwife), Chalmers Sexual Health Centre
- Scott Taylor, Consultant Nurse Learning Disability
- Izy Utley, Speech and Language Therapist, NW Edinburgh Learning Disability Team

NHS Lothian and Strathclyde University have established a joint 'Doctorate at Work' programme for pharmacists to work towards achieving a PhD whilst in full time employment. The first two participants of the programme are both involved in the implementation of electronic prescribing in NHS Lothian:

- David Clifford, Lead Pharmacist HEPMA & PSC System
- Nikki Gilluley, Advanced Pharmacist HEPMA

Doctoral students and completions

There are currently 38 NMAHP and pharmacy doctoral students working in NHS Lothian (Figure), involving a range of funding models and with most studying part-time, often alongside full time NHS roles. They are supported in terms of peer networking through the Lothian NMAHP Doctoral Network.
Since the last report there have been five doctoral completions, including the first pharmacist:



- Donna McGowan, Nurse Clinician Chemotherapy - Lung cancer patients' experiences and perceptions of outpatient chemotherapy services - A qualitative case study approach
- Gearoid Brennan, Nurse Specialist in Liaison Psychiatry - The role of the mental health nurse in addressing the physical health needs of those with a serious mental illness: A qualitative study
- Kenny Davidson, Community Mental Health Nurse (Care Homes), East Lothian Health and Social Care Partnership - Understanding the Lifeworld of people with dementia and other stakeholders within the discharge process from Orthopaedic Trauma
- Ann McMurray, Asthma Nurse Specialist, Royal Hospital for Children & Young People - Parent and patient perspectives of fatal and near fatal asthma - a qualitative study
- Amanda McLean, Specialist & Principal Pharmacist Quality/Risk & Education, Research & Development - A theoretical exploration of hospital clinical pharmacists' perceptions, experiences and behavioural determinants in relation to provision of optimal and suboptimal pharmaceutical care

Gateways opportunities

NHS Lothian has secured £250,000 over five years from the Edinburgh and Lothian Health Foundation to establish a unique funded programme of Clinical Academic Gateway Awards. These are aimed at providing funded time and mentorship at different stages of a clinical academic career:

1. **First Steps into Research Gateway** – aimed at early career NMAHPPS, this award will provide 'real life' engagement with an established research team and mentorship focussed on the individual's future career.
2. **Masters in Research Gateway** – funding for a part-time Masters by Research degree
3. **Pre-doctoral clinical academic bridging Gateway** – salaried time and mentorship to prepare an application for a competitive, peer reviewed doctoral level research training fellowship.
4. **Post-doctoral clinical academic bridging Gateway** – salaried time to complete peer-reviewed publications, develop clinical academic networks and prepare an application for a competitive, peer reviewed post-doctoral level research fellowship.
5. **Advanced Methodological Gateway** – funding attendance at an external intensive methodological training programme to develop their knowledge and skills to inform their study design and future data analysis.

The awards programme is currently under development in partnership with six academic institutions and will be launched in spring 2022.

Clinical and Academic Homes

Clinical and Academic Homes are collaborative developmental arrangements across the NHS/HEI boundary for NMAHPPS working in NHS Lothian or our partner universities. They are based on an honorary contract and agreed following discussion between an individual member of staff, their line manager, and the manager in the hosting service where all anticipate mutual benefits for all three parties. Clear objectives and a timetable for regular review in relation to these are established prior to the home starting. This concept was first established for NMAHPs a number of years ago with a sole focus on the 'evidence, research and development' pillar of practice. In recent times, through partnership working, it has been broadened to include:

- the 'clinical', 'education' and 'leadership' pillars
- Pharmacy, Psychology and Healthcare Science
- more university partners, namely the University of Stirling and Robert Gordon University

In October 2021 a new Framework to support Clinical and Academic Homes was established with clear principles, suggestions for honorary post titles aligned to career development frameworks, guidance on how to set up a home, and a variety of document templates for common use in different settings.

As of March 2022 there are four clinical homes (three nurses and one AHP) ongoing and 26 under development (three AHP; two exercise instructors; 21 nurses)

NHS Lothian AHP Innovation, Research, and Improvement Strategy 2022-2027

In recent months a multi-stakeholder approach, including patients, has been taken to developing an Innovation, Research, and Improvement Strategy for AHP services in NHS Lothian – this represents a first for this group of services. The draft strategy is due to be circulated for a wider consultation process during March 2022.

NRS Career Development

Edinburgh Clinical Research Facility Education Programme

Education Core, Edinburgh CRF

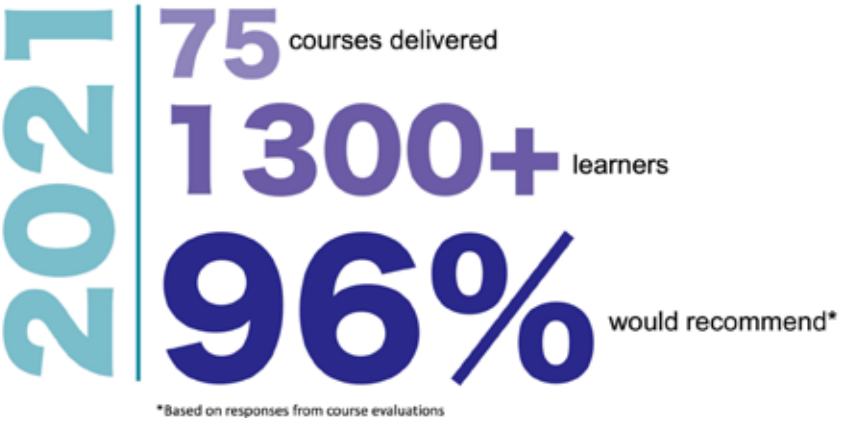
The Education Core at Edinburgh Clinical Research Facility (CRF) continues to offer a diverse range of short courses to the local, national, and international clinical research community. Moving our courses online during the pandemic has increased accessibility to our already popular courses and has expanded our audience.

Further information about the courses we offer can be found on our website: www.ed.ac.uk/crfcourses

The Education Core continued to facilitate the 'Research During the Pandemic' webinar series in collaboration with ACCORD, showcasing the achievements of research teams across Edinburgh. The full series can be accessed here: www.ed.ac.uk/rdtp-webinars

We were pleased to be able to organise the Edinburgh Clinical Research Methodology (ECRMC) course and support the Scottish Metabolomics Network Annual Symposium virtually in November 2021. In person events are being planned for 2022, including: Scottish Research Nurse, Midwife and Coordinators' Conference (SRNCN), the Dementia Prevention Summer School, and the Edinburgh Clinical Trial Management Course (ECTMC).

We continue to be active members of the NRS Training Forum and the Education Workstream for the UKCRF Network. We have collaborated with colleagues to help develop the Edinburgh Clinical Trials Manager Group and have supported local training and development within the Nursing and Clinical Core at Edinburgh CRF.



"Very, very well presented, in language even I could follow!"
Attendee on 'An Introduction to Health Economics' (online) 2021

"Thank you for your impeccable organisation of another useful CRF course"
Attendee on 'The whys and hows of applying to PBPP' (online) course 2022

"Excellent course, very well organised and presented"
Attendee on 'Bitesize Project Management Course for Clinical Researchers' (online) 2021

"Brilliant course, far more engaging than previous GCP courses I have done. Really informative, great sides and tutors."
Attendee on 'NRS Introduction to GCP Course' (online) 2021

Research During the Pandemic Webinar Series

Recordings available at: www.ed.ac.uk/rdtp-webinars

Webinar 1: The ACCORD Office and how we managed our response to Covid
Dr Heather Charles and Paul Dearie, ACCORD

Webinar 2: The ISARIC Study
Dr Annemarie Docherty, Wellcome Fellow and Consultant in Critical Care

Webinar 3: Providing a Genomics Platform for Covid Research
Lee Murphy, Head of the Genetics Core, Edinburgh Clinical Research Facility

Webinar 4: How expedited processes that came in for Covid speeded things up & what will happen when these return to normal
Alex Bailey, MRC

Webinar 5: Doing the best we can; Clinical research staff's activity to date in the Covid 19 pandemic
Miranda Odam, EMERGE and Steve McSwiggan, Edinburgh CRF, NHS Lothian

Webinar 6: Grant opportunities and funding landscape changes in the Covid-19 era
Dr Andy Liken and Al Innes, Edinburgh Research Office (ERO)

Webinar 7: Medicines Regulation: Covid-19 and Beyond
Professor Stuart Ralston, Chair of the Commission on Human Medicines

Webinar 8: Monitoring During a Pandemic
Elizabeth Craig, Senior Clinical Trials Monitor in ACCORD

Webinar 9: Multi-site research across 3 nations during a Pandemic
Katie Wells, National Coordinator for the PREVENT Dementia Programme

Webinar 10: Living through Covid - a reflection from a Nurse Director's perspective
Professor Alex MaMahon, Executive Nurse Director for NHS Lothian

Webinar 11: Setting up a Covid Vaccination Programme
Ellie Hunter, Clinical Vaccination Manager and Pat Wynne, Director of Nursing Primary and Community Care

Webinar 12: Research, Covid 19 and Beyond
Sheila Morris, Lead Research Nurse Infectious Diseases in NHS Lothian

Webinar 13: Reflections on managing research during the pandemic
Professor Tim Walsh, previous NHS Lothian R&D Director

Featured COVID-19 Projects

The COVID-19 in pregnancy in Scotland (COPS) Study

The COVID-19 in pregnancy in Scotland, or COPS Study is providing population-based information for the whole of Scotland on the incidence of, and outcomes following, COVID-19 infection and COVID-19 vaccination in pregnancy (1). COPS is co-led by Dr Sarah Stock a Reader at the University of Edinburgh, and Honorary Maternal Fetal Medicine Consultant in NHS Lothian and Dr Rachael Wood who is a Consultant in Public Health in Public Health Scotland.

COPS uses healthcare data from across Scotland, with records from all pregnancies including early pregnancy losses (e.g. miscarriage, ectopic pregnancy), terminations of pregnancy, live and stillbirths and neonatal health records, linked with COVID-19 test results and COVID-19 vaccine records (2) (Figure 1). COPS includes information on all women who were pregnant on 1st March 2020, and pregnancies from 1st March 2020 onwards - the date of the first confirmed COVID-19 case in Scotland. Records are updated monthly, so the number of women whose data are included in COPS continues to grow. As at mid-February 2022, the COPS cohort included 162,511 pregnancies in 144,143 women. Among these, there were a total of 11,298 confirmed cases of COVID-19 (in 11,193 pregnancies in 11,176 women). There have been 109,114 pregnancies in 102,968 women from 1 December 2020, the month the COVID- 19 vaccination programme started. Among these, we have identified a total of 40,619 COVID-19 vaccinations in 28,584 pregnancies (28,301 women) (3).

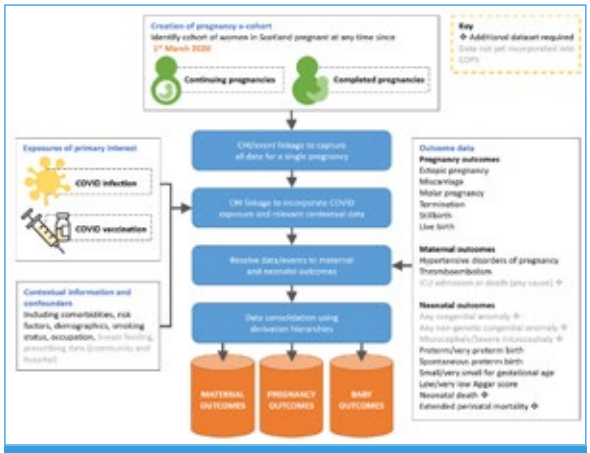


Figure 1 *Visual summary of the Covid-19 in pregnancy (COPS) cohort*

Dr Sarah Stock – study co-lead

Reader at the University of Edinburgh, and Honorary Maternal Fetal Medicine Consultant in NHS Lothian

Dr Rachael Wood – study co-lead

Consultant in Public Health Medicine, Public Health Scotland; and Honorary Reader, University of Edinburgh

The COPS team have used these healthcare records to describe how many pregnant women had COVID-19 and how many were vaccinated. We are also studying if COVID-19 increases the risk of miscarriage, stillbirth, congenital anomalies, low birthweight, preterm birth, need for specialist baby care (admission to a neonatal unit) or baby death; the effect of COVID-19 variants on pregnancy; and provide evidence on the safety and effectiveness of COVID-19 vaccination for women and their babies. Understanding the effects of COVID-19 and COVID-19 vaccination at different stages during pregnancy from conception through to birth helps inform policy and advises pregnant women and those considering pregnancy.

Using whole population data, on all pregnancies, is unique to COPS, and allows the most accurate estimates of the effect of COVID-19 and vaccinations on the health of women and their babies. The results of the COPS study are used by Public Health Scotland and the Scottish Government, and have influenced UK and international policy.

Our data add to the evidence that vaccination in pregnancy does not increase the risk of complications in pregnancy, but Covid-19 does

Dr Sarah Stock
Study co-lead and consultant obstetrician

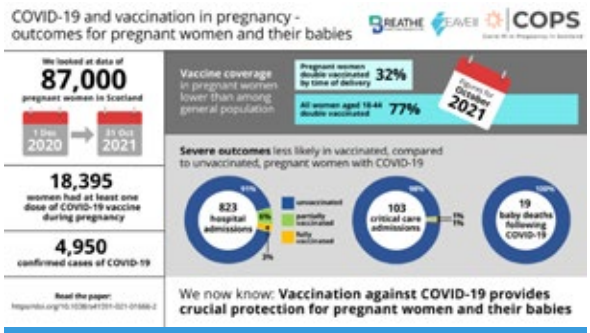


Figure 2 *Summary of Stock, S.J., Carruthers, J., Calvert, C. et al. SARS-CoV-2 infection and COVID-19 vaccination rates in pregnant women in Scotland. Nat Med (2022). https://doi.org/10.1038/s41591-021-01666-2. Courtesy of Dawn Cattanach, Susan Buckingham and Lana Woolford.*

In a paper published in January 2022 (4) (Figure 2), the COPS team showed that COVID-19 vaccine uptake in pregnancy is lower than that in the general population of women of reproductive age (18-44 years), and these data influenced policy on vaccination for pregnant women. Of women giving birth in October 2021, only around one third had received two doses of vaccine by the time of delivery, compared to 77% of the general population of reproductive age. Following policy changes and increased provision of antenatal vaccination services, vaccination rates in pregnant women have increased, with 54% of the women giving birth in January 2022 having received at least two doses of vaccine. This compares to 82% of women aged 18-44 years in January having received at least two vaccine doses. Nevertheless, disparities remain, with coverage of vaccination higher in women living in the least, compared to the most, deprived areas of Scotland, and lower in women with Black, Caribbean, or African ethnicity compared to women with White; South Asian; or Other or mixed ethnicity.

We have also shown that infection with SARS-CoV-2 (the virus causing COVID-19) can occur in any stage in pregnancy and infections are roughly evenly spread across pregnancy. Our data have supported those of other studies that have shown although COVID-19 infection rates are similar to the general population, pregnant women are more susceptible to severe COVID-19, with higher rates of admission to critical care, especially in later pregnancy. COVID-19 in pregnancy is linked to higher rates of pregnancy complications, including preterm birth (birth before 37 weeks gestation) and stillbirth. For example, in COPS we found that 23 per 1000 babies who were born within 28 days of their mothers having COVID-19 were stillborn or died within the first month of life. This compares to a rate of 8 per 1000 for babies born following COVID-19 at any point during pregnancy and 6 per 1000 for babies born to women with no confirmed SARS-CoV-2 infection. Most recently we have looked at COVID-19 rates in newborns, and shown that neonatal COVID-19 is comparatively rare. Of the 91,515 liveborn babies born between March 2020 and January 2022, we have identified a total of 138 confirmed cases of COVID-19 in neonates.

Data from COPS has shown that COVID-19 complication rates such as hospital admissions, critical care admissions, preterm birth and baby deaths were lower in pregnant women who had been vaccinated against COVID-19 than in unvaccinated pregnant women (Figure 2). We found no signal that COVID-19 vaccination itself increased rates of preterm birth and stillbirth or death in the newborn period.

These data support the importance of women being vaccinated during pregnancy, and vaccination is the safest and most effective way for women of all ages and backgrounds to protect themselves and their babies against COVID-19 infection. Further information about the risks of COVID-19 infection for mother and baby, and support for decision making about vaccination can be found on the Royal College of Obstetricians and Gynaecologists (RCOG) and Royal College of Midwives (RCM) websites. We are currently finalising analyses of the effects of COVID-19 and COVID-19 vaccination on other pregnancy complications including miscarriage and congenital anomalies.
In future we hope to use the COPS infrastructure to support studies of other medications in pregnancy, to improve information about treatments for women and their babies.

Funding and Ethics

COPS is funded by Tommy's charity (1060508; SC039280) and Public Health Scotland. Sarah Stock is supported by Wellcome Trust (209560/Z/17/Z). COPS is a substudy of EAVE II, which is funded by the Medical Research Council (MR/R008345/1) with the support of BREATHE - The Health Data Research Hub for Respiratory Health [MC_PC_19004], funded through the UK Research and Innovation Industrial Strategy Challenge Fund and delivered through Health Data Research UK. Additional support has been provided through the Scottish Government DG Health and Social Care.
The COPS study has been approved by the Public Benefit and Privacy Panel for Health and Social Care and has full ethical approval from the National Research Ethics Service Committee, South East Scotland 02

References:

1. Stock SJ, McAllister D, Vasileiou E, Simpson CR, Stagg HR, Agrawal U, McCowan C, Hopkins L, Donaghy J, Ritchie L, Robertson C, Sheikh A, Wood R. COVID-19 in Pregnancy in Scotland (COPS): protocol for an observational study using linked Scottish national data. BMJ Open. 2020 Nov 26;10(11):e042813. doi: 10.1136/bmjopen-2020-042813.

2. Stock SJ, Carruthers J, Denny C, Donaghy J, Goulding A, Hopcroft LEM, Hopkins L, Mulholland R, Agrawal U, Auyeung B, Katikireddi SV, McCowan C, Murray J, Robertson C, Sheikh A, Shi T, Simpson CR, Vasileiou E, Wood R. Cohort Profile: The COVID-19 in Pregnancy in Scotland (COPS) dynamic cohort of pregnant women to assess effects of viral and vaccine exposures on pregnancy. Int J Epidemiol. 2022 Jan 3:dyab243. doi: 10.1093/ije/dyab243. Epub ahead of print.

3. Available from https://publichealthscotland.scot/media/12100/22-03-09-covid19-winter_publication_report.pdf . Accessed 16th March 2022

4. Stock SJ, Carruthers J, Calvert C, Denny C, Donaghy J, Goulding A, Hopcroft LEM, Hopkins L, McLaughlin T, Pan J, Shi T, Taylor B, Agrawal U, Auyeung B, Katikireddi SV, McCowan C, Murray J, Simpson CR, Robertson C, Vasileiou E, Sheikh A, Wood R. SARS-CoV-2 infection and COVID-19 vaccination rates in pregnant women in Scotland. Nat Med. 2022 Jan 13. doi: 10.1038/s41591-021-01666-2. Epub ahead of print.

Featured COVID-19 Projects

GenOMICC Consortium: Genetic study gives extensive insights into severe COVID-19

The world's largest study of the genetics of critical COVID-19, involving more than 57,000 people, has revealed fresh details about some of the biological mechanisms behind the severe form of the disease.

Some 16 new genetic variants associated with severe COVID-19, including some related to blood clotting, immune response and intensity of inflammation, have been identified.
These findings will act as a roadmap for future efforts, opening new fields of research focused on potential new therapies and diagnostics with pinpoint accuracy, experts say.

Researchers from the GenOMICC consortium – a global collaboration to study genetics in critical illness – led by University of Edinburgh in partnership with Genomics England, made these discoveries by sequencing the genomes of 7,491 patients from 224 intensive care units in the UK.
Their DNA was compared with 48,400 other people who had not had COVID-19, participants in Genomics England's 100,000 Genomes Project and that of a further 1,630 people who had experienced mild COVID.

Determining the whole genome sequence for all participants in the study allowed the team to create a precise map and identify genetic variation linked to severity of COVID-19.
The team found key differences in 16 genes in the ICU patients when compared with the DNA of the other groups.
They also confirmed the involvement of seven other genetic variations already associated with severe COVID-19 discovered in earlier studies from the same team.
The findings included how a single gene variant that disrupts a key messenger molecule in immune system signaling – called interferon alpha-10 – was enough to increase a patient's risk of severe disease.

> **Our latest findings point to specific molecular targets in critical COVID-19. These results explain why some people develop life-threatening COVID-19, while others get no symptoms at all. But more importantly, this gives us a deep understanding of the process of disease and is a big step forward in finding more effective treatments.**
>
> **It is now true to say that we understand the mechanisms of COVID better than the other syndromes we treat in intensive care in normal times – sepsis, flu, and other forms of critical illness. COVID-19 is showing us the way to tackle those problems in the future.**
>
> **Professor Kenneth Baillie**
> Project chief investigator and Consultant in Critical Care Medicine at University of Edinburgh

This highlights the gene's key role in the immune system and suggests that treating patients with interferon – proteins released by immune cells to defend against viruses – may help manage disease in the early stages.
The study also found that variations in genes that control the levels of a central component of blood clotting – known as Factor 8 – were associated with critical illness in COVID-19.
This may explain some of the clotting abnormalities that are seen in severe cases of COVID-19. Factor 8 is the gene underlying the most common type of haemophilia.

Professor Kenneth Baillie, the project's chief investigator and a Consultant in Critical Care Medicine at University of Edinburgh, said: "Our latest findings point to specific molecular targets in critical COVID-19. These results explain why some people develop life-threatening COVID-19, while others get no symptoms at all. But more importantly, this gives us a deep understanding of the process of disease and is a big step forward in finding more effective treatments.

"It is now true to say that we understand the mechanisms of COVID better than the other syndromes we treat in intensive care in normal times – sepsis, flu, and other forms of critical illness. COVID-19 is showing us the way to tackle those problems in the future."

Professor Sir Mark Caulfield from Queen Mary University of London, formerly Chief Scientist at Genomics England and co-author on this study, said: "As COVID-19 evolves, we need to focus on reducing the number of people getting seriously ill and being hospitalised. Through our whole genome sequencing research, we've discovered novel gene variants that predispose people to severe illness – which now offer a route to new tests and treatments, to help protect the public and the NHS from this virus."

Dr Rich Scott, Chief Medical Officer at Genomics England, said: "Strategically, we're at a point where genomic science is becoming an integral part of the national infrastructure in routine healthcare. This study illustrates the value of whole genome sequencing to detect rare and common variants that influence critical illness requiring intensive care. It represents a major leap forward in our understanding of how our genetic makeup influences severe illness with COVID-19."

"All those involved in the study went to great efforts to engage with all communities within the UK – including groups that have historically been under-represented in medical studies. The inclusive element of our work has generated meaningful results for everyone in the country."

Lord Kamall, Minister for innovation at the Department of Health and Social Care (DHSC), said: "Clinical research has been vital in our fight against COVID-19 and the UK's innovation is enabling us to transform our health service and ensure the NHS is able to deliver world-class care.
"This research is an important step forward in better understanding how COVID-19 impacts certain people, allowing us to take the necessary action to protect the most vulnerable and save lives."

The findings have been published in Nature: https://www.nature.com/articles/s41586-022-04576-6

GenOMICC (Genetics of Susceptibility and Mortality in Critical Care) started in 2015 as an open, global consortium of intensive care clinicians dedicated to understanding genetic factors influencing outcomes in intensive care from diseases such as SARS, flu and sepsis.
The consortium is led by the University of Edinburgh, and since 2020 it has been focused on COVID-19 research in partnership with Genomics England and in collaboration with NHS Lothian, the Intensive Care National Audit and Research Centre (ICNARC), and Queen Mary University of London.

The ground-breaking 100,000 Genomes Project was established in 2014 to sequence 100,000 genomes from people with a rare disease or cancer. The Project was completed in 2018 and paved the way for the creation of a new genomic medicine service for NHS England, transforming patient care by bringing advanced diagnosis and personalised treatments.

GenOMICC is funded by DHSC, LifeArc, the charity Sepsis Research FEAT, the Intensive Care Society, Wellcome, UK Research and Innovation, Scotland's Chief Scientist Office, the Department of Health and Social Care and the National Institute for Health Research (NIHR), and supported by Illumina.

Featured COVID-19 Projects

Risks of myocarditis, pericarditis, and cardiac arrhythmias associated with COVID-19 vaccination or SARS-CoV-2 infection

Why did we do this study?

By the end of March 2022, more than 11.1 billion doses of COVID-19 vaccination had been administered worldwide. Clinical trials of COVID-19 vaccines were underpowered to detect the rare adverse events that are important for risk–benefit evaluations and to inform clinical practice post-vaccination. Concerns have been raised about the safety of vaccination and in particular about the risk of adverse cardiovascular events, including myocarditis and pericarditis. As of November 2021, there had been 1,783 reports to the United States Vaccine Adverse Event Reporting System of cases of myocarditis or pericarditis, among people aged 12–29 years who received COVID-19 vaccines, in particular following mRNA vaccination, that is, BNT162b2 (Pfizer) and mRNA-1273 (Moderna) vaccines. However, myocarditis and pericarditis have also been reported after infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Our aim was to estimate the risk associated with COVID-19 vaccination and compare this to the risk following infection in order to guide public health policy and vaccine campaigns.

What did we do?

Together with Professor Julia Hippisley-Cox and researchers from the Nuffield Department of Primary Health Care Sciences, University of Oxford, we undertook a self-controlled case series study of people aged 16 or older vaccinated for COVID-19 between 1 December 2020 and 24 August 2021 to investigate hospital admission or death from myocarditis, pericarditis and cardiac arrhythmias in the 1–28 days following adenovirus (ChAdOx1 [Oxford AstraZeneca], n = 20,615,911) or mRNA-based (BNT162b2, n = 16,993,389; mRNA-1273, n = 1,006,191) vaccines or a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) positive test (n = 3,028,867).

What did we find?

We found an increased risk of myocarditis associated with the first dose of ChAdOx1 and BNT162b2 vaccines and the first and second doses of the mRNA-1273 vaccine over the 1–28 days postvaccination period, and after a SARS-CoV-2 positive test. We estimated an extra two (95% confidence interval (CI) 0, 3), one (95% CI 0, 2) and six (95% CI 2, 8) myocarditis events per 1 million people vaccinated with ChAdOx1, BNT162b2 and mRNA-1273, respectively, in the 28 days following a first dose and an additional ten (95% CI 7, 11) myocarditis events per 1 million vaccinated in the 28 days after a second dose of mRNA-1273. This compares with an extra 40 (95% CI 38, 41) myocarditis events per 1 million patients in the 28 days following a SARS-CoV-2 positive test.

What does it mean?

This population-based study quantified for the first time the risk of several rare cardiac adverse events associated with three COVID-19 vaccines as well as SARS-CoV-2 infection. Vaccination for SARS-CoV-2 in adults was associated with a small increase in the risk of myocarditis within a week of receiving the first dose of both adenovirus and mRNA vaccines, and after the second dose of both mRNA vaccines. By contrast, SARS-CoV-2 infection was associated with a substantial increase in the risk of hospitalization or death from myocarditis, pericarditis, and cardiac arrhythmia.

What's next?

Myocarditis is more common in younger persons under the age of 40 and in males in particular. Additional analyses stratified by age and sex are important as vaccine campaigns are rapidly being extended to include children and young adults. Furthermore, given the consistent observation that the risk of myocarditis is higher following the second dose of vaccine compared to the first dose, there is an urgent need to evaluate the risk associated with a booster dose as booster programmes are accelerated internationally to combat the omicron variant. In our ongoing studies, we are extending our analysis to include persons aged 13 years or more and those receiving a booster dose, and we are broadening our cardiovascular outcomes to evaluate whether there are benefits of vaccination for acute myocardial infarction associated with SARS-COV-2 infection.

If you would like to find out more

https://www.nature.com/articles/s41591-021-01630-0
https://www.medrxiv.org/content/10.1101/2021.12.23.21268276v1

Professor Nicholas L Mills
British Heart Foundation Chair of Cardiology
Royal Infirmary of Edinburgh

Research Highlights

A cluster randomised trial to determine the effectiveness of bridging from emergency to regular contraception: The Bridge –it study

Sharon T Cameron Anna Glasier, Lisa McDaid, Andrew Radley, Paula Baraitser , Judith Stephenson, Richard Gilson , Claire Battison, Kathleen Cowle, Mark Forrest, Beatriz Goulao, Anne Johnstone, Alessandra Morelli, Susan Patterson, Alison McDonald, Thenmalar Vadiveloo , John Norrie

Background

Emergency contraception (EC) can prevent pregnancy following an episode of unprotected sex, but unless women start a regular method of contraception following EC they remain at risk of pregnancy. Most women in the UK go to a community pharmacy to get EC but the pharmacist can usually only provide barrier contraception like condoms without a prescription. This means that women need an appointment with a GP or a sexual and reproductive health (SRH) clinic. Getting an appointment is not always easy and can take time. During this time, an unintended pregnancy can occur.

The progestogen only pill (POP) also known as 'mini-pill' is an effective contraceptive that most women can safely use. It does not contain estrogen and is not associated with the risk of blood clots like the combined oral contraceptive pill. If the pharmacist could give provide a 'bridging' supply of the POP along with the EC then this would provide temporary effective contraception for women (bridge the gap) until they can get an appointment at a clinic. We designed a research study called the 'Bridge -it' study to determine if pharmacy provision of a three-month supply of a POP along with the EC, together with a card that helped get an appointment at a local SRH clinic would result in more women using effective contraception four months later, compared to just giving EC alone. Increased use of effective contraception should result in fewer unintended pregnancies. The study was funded by HTA, NIHR Programme Project 15/113/01. The main findings were published in Lancet in November 2020.

Bridge-it

We undertook the study in 29 pharmacies in Lothian, Tayside and London. The pharmacies provided either 'control' care (their standard advice about where to get contraception) or the intervention, to women receiving EC. The intervention was a composite one of three months of the POP plus a card which upon presentation at the local SRH clinic would help the woman get seen as a 'drop-in'. This combined both temporary contraception (giving women time to get an appointment with their usual contraceptive provider) and facilitated access to a contraceptive service where all methods of contraception were available. The study was a pragmatic cluster randomised design which meant that pharmacies provided both control and intervention and the order of this was randomised with a washout period in between, during which recruitment halted. Pharmacists were trained in the study requirements and assessed women's eligibility for the study, invited them to participate, obtained written informed consent and collected a baseline questionnaire from them. The main outcome of the study was women's use of an effective method of contraception four months later (after the POP supply had run out) and we obtained this information from surveys conducted by telephone or online. Effective contraception was defined as any hormonal method of contraception or an intrauterine method ('coil'). We also conducted interviews of a subset of women, pharmacists and SRH clinic staff to evaluate the intervention.

Findings

Between December 2017 and June 2019 a total of 636 women were recruited to the intervention (316) and control (320) groups. We had information on contraceptive use at four months on 65% of participants. Use of an effective method of contraception was around 20% higher amongst women in the intervention group compared to the controls. Also, significantly fewer women in the intervention had to use EC again within that time. Very few women made use of the rapid access card and most women in both groups obtained their ongoing contraception from a GP. Interviews with pharmacists, SRH staff and women confirmed the acceptability of providing POP from the pharmacy and the potential for this to be widely implemented and successfully embedded within routine pharmacy practice.

Summary

Providing a bridging supply of POP along with EC from the community pharmacy resulted in a large and clinically important increase in use of effective contraception. If widely implemented, this simple intervention has potential to prevent more unintended pregnancies for women after EC.

Publications

Cameron ST, Glasier A, McDaid L, Radley A, Baraitser P, Stephenson J, Gilson R, Battison C, Cowle K, Forrest M, Goulao B, Johnstone A, Morelli A, Patterson S, McDonald A, Vadiveloo T, Norrie J. Use of effective contraception following provision of the progestogen-only pill for women presenting to community pharmacies for emergency contraception (Bridge-It): a pragmatic cluster-randomised crossover trial. **Lancet. 2020** Nov 14;396(10262):1585-1594.

Glasier A, Baraitser P, McDaid L, Norrie J, Radley A, Stephenson JM, Battison C, Gilson R, Cameron S; Trial Steering Committee; Data Monitoring Committee; Trial steering committee. Emergency contraception from the pharmacy 20 years on: a mystery shopper study. BMJ Sex Reprod Health. 2021 Jan;47(1):55-60.

Patterson S, McDaid L, Saunders K, Battison C, Glasier A, Radley A, Stephenson J, Johnstone A, Morelli A, Deirdre S, Stewart N, Cameron ST. Improving effective contraception uptake through provision of bridging contraception within community pharmacies: findings from The Bridge-it Study process evaluation. BMJ Open 2022 Feb 11;12(2):e057348.

Cameron ST, Glasier A, McDaid L, Radley A, Patterson S, Baraitser P, Stephenson J, Gilson R, Battison C, Cowle K, Vadiveloo T, Johnstone A, Morelli A, Goulao B, Forrest M, McDonald A, Norrie J. Provision of the progestogen-only pill by community pharmacies as bridging contraception for women receiving emergency contraception: the Bridge-it RCT. Health Technol Assess. 2021 May;25(27):1-92.

Cameron ST, Baraitser P, Glasier A, McDaid L, Norrie J, Radley A, Stephenson JM, Trussell J, Battison C, Cameron S, Cowle K, Forrest M, Gilson R, Goulao B, Johnstone A, McDonald A, Morelli A, Patterson S, Sally D, Stewart N; Bridge-It Study Group. Pragmatic cluster randomised cohort cross over trial to determine the effectiveness of bridging from emergency to regular contraception: the Bridge it protocol. BMJ Open. 2019 Oct 30;9(10):e029978

Impact of Bridge -It

- In October 2021, the Scottish Government introduced a national service specification so that the 'Bridge-it' intervention (3 months 'free' POP) became a routine option for women seeking EC from a community pharmacy. https://www.gov.scot/news/supporting-womens-health/

- Bridge-it showed the safety, acceptability and feasibility of community pharmacists providing the POP for women. This was used in the public consultation that informed the MHRA decision to reclassify POP from a prescription-only-medicine to a pharmacy medicine enabling the POP to be purchased from pharmacist in the UK without a prescription. https://www.gov.uk/government/news/first-progesterone-only-contraceptive-pills-to-be-available-to-purchase-from-pharmacies

Acknowledgements

Bridge-it team, ECTU, Chart, DMC and Steering committee, participating pharmacists, PPI and participants.

Research Highlights

Translational Science in Crohn's disease and Ulcerative Colitis: Emerging from COVID-19 MUSIC, GI-DAMPs, MARVEL and Mini-MARVEL IBD studies.

Emma Ward, Trial Manager for MUSIC/GI-DAMPs and Gwo-tzer Ho, Chief Investigator.

Background

Crohn's disease (CD) and Ulcerative Colitis (UC), collectively the Inflammatory Bowel Diseases (IBD) are incurable, complex immune-mediated conditions with a sharply rising global prevalence. Treatments have improved but they are expensive and involve a general approach of long-term inhibition of the immune response. Edinburgh has a long track record in IBD and inflammation research. In the last 2 years, common to trends across the world and understandably so, all focus has been on COVID-19 research. We tell the story of how we have creatively combined the best of our clinical and scientific talents during this challenging pandemic period to emerge with a stronger and more holistic translational program involving many more stakeholders and new opportunities.

Our Research

In 2018, we formed the Edinburgh IBD Gut Science group with a strategic emphasis to underpin all our scientific work directly on NHS patients – from experimental science to interventional trials. Presently, we have 4 main human clinical studies MUSIC, MARVEL, mini-MARVEL and GI-DAMPs that also provide support for 9 aligned translational research studies (funded by MRC, ERC, CSO and Wellcome Trust). We have also sought to creatively synergise and develop vital areas such as Patient Public Involvement (PPI) since so much of our research relies on their goodwill! We took the extra step to bring patients into the heart of our program (see PPI section).

Our main studies

Our organic research (2009-2018), has directly resulted in these on-going UK multi-centre projects which we have developed and now lead (full range of studies www.ed.ac.uk/inflammation-research/research/gut-research-unit). Throughout the pandemic, ACCORD has provided much needed guidance to navigate the repeated cycles of lockdowns and how to helpfully contribute to NHS Covid19 patient care.

1. MUSIC (www.musicstudy.uk/) is a prospective longitudinal study that investigates key molecular signals that drive gut inflammation or healing in IBD. MUSIC provides very close monitoring of participants over a 12-month period, monitoring reported symptoms, carrying out standard blood and stool tests every 3-months, and providing follow-up colonoscopy to check for gut mucosal healing. Importantly MUSIC is aligned closely to NHS, our study has sped up access for patients to clinical tests such as colonoscopy; and provides more data for NHS clinicians to help the management of these patients.
2. GI-DAMPs is a large cross-sectional study aiming to recruit >1000 participants with active IBD and 200 healthy subjects to test and validate new IBD blood and gut biomarkers in conjunction with MUSIC. Both studies are set in an integrated network of GI units in Edinburgh, Glasgow and Dundee. In total, we have recruited over 500 patients in MUSIC and GI-DAMPs over the pandemic period! Such progress was only possible when we synergised our research capabilities whilst helping to address clinical IBD burden in NHS.
3. MARVEL (www.marvelstudy.uk) is a phase 2b placebo-controlled RCT into the efficacy of oral mitochondrial anti-oxidant therapy in adult-onset UC. MARVEL will enrol > 200 UC patients across UK and crucially, will channel many flaring patients from NHS care into research.
4. Mini-MARVEL is a parallel phase 2b feasibility RCT aiming to recruit >120 paediatric UC patients across all main centres in the UK. This will be one of the largest paediatric RCTs in the world; and running simultaneously with MARVEL, will form the first combined adult- and paediatric IBD RCT.

Key highlights

1. All Ages IBD Research: Our clinical and scientific work now fully encompasses adult and childhood onset IBD as a major theme. MiniMARVEL as the first large UK-wide paediatric RCT forms the platform for a national paediatric IBD clinical trial network.

2. Building Patient Public Involvement at the Heart of our Program: Our PPI group is the major driver in our program with many ongoing projects including measuring patients' research experience to improve clinical trials, Open days; and Media engagements in an 'All-ages' approach.

3. Development of new diagnostics: Our collaboration (as part of GI-DAMPs) with Prof Marc Vendrell's Chemistry team (www.dynafluors.co.uk) has led to patented in-vivo molecular probes that recently received funding from European Research Council and more recently, Scottish Enterprise to facilitate commercialisation.

4. Developing our new operational solutions: Our team has built our own innovative data-sharing, sample tracking and bioresource system which is aligned with our digital multi-omics data analytic pipeline – to handle more than 50 000 biological samples with associated clinical metadata (G-trac [Dr S Chuah]). Our Endoscopy Unit in the Western General Hospital (led by charge nurse Mrs. Frances Gallagher) has helped to support our combined IBD research colonoscopy lists whilst also tackling the NHS endoscopy waiting times!

5. Establishing integrated Edinburgh-Glasgow-Dundee GI research: Our collaborative framework and shared research themes have catalysed the integration of key Scottish IBD GI Units. This year, in addition to our current studies, we will bring in BIOPIC, a major interventional dietary trial in Crohn's disease organically developed and led by Professor Kostas Gerasimidis, Glasgow. We are working on several new combined projects for 2023 which will tangibly exploit our diverse strengths in Scotland.

6. Developing the next generation of researchers: Our program currently has 11 MD/PhD students (clinical and science at various stages; supported by MRC, EastBio, CSO, Wellcome and ERC). In addition, we have Dr Gareth Rhys Jones as Wellcome Intermediate Fellow and Dr Rahul Kalla, as NRS Fellow (both currently consultant gastroenterologists).

7. Providing input into COVID-19 patient care and research: Our clinical research nurses and fellows; in addition to trial managers have all stepped in to provide patient care during COVID-19 and also the important COVID-19 clinical trials that have made the difference in our recovery from this pandemic.

8. Summary and Future Directions: All our team members (from nurses to basic scientists) have played key roles in adapting and improving our studies in the face of COVID-19 challenges. Emerging from the pandemic, we feel that we have become stronger as a team and that our science is significantly stronger.
   All our studies are now active and the team is now busied, focusing on delivering on our research. We have received much guidance from Professor John Norrie, Director of ECTU; and countless advice from Paul Dearie and Fiach O'Mahony from ACCORD. Finally, we are very grateful to our main funders, the Helmsley Trust and Jon Moulton Foundation and our NHS clinical colleagues led by clinical director, Dr Colin Noble for their support.

Summary and Future Directions

All our team members (from nurses to basic scientists) have played key roles in adapting and improving our studies in the face of COVID-19 challenges. Emerging from the pandemic, we feel that we have become stronger as a team and that our science is significantly stronger. All our studies are now active and the team is now busied, focusing on delivering on our research. We have received much guidance from Professor John Norrie, Director of ECTU; and countless advice from Paul Dearie and Fiach O'Mahony from ACCORD. Finally, we are very grateful to our main funders, the Helmsley Trust and Jon Moulton Foundation and our NHS clinical colleagues led by clinical director, Dr Colin Noble for their support.

Our Endoscopy team in Western General Hospital who has supported much of our human IBD studies throughout the pandemic.

Lisa Derr and Alix MacDonald, trial managers for MARVEL and Mini-MARVEL.

Building strong science in creative and synergistic partnerships

Professor David Wilson, Professor of Paediatric Gastroenterology

IBD is particularly severe in children and young people at an important stage of growth and development. In collaboration with Dr Ho, we have set up Mini-Marvel, a UK-wide multicentre randomised clinical trial in paediatric UC. This is a rare opportunity to develop IBD clinical trials and also, provide the much needed in-depth scientific work in children.

Dr Gareth Rhys Jones, Wellcome Career Development Fellow and Honorary Consultant Gastroenterologist

With the unique ability to study the gut mucosa in Crohn's disease at diagnosis, during treatment and when the gut heals in the MUSIC study, I am able to apply powerful scientific approaches such as single-cell RNA sequencing technology to study how macrophage populations contribute to the inflammatory process. This forms a key part of my Wellcome Trust Intermediate Fellowship.

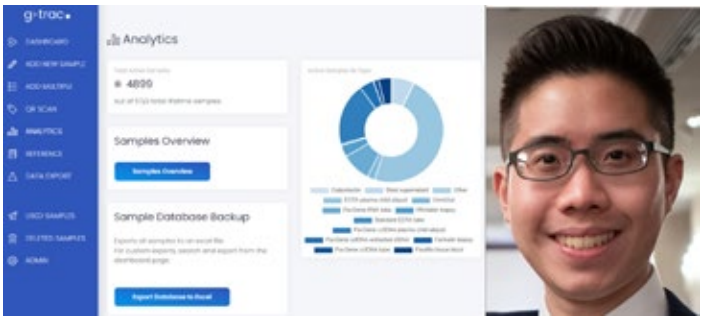
Professor Marc Vendrell, Professor of Translational Chemistry

Molecular probes are powerful biomarkers for precision medicine. Relevant to IBD, one of our probes target Granzymes, which are direct reporters of inflammation, and we have collaborated with Dr Ho to validate our technology in IBD patients. This work has created unique opportunities to further translate our best technologies as molecular imaging reagents for humans as well as point-of-care technologies.

Turning challenges into opportunities

Dr Shaun Chuah, Clinical Research Fellow

When I first joined the MUSIC study, we faced a daunting challenge of coordinating 50 000 experimental samples from Edinburgh, Glasgow, and Dundee, involving multiple hospital sites and laboratories! There weren't any simple off-the-shelf solutions available and after much consideration, I decided to write our own bespoke sample tracking web application, G-Trac. This has allowed us to scale up, and migrate to highly time-efficient QR-code system enabling our research nurses to focus on recruiting patients and our scientists to work on their experiments. As of February 2022, we have successfully tracked over 5000 experimental samples with zero downtime.



Mrs Beena Poulose, Senior Research Nurse

I joined just before the COVID-19 lockdown in February 2020! In the ensuing months, I helped in many COVID-19 trials which I enjoyed. However, when non-COVID-19 research re-opened, we encountered many difficulties in particular, regular access to Clinical Research Facilities that are needed for our human studies. Together with a highly supportive team, I set-up our own wholly independent clinical pathway that enabled our recruitment to progress throughout the pandemic period. This wasn't an easy route but I am thankful for this experience that gave me confidence to adapt to challenging situations like COVID-19. Our platform has now grown to support our 3 main studies with an expanding research nursing team.

Miss Emma Ward, Trial Manager for MUSIC

Setting up a multi-centre study that relies on NHS services during a pandemic is definitely no easy feat, however the optimism and engagement of the study and site teams ensured that we were ready to re-start activity as soon as we were able. We're fortunate that our funders have also been equally as supportive, and we ensure to check in with them regularly with updates on our progress. The downtime we encountered at the beginning of the pandemic allowed us to assess our situation and really optimise the protocol in order to transition from a single-centre study to multi-centre. It also allowed us to focus on the PPI group and establish some aims for this within MUSIC and across the IBD research portfolio.

Our PPI group

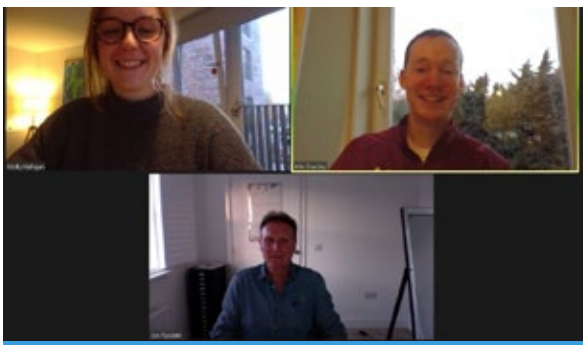
Our recent joint patient PPI and clinical team meeting in March 2022

Background: Over the last 20 years, I have worked with patient charitable bodies such as Crohn's Colitis UK and Guts UK who have kindly provided research funding and helped with our patient engagement. As our human studies grew, I became increasingly aware of the importance of PPI – quite simply for everyone, from lab scientist to senior clinicians! Hence, I wanted to develop a new all-inclusive approach where everyone has a role in shaping our program. We formed in 2019 and I have given the group, a lot of room to develop our PPI program and I am so pleased to see how this has flourished! Together, we have put together a strategy document, deliver many engagement activities and outputs and learned a lot along the way. Our group also involves Dr Kris McGuire and Ola Helwak who are PPI reps for MARVEL and miniMARVEL respectively. Carol Porteous, Molly Osborn and Lana Woolford (PPI engagement experts) have provided so much help and education to us. Michelle Wilson our paediatric research associate has recently put together an all-afternoon Paediatric IBD engagement day that will take place in May 2022. As highlighted by the following report written by our PPI group, we have a few key lines of work that will hopefully improve the patients' research and clinical experience, whilst also improving our scientific work! Finally, as a busy clinician and researcher, our PPI meetings remain the highlight of my schedule and I (and my team) very much enjoy our interactions!

Dr Gwo-tzer Ho

MUSIC PPI overview from our patient group (Jon, Kris and Molly)

Since starting the MUSIC PPI group, multiple benefits have become apparent as to how our work can have a positive impact on individuals with IBD. As three individuals who have had to live with IBD for several years, we firmly believe in improving communications; and importantly also, the need for the patients' perspectives and experiences to be the main focus of clinical research studies such as MUSIC. We believe that our input has made the study better for both the participants and the clinical team. We have challenged ourselves with making it vitally clear that research is the way in which an eventual cure for IBD can be discovered, and every patient's role in research is vital. We also pride ourselves with the ability to make information patients receive from nurses or consultants more understandable and relatable, as it can sometimes be overwhelming. The aforementioned is not just written down, it's displayed in a manner that is interactive and educational. For example, through media (podcasts and video clips), through interaction (questionnaires) and personal connection, including speaking to patients. We believe our role can have several positive impacts on the way patients live and understand their condition and are extremely fortunate to be given the chance to do so. Going forward, we plan to make more resources available and update our website to make it more educational and interactive, also lowering the amount of medical jargon to help people understand their condition and updates as MUSIC IBD develops. A series of podcasts are also planned for us to introduce ourselves and perhaps help provide clarification and guidance on a number of issues. We are preparing an ongoing study to capture and improve the participants' research experience in MUSIC that we have excitedly conceived the idea and will play a big part in leading this up soon!
Molly and Kris share their lived experiences in our webpage (www.musicstudy.uk).



Molly, Kris and Jon – our MUSIC PPI representatives.

Our Paediatric IBD PPI engagement day led by Mrs Michelle Wilson (Mini-Marvel research associated) and Molly Osborn (Centre for Inflammation, PPI Engagement Officer).

Our stories

Mr Jon Rysdale

For me, the role of PPI in research can add a great deal to any given research study. Being a patient can be a stressful experience at the best of times and participating in a research trial can be particularly daunting, especially if you do not know what to expect. Gwo-Tzer and I first met in 2006. He was a GI registrar and I was a Nurse practitioner. Gwo-Tzer was involved in IBD research even then and by that time I had already being living with IBD for over 15 years. During the last three decades, I have worked in all three NHS Lothian hospitals as a Nurse Practitioner and more recently as an ANP in General practice. Having experienced nearly three decades of working in the NHS as well as living with IBD, I felt this placed me in an ideal position to help Gwo-Tzer and his team think about the practicalities of their research when viewed from a patient's perspective. For our team, PPI is all about improving communication between the research team and the patient. As the saying goes 'A picture is worth a thousand words', and this year we are particularly looking forward to integrating illustration within our patient facing materials (Patient information sheet/ consent form and web presence).

Mr Kris Gourlay

Since I was diagnosed with Crohn's Disease in 2017, I have come to the conclusion that both patients and researchers must work together if we are to find more effective treatments and potentially a cure for both Crohn's disease and Ulcerative Colitis. Being part of the PPI team for the MUSIC study has given me the opportunity to develop my understanding of my condition as well as helping others navigate that stressful period of establishing a diagnosis and beginning treatment for a flare of their IBD. I first met Gwo-Tzer a couple of years ago when he helped me with a final year journalism project. The project was centred around raising awareness for IBD and his passion for his research shone through during our meetings. Being part of a patient public engagement team means that we can help improve communication between the patient and their clinical team and I am personally very much looking forward to exploring how we can raise the awareness of IBD through traditional and newer journalistic media.

Miss Molly Halligan

During the several years that I have been living with Crohn's Disease, I have participated in a number of research studies. These studies have allowed me to be part of the advancements in care and understanding of IBD and have also developed my confidence to ask questions, spread awareness, and even conduct my own qualitative research into IBD as part of an MSc project. For these reasons, I am proud to be a part of the MUSIC IBD PPI group where we can offer patient participants the same opportunities. Taking part in research allows patients to feel empowered in their IBD knowledge and feel connected to their treatment through the integrated efforts of patient representatives and clinical teams responsible for the study. Over the course of the next year, I am particularly looking forward to developing the qualitative evaluation of the MUSIC study to ensure that we are doing everything possible to make the experience of participating in the study both smooth and worthwhile for the patient.

Research Highlights

Rapid Assessment of Potential Ischaemic Heart Disease with CTCA: the RAPID-CTCA Trial. A Randomised Controlled Trial.

Why did we do RAPID-CTCA?

Chest pain is a common medical emergency presenting to UK hospitals. Immediate assessment includes an ECG and high-sensitivity cardiac troponin measurement. For most patients, this will allow myocardial infarction to be excluded or diagnosed in the Emergency Department. However, for some patients significant coronary artery disease may be still missed, and others will receive further unnecessary investigations such as invasive coronary angiography and treatments that may cause harm. Recent international guidelines from both Europe and North America have suggested that CT coronary angiography (CTCA) should be considered for the investigation of underlying coronary artery disease in patients with acute chest pain. The clinical or cost effectiveness of this strategy is unknown.

"Participant satisfaction was higher in the early CTCA arm than the standard of care arm (83.3% vs. 79.7%) and the attending clinician reported increased diagnostic certainty following CTCA."

What did we do?

The Edinburgh-led RAPID-CTCA trial was co-ordinated by ECTU and funded by NIHR. It was a randomised controlled trial investigating the potential benefit of early CTCA in 1749 patients with suspected acute coronary syndrome presenting to the Emergency Department of 37 UK hospitals. Overall, 877 participants were randomised to early CTCA and 871 to standard of care. The trial was powered for a clinically relevant primary endpoint of myocardial infarction or all cause death at one year

What did we find?

The participants were on average 62 years old and around two thirds were men. Chest pain was the primary complaint in 1549 (88.7%) participants, 1004 (57.4%) at an elevated troponin at presentation and 857 (49.0%) had an acute coronary syndrome diagnosis (myocardial infarction or unstable angina) at discharge from index hospitalisation. 410 (23.5%) participants having a high (>140) GRACE score, a measure of cardiac risk.

CTCA identified normal coronary arteries in 178 (23%), non-obstructive disease in 222 (29%) and obstructive disease in 359 (47%). There was no clear difference in the primary endpoint between CTCA and standard of care arms (5·8% vs. 6·1%). CTCA was associated with reduced invasive coronary angiography but no change in coronary revascularisation, acute coronary syndrome therapies or preventative therapies on discharge. Subsequent investigation and hospital attendances with chest pain were similar between arms, although CT reduced downstream non-invasive investigation for coronary artery disease.

Participant satisfaction was higher in the early CTCA arm than the standard of care arm (83.3% vs. 79.7%) and the attending clinician reported increased diagnostic certainty following CTCA.

What does it mean?

Routine early assessment with CTCA does not influence subsequent 1-year clinical events in patients with acute chest pain presenting to the Emergency Department although it provided clinicians with increased diagnostic certainty and reduced the need for invasive coronary angiography and other investigations used to determine underlying coronary artery disease.
This suggests it may have a role in selected patients where there is uncertainty regarding the presence and extent of coronary artery disease or limited access to invasive cardiac catheterisation facilities although this needs further prospective evaluation.
Given the lack of overall clinical and cost effectiveness, the routine use of early coronary CT angiography to prevent clinical events should not be recommended in all patients with acute chest pain.

What's next?

The value of anatomical characterisation in acute chest pain is likely to be greatest in a group of patients known to be at risk of subsequent coronary events who currently receive limited assessment beyond the rule out of myocardial infarction. This occurs in patients who do not have myocardial infarction but have higher cardiac troponin concentrations within the normal reference range. In large UK Emergency Department cohorts, these patients have a ten-fold risk of subsequent cardiovascular events at one year compared to patients with very low or undetectable troponin levels who are at low risk of events. The TARGET-CTCA trial, also led by investigators in Edinburgh and coordinated by ECTU, is addressing the question of whether early outpatient CTCA reduces longer term cardiovascular outcomes in patients who have had myocardial infarction excluded but have no clear alternative diagnosis and have increased troponin levels within the normal reference range. It is currently recruiting in 14 UK centres with ~1700 patients enrolled as of the March 2022. It is due to report in 2024.

If you would like to find out more

www.bmj.com/content/374/bmj.n2106

www.ed.ac.uk/usher/edinburgh-clinical-trials/our-studies/ukcrc-studies/target-ctca

Research Highlights

Precision Medicine Alliance Scotland

The Precision Medicine Alliance Scotland (PMAS) is a Government Programme to support research in Precision Medicine. The strategic aim of PMAS is to stimulate research and delivery in the NHS through specific programmes of work that will tackle health conditions of major importance in Scotland, including diseases that disproportionately affect those at risk of socioeconomic disadvantage.

Three Scottish clinical research projects being run in collaboration between NHS Lothian and the University of Edinburgh aim to address these issues through the exploration of Precision Medicine, an approach which focuses on the delivery of the right treatment, at the right time to the right patient.

Thanks to over 6.9 million pounds in Scottish Government funding, made available by Precision Medicine Alliance Scotland research awards, these projects have the potential to provide new treatment options for some of Scotland's most prevalent, deadly and devastating conditions.

Precision Medicine is an emerging approach for disease treatment and prevention that considers individual variability in genes, environment, and lifestyle for each person. The approach allows doctors and researchers to more accurately predict which treatment and prevention strategies for a particular disease will work best in particular groups of people.

Two of the research projects will focus on the use and impact of precision medicine on distinct medical conditions, with one concentrating on multiple sclerosis, and the other focusing on liver conditions including liver cirrhosis.

Multiple sclerosis (MS) is the leading cause of acquired neurological disability in young people and with rates in some of Scotland being amongst the highest in the world, more precise and accurate ways of measuring MS disease activity are urgently needed. This research project will use precise measurements of brain health to help people with MS achieve better control of their disease and in doing so help to positively impact on their potential risk of disability.

> **I am delighted these research projects have been selected to receive Scottish Government funding. Tackling Scotland's most prevalent health conditions is vital and clinical research plays a critical role in doing just that. Each of these research projects has the potential to dramatically increase available treatment options, improve patient outcomes and support a healthier Scotland for years to come.**
>
> **Professor Alasdair Gray**
> Research and Development Director,
> NHS Lothian

Liver disease is a silent epidemic. Since 1970, deaths due to liver disease have increased by 400% and in people below the age of 65 they have risen five-fold. Liver disease kills 1 in 50 people in Scotland - where death rates are 70% higher than the UK average and 60% higher than 30 years ago. Liver transplants cannot currently meet the numbers of Scottish patients with advanced liver disease, stressing the need for alternative treatment approaches.

This research project aims to translate advanced precision therapies for treatment of liver disease across Scotland. By focusing the research on therapies targeting the liver

that are at different stages of development, the team believed they have a real chance of facilitating new treatment options within five years. Treatment options that may greatly improve patient outcomes.

The third project will focus on the impact of time-critical precision medical treatment for critically ill patients admitted to Intensive Care Units. Annually, around 45,000 severely ill or injured patients will require specialist care and treatment in one of Scotland's critical care units. These units provide a vital and highly specialised service both for emergencies and in support of planned elective procedures, however survival rates for ICU patients are around 60%. For patients who do survive, they can experience substantial physical and psychological impacts because of their experience.

This research project will begin by assessing two time-critical precision medicine treatments to understand their impact on survival rates, when administered alongside existing treatment and care. The hope is that through this research, new treatment options will emerge which will positively impact ICU survival rates.

All of these projects will commence in 2022 and will recruit participants from across Scotland.
Professor Alasdair Gray, Research and Development Director, NHS Lothian said, "I am delighted these research projects have been selected to receive Scottish Government funding. Tackling Scotland's most prevalent health conditions is vital and clinical research plays a critical role in doing just that. Each of these research projects has the potential to dramatically increase available treatment options, improve patient outcomes and support a healthier Scotland for years to come."

Project 1: Integrating precision metrics of brain health into early treatment of multiple sclerosis

Research led by: Professor David Hunt

Multiple sclerosis (MS) is the leading cause of acquired neurological disability in young people, and rates of MS in some regions of Scotland are the highest in the world. However, if MS is under good control then the risk of future disability is much less.

At present, the methods used to monitor activity of MS in Scotland are imprecise and variable. More precise and accurate ways of measuring MS disease activity are needed if we are to give the right treatment at the right time, to the right person.

This research project will introduce precise measurements of brain health to people with MS, to help them make more informed treatment decisions about their disease.

The team will carefully monitor how these more precise measurements help people with MS achieve better control of their disease and what impact this has on their future risk of disability.

The aim of this research is to enable precision testing to be more widely available across Scotland and in doing so transform MS care. As part of the study, the research team will build the expertise and structures to make these approaches available to all people with MS in Scotland.

Project 2: Precision Medicine for the Liver

Research led by: Professor Stuart Forbes

Liver disease is a silent epidemic. Since 1970, deaths due to liver disease have increased by 400% and in people below the age of 65 they have risen five-fold. Liver disease is now the biggest cause of death in those aged between 35-49 years old. Liver disease kills 1 in 50 people in Scotland - where death rates are 70% higher than the UK average and 60% higher than 30 years ago. Because liver disease disproportionally affects the poorest and the most vulnerable in society, it is a major factor in generating socioeconomic health inequalities.

People living with advanced liver disease (cirrhosis) may experience debilitating and uncomfortable complications and report impaired health-related quality of life. Liver transplants are curative, but only for selected patients and the therapy is limited by the supply of suitable organs. A global shortage of donor organs means that many patients die waiting for a suitable liver. There are consistently 35-50 patients in Scotland waiting for a liver transplant.

Liver transplants cannot meet the numbers of Scottish patients with advanced liver disease and alternative approaches are required. As 75% of patients with chronic liver disease are diagnosed at an advanced stage, there will always be a need to develop better therapies for patients with advanced liver disease.

The aim of this research project is to translate advanced precision therapies for treatment of liver disease to the NHS for the benefit of Scotland's patients. Because of the different types of liver diseases, a different precision medicine approach is required for each specific disease.

The team have chosen to focus their research on therapies targeting the liver that are at different stages of development, but which all have a realistic chance of facilitating new treatment options within five years.

Project 3: Time critical precision medicine for acute critical illness

Research led by: Professor Manu Shankar-Hari

Annually, around 45,000 severely ill or injured patients will require specialist care and treatment in one of Scotland's critical care units. These units provide a vital and highly specialised service both for emergency medicine, and in support of planned elective procedures.

40% of ICU patients die within 60-days of admission. For patients who survive, they can experience substantial physical and psychological impacts because of their experience.

This project aims to enable time-critical precision medicine (TCPM) to be used in critically ill patients presenting to emergency departments and Intensive Care Units (ICUs) throughout Scotland.

In this project, two treatments will be assessed to understand their impact on survival rates, when administered alongside existing treatment and care.

The research team will not only assess the immediate impact of these treatments but will review their wider impact on health-related quality of life, as well as rehospitalisation rates.

It is hoped that through the research, new treatment options become available across Scotland for those patients who are critically unwell.

Selected Developments and Partners

Patient Public Involvement

Patient Public Involvement (PPI) in Research has again faced challenges and increasing demands throughout 2021, however a huge thanks must go to our dedicated Patient Advisory Group who have once again supported the PPI activity and the large volume of work that has been asked of them this last year.

Education and Training

Throughout this year we have continued to provide our Virtual Training programme as part of the ECRF Education Programme www.ed.ac.uk/clinical-research-facility/patient-and-public-involvement/ppi-training
We have established a new Virtual PPI Summer School, which was highly rated by attendees and has led to developments in PPI activity, including inspiring patient engagement events and applications for funding. We are also in the process of creating courses for roles in clinical research, including 'Training for Chief Investigators'. Our popular Practical Guide to Patient Public Involvement has been translated into a free have Open Education Patient Public Involvement Module, to open-up access to PPI training to support the clinical research community. The course is available to anyone at any time here:
www.ed.ac.uk/clinical-research-facility/core-services/education/oer/ppi

Funding Applications

This year has been a busy one and we have been collaborating with research teams submitting grants to Charities, the Medical Research Council, NIHR and the Chief Scientist Office. During this year alongside colleagues from NHS Lothian we supported the PPI activity within the successfully funded CSO Precision Medicine Centre - Time Critical Precision Medicine for Acute Critical Illness Using Treatable Trait Principles: Data Enabled Adaptive Platform Trial with Embedded Biological Characterisation, led by Professor Manu Shankar-Hari
www.nhsresearchscotland.co.uk/news/outcome-of-the-precision-medicine-alliance-scotland-funding-call

Scottish PPI Workshops

In 2021 we were fortunate to have PhD Intern, Georgia Kerr working with us to deliver National workshops funded by NHS Research Scotland to explore PPI needs across Scotland and exploring the future PPI needs of the research community.

The findings from this included:

1. A need to increase the diversity and inclusivity of PPI in research
2. A review of current funding mechanisms to support longer-term PPI activities and relationship building
3. The establishment of a central website/ directory for PPI in Scotland; and
4. A need to engage with primary care services to support inclusive and community-based PPI

The findings from this and ongoing PPI work continue to drive PPI objectives for health research.

Collaborative Working

Throughout 2021 the PPI team has continued to provide strategic support across NHS Lothian and the University of Edinburgh with a focus on building capacity to meet the growing demands for PPI support. These activities have included

- Supporting strategic plans for PPI activity in health research
- Supporting researchers to build capacity locally by gaining engagement involvement funding including supporting two successful Seed Fund bids and a successful ScotPen Application, one of these bids has already supported a grant application to a major funder
- The relaunch of our PPI Bursaries in 2021 to support pre-award PPI activities (these will run again in 2022)
- Hosting and supporting (alongside the ECRF Education Team) three Nuffield Student placement students who explored PPI and education in health research
- Collaborating in UK wide meetings to support costings and payments for PPI in research and developing UK wide strategic PPI activities (including the recent publication of the Shared Commitment Statement www.hra.nhs.uk/about-us/news-updates/health-and-social-care-leaders-unite-improve-public-involvement-research/)

Future Look

The Publication by the UK Government of *'Saving and improving lives: the future of clinical research delivery'* clearly details the central role of inclusivity, patient involvement and research participation. Indicating the increasing need to support the inclusion of under- served communities in research and in preceding PPI activities. This focus, alongside the findings from the National workshops will feed into the future NHS Lothian Research and Development Strategy. The PPI team anticipate the team will need to grow to meet the increasing demands for PPI in research, to place us in the best position to deliver for both the clinical research community and our local communities. To address this increasing demand, the PPI team have moved into their own core within the Clinical Research Facility.

Selected Developments and Partners

Edinburgh Imaging

Edinburgh Imaging
www.ed.ac.uk/edinburgh-imaging

Edinburgh Imaging is a world leading multidisciplinary imaging team – a working partnership between the University of Edinburgh and NHS Lothian to deliver cutting edge research and advanced clinical services. Edinburgh Imaging aims to enhance the quality of life for patients and to create solutions to disease, through its medical imaging research, its NHS clinical service & its online education programmes.

Edinburgh Imaging is an academic hub of expertise in medical imaging, imaging trial management, image analysis, imaging education, microscopy, pre-clinical imaging, and veterinary imaging.

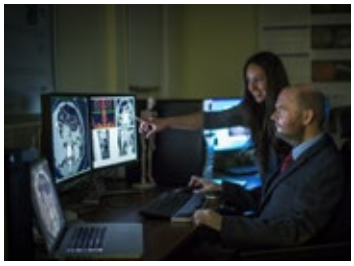
The Edinburgh Imaging community encompasses a wide variety of training & skills, & includes academics, doctors, radiographers, scientists, technicians, analysts, processors, information technologists, veterinarians, & managers. Edinburgh Imaging employs directly, approximately 70 staff on a mixture of University and NHS contracts.

Edinburgh Imaging Facilities

Edinburgh Imaging facilities & equipment are spread across several campuses in & around Edinburgh, but are focused mostly at Edinburgh's BioQuarter.

Co-location on the BioQuarter site with NHS Lothian Little France hospitals allows Edinburgh Imaging to operate a hugely successful collaborative partnership with NHS Lothian.

Edinburgh Imaging's Bioquarter facilities represent a total investment of around £45million, and include cutting-edge advanced imaging equipment (4 University and 1 NHS scanners), associated laboratories (cyclotron and radiochemistry facilities), and a comprehensive portfolio of supporting imaging resources and expertise to ensure start-to-finish implementation of world-class imaging activity.



accord
Academic and Clinical Central Office for Research and Development
NHS Lothian

Edinburgh Imaging Facility QMRI

In the University of Edinburgh's Queen's Medical Research Institute (QMRI), our state-of-the-art and world leading imaging facility houses the following:

- Siemens Biograph mMR PET-MR scanner
- Siemens Skyrafit 3T MR scanner
- Siemens Biograph mCT PET-CT scanner
- GE Discovery PET-CT scanner
- PETtrace Cyclotron GE Healthcare
- Radiochemistry suite, MHRA licensed for Good Manufacturing Practice (GMP) activities with multiple hot-cell and production routes, plus support for R&D of novel radiotracers and labelled compounds
- Retinal Imaging facilities, including a standard fundus camera, a hand-held fundus camera and an ultra-widefield scanning laser ophthalmoscopy
- Image Analysis Laboratory
- Data Management infrastructure and software team
- Edinburgh Imaging Facility RIE
- Embedded in the Royal Infirmary of Edinburgh (RIE) hospital, this custom-built imaging facility houses our:
- Siemens Magnetom Prisma 3T MR scanner
- Retinal imaging facility, including a Heidelberg Spectralisc retinal camera
- Trials Image Management service (SMARTIS)

Case study – SCOT-HEART latest findings & SCOT-HEART 2

The Scottish COmputed Tomography of the HEART (SCOT-HEART) assessed the added value of computed tomography imaging to measure coronary artery calcium scores and undertake coronary angiography, in over 4000 patients attending rapid access chest pain clinics across Scotland.

In the most recent analysis of the data, researchers found that in patients who presented with stable coronary disease symptoms, the burden of low-attenuation plaque as measured by quantitative analysis was a stronger predictor of future cardiovascular event compared to standard cardiovascular risk scores, coronary artery calcium score & even severity of luminal stenosis. This observation challenged the current clinical paradigm of assessing coronary artery disease & risk of future cardiovascular event.

The success of the SCOT-HEART study enabled launch of SCOT-HEART 2, to study CT coronary angiography use in patients who have no symptoms of coronary disease. This study hopes to identify whether initiating preventative therapies based on the presence of coronary disease on CT is superior to the current practice of using risk scores.

The Edinburgh Imaging Alliance

The Edinburgh Imaging Alliance is a virtual hub which promotes multi-centre collaboration between clinicians, researchers and scientists. It brings together not just those working in various University of Edinburgh departments, but also those at Heriot Watt University, NHS Lothian, and both local and international commercial clinical imaging organisations.

The Edinburgh Imaging Alliance aims to break down barriers between disciplines and encourage the sharing of data, knowledge, skills and facilities in order to advance healthcare across and beyond Edinburgh.

Through this collaborative work, staff successfully draw on each other's expertise, resulting in true multi-disciplinary teams of clinical and non-clinical researchers, physicists, chemists, technicians, image analysts, data managers and many other scientists working together for one common goal; improving patient health.

For further information, please visit www.ed.ac.uk/edinburgh-imaging, or email edimg.studyinfo@ed.ac.uk.

Selected Developments and Partners

Edinburgh Clinical Research Facility

Edinburgh Clinical Research Facility (CRF) operates as a partnership between NHS Lothian and the University of Edinburgh to provide state-of-the-art clinical facilities, training and support for clinical researchers.

Edinburgh was awarded Wellcome Trust Millennial funding in 1997 to establish the first Clinical Research Facility in Scotland and one of the first five Wellcome Trust CRFs funded in the UK.
What commenced with three members of staff working in one section of a clinical ward has now grown to over 100 clinical, scientific and support staff employed at three separate sites in Edinburgh. In this period 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.

Clinical Facilities:

Edinburgh CRF's clinical facilities provide researchers with access to experienced research nurses and clinical support teams, dedicated clinical research space and equipment for the safe conduct of clinical studies. Putting patient safety and quality at the heart of activity, the CRF provides unparalleled support for the conduct of experimental medicine research in Lothian.

Our three clinical facilities are located across two hospital sites, Wellcome Trust CRF (WTCRF) at the Western General Hospital, Royal Infirmary of Edinburgh Clinical Research Facility (RIECRF), and the Children's CRF at the Royal Hospital for Children and Young People, which are both in the Edinburgh Bio-quarter.

Edinburgh CRF is proud of its large portfolio of high quality studies and supports a diverse range of clinical specialities, with over 260 research active local investigators benefiting from the use of the CRF Cores. In 2021, the nursing and clinical core conducted over 6600 patient visits, of which 1000 were done as visits in patients' homes or clinical areas. Almost 300 high intensity study visits were undertaken where participants were in the facilities for more than 6 hours, or overnight. In 2021 over 160 studies were being actively supported in the nursing and clinical core of the CRF.

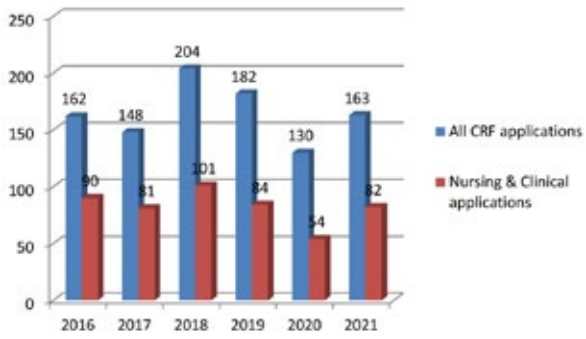


Figure 1: New study applications for support in Edinburgh CRF

MHRA Phase I Accreditation

Edinburgh CRF is one of only three non-commercial units in the UK to be accredited under the MHRA Phase I Accreditation Scheme, having maintained this status now for over a decade. All three of the CRF's clinical units – both adult facilities at WGH (WTCRF) and RIE (RIECRF), and our children's facility at RHCYP (CCRF) – are included within the accreditation. They provide the infrastructure, expertise and quality management system required to facilitate the delivery of complex experimental medicine studies and early phase clinical trials across multiple specialities in Lothian.

Units accredited under the Scheme must undergo regular and rigorous inspection by the MHRA to demonstrate that the highest standards for avoiding harm to trial participants and for handling medical emergencies are being maintained.

Edinburgh CRF's most recent re-accreditation inspection took place in December 2021, with work ongoing in the background throughout the year to prepare our facilities and the three studies that had been selected for review – Prof David Newby's BMS Apelin study in patients with chronic heart failure, Dr Iain MacIntyre's ALN-AGT01-001 study in patients with hypertension, and Dr Nik Hirani's Indalo study in patients with idiopathic pulmonary fibrosis.

In line with recent adaptations to MHRA processes, driven partly by the COVID-19 pandemic, this inspection took more of a hybrid approach, with a greater mix of on-site and remote elements. A significantly increased submission dossier allowed the inspectors to review many of the CRF's processes from their base, and further remote requests for documentation followed over a number of months. However, we were still able to welcome our lead inspector on-site for four days in December to showcase our facilities in person. The result was another excellent inspection outcome for the CRF with all three units maintaining their accreditation status and no major findings again.

Quality Assurance

Edinburgh CRF's Quality Assurance team continues to support a quality management system covering all Cores of the CRF, ensuring that regulatory requirements and MHRA Phase I Accreditation Scheme standards are upheld across all our research activity. This includes a dedicated QA Manager for Edinburgh Imaging Facilities (a post that has been vacant for some time, but will be filled in early-mid 2022), as well as a further QA Manager, Caroline Garth, to support the quality system within Edinburgh Clinical Trials Unit. These essential posts have served to strengthen the already close links between the CRF and other research infrastructure in Lothian.

Following the disruption caused by the COVID-19 pandemic, 2022 will see the QA team return to a more normal programme of work, including the restart of a full annual internal audit schedule. This activity will be vital in ensuring the CRF continues to practice in compliance with regulatory expectations, and to drive continuous quality improvement over the coming year and beyond.

At a national level, the CRF's QA Lead, James Gibson, continues to chair the UKCRF Network QA Theme Group, overseeing projects to support quality objectives within CRFs across the UK. This is just one of the ways in which the CRF's QA team engages with and supports research infrastructure beyond Edinburgh.

Success stories from the CRFs

Collaborations across the CRFs and wider research community.

2021 was a particularly busy year within the Nursing and Clinical Cores of the CRF. A drive to restart research activity that had been paused or delayed due to covid, coupled with a heavy burden of follow up visits from covid trials and higher than average staff absence rates saw all the CRF resources pivoting regularly to where they were needed. This was perhaps best exemplified in the latter part of the year, when nurses and support staff from the RIECRF and CCRF were moved across to support recruitment and follow up activity on Dr Iain Page's Valneva covid vaccine study at the WTCRF. 198 participants were recruited in a two week period and have returned for regular visits in the intervening period. At the same time of a 3rd booster being deployed in this study, there was pressure in December to achieve a hard target of 1000+ recruits to Prof Newby's SCOTHEART-2 study at the WTCRF. At least 10 participants a day were seen at the WTCRF for screening visits that month with Catherine Beveridge, a senior research nurse in our community team, volunteering to assist colleagues with this task. That enabled us to end 2021 with 1030 recruits in the trial, exceeding the funder's end of year target. The CRFs also answered short notice calls from clinical services in the autumn to provide nursing support, where capacity allowed, due to high levels of absence and pressure on clinical services.

In terms of early phase research activity, 2021 saw the Children's CRF gear up for their first Phase I study in the new facility with preparation now in place to recruit to a Dravet syndrome trial supporting Dr Ailsa McLennan in 2022. At least one further Phase I study will commence there in the coming year. The 24th March 2022 will be our first anniversary in the new CCRF with the appointment of Dr Katherine Jack to a clinical research fellow post, a welcome addition to the team. Kat's role is largely to support PIs in delivering the medical care

Picture from purpose built, Children's Clinical Research Facility (CCRF) in the new Royal Hospital for Children & Young People (RHCYP)

and oversight required in their paediatric trials. She Is also taking a lead in helping develop new clinical skills for our nursing staff to support studies e.g. skin allergy testing and spirometry in children as young as four.
In November 2021, Corrienne McCulloch joined the CRF team as our new Research Nurse Manager. Corrienne has a background in critical care research having worked with the Edinburgh Critical Care Research Group for many years as a Lead Research Nurse and NRS Clinician and previously having worked in the CRF as a senior research nurse.

The staff at the RIECRF have begun piloting local bi-monthly education sessions, focusing on areas that can complement the work profile of CRF staff. These are MDT sessions and have included topics such as non-technical skills and leadership, as well as more research-specific areas such as the use of CRF Manager Software.

Phase I / Education

We are building on our current portfolio of Phase I studies across the three facilities, with at least seven Phase I and two First in Human studies coming online this year. In 2022, we will be collaborating with various clinical specialities including respiratory, infectious diseases, hepatology, cardiology and paediatric neurology. Study visits for our upcoming Phase I work will involve our nurses seeing participants in the facilities, in the wards and out in the community.
Our specialist Phase I / Education Lead Nurses, Lesley Briody and Fiona Mitchell played an active role in the successful MHRA Phase I Accreditation Inspection.

They helped ensure that our studies, facilities, staff (including external research teams) were inspection ready. They have also been working closely with our Education Core in developing and delivering a new induction programme for Band 5 research nurses. Our first research nurse to trial this is Amy Hunter who joined us in February 2022 at the RIE CRF.

SCOTHEART-2 trial (note From PI)

The COVID-19 pandemic generated many challenges and I know that Edinburgh Clinical Research Facility had taken on additional clinical duties as well as numerous vaccine and COVID-19-related trials. This massive amount of work was very important during the first waves of the pandemic. This did however lead to deprioritisation of non-COVID-19 research studies and this led to delays in the delivery of the SCOT-HEART 2 trial which opened (and immediately closed!) to recruitment as the pandemic started. This left us with the apparently impossible task of meeting our funder's recruitment target of 1000 participants in the SCOT-HEART 2 trial by the end of 2021. However, with a concerted, dedicated and co-ordinated approach, I was absolutely delighted that the we were able to hit and exceed our recruitment before the funders deadline. As such, I wanted to give a huge thanks to Edinburgh Clinical Research Facility for their tremendous efforts in helping us reach our recruitment target for the SCOT-HEART 2 trial. At a time when many departments were struggling with reduced staffing and increased pressures, I was delighted that Edinburgh Clinical Research Facility and Edinburgh Clinical Trials Unit went the extra distance to deliver and to exceed the recruitment target and ensure the ongoing success of the trial. Thank you all so very much!

Finny Paterson tribute

It is hard to reflect on the past year within Edinburgh CRF without acknowledging the huge impact and major loss, as both a friend and colleague, of Finny Paterson, Research Nurse Manager. Finny was well known throughout the NHS Lothian research community and indeed beyond but sadly died on 6th October 2021, after a period of ill health.

Finny started her training at North Lothian College of Nursing and Midwifery in 1986 and worked in NHSL throughout the past 35 years up to her recent retirement in Sept 2021. Finny spent her first year post qualification on night shifts on the staff pool at the Royal Infirmary of Edinburgh, before moving into the acute assessment unit for the elderly for the next four years. She was promoted to Nursing Sister in the Medical Unit in 1995, before moving into staff nurse roles for two years in the acute medical unit and then for four years in the HDU at the RIE.
In 2002 Finny joined Edinburgh CRF as a Band 5 research staff nurse. Her dynamism and drive earned her promotions in the CRF in the intervening period before she took on the role of Research Nurse Manager in 2013. She held and developed this role up to her recent period of ill health and retirement.

Finny took a real pride in being a nurse. She never lost sight of and commented often in her teaching and supervision of staff on the privileged role that we have in healthcare looking after patients at their most vulnerable. She was passionate about research being a driver for change and improvements in health care and was exemplary in her dedication to her job and care of her colleagues. Those that had the honour of working with her will remember her kindness, humble intelligence, and wonderful sense of humour. Her expertise in clinical research coupled with her can-do attitude is sorely missed by her friends and colleagues. No request for help was ever too much trouble for Finny. It was with deep sadness that many in our community reacted to the news of her death at 55 years old. We do know however, that Finny would have been enormously proud of her colleagues' many achievements over the past year, not least of all her pride in Edinburgh CRF's maintenance of MHRA phase 1 accreditation status. Finny dedicated much of her professional life towards ensuring we mitigate risk and train staff to have the confidence and competence to deliver early phase clinical research safely to participants. The independent review of our processes and practices from expert GCP Inspectors was something she welcomed. The fact that her team navigated their way through this inspection whilst grieving her loss would have been what she expected of her friends and colleagues in the CRF.

Scientific Cores of Edinburgh CRF

Genetics Core

In response to the COVID pandemic, and local need, Edinburgh CRFs Genetics Core has changed significantly. We have added new equipment, automation and workflows to ensure we can continue to provide access to cutting-edge equipment and technical skills.

To enable processing the large number of samples arriving in the lab for the GenOMICC project, we automated our DNA extractions using Perkin Elmer Chemagic platforms. We now have three platforms and have quadrupled our throughput from about 5,000 samples extracted each year to 20,000 extracted in 2021. The majority of our capacity has been utilised for COVID-19 projects but as those numbers have reduced, we are now processing more non-covid projects, and testing the system to automate our RNA extractions.

The GenOMICC project has been a great success, showing the strength of having a genetics core embedded within the Clinical Research Facility. We were able to receive the blood samples from patients across the UK, to receipt them in our LIMS computer system and then track through DNA extraction and then to the genomic analysis. We have now extracted DNA from 25,000 samples and have analysed over 18,000 of these. This work has led to new insights into the disease mechanisms of the host-response to the virus and successfully identified baricitinib as a potential treatment.

During this time we have also increased our sequencing capacity. We purchased the NextSeq2000 in 2020 to enable the RNA sequencing of patients enrolled in the ISARIC study. We added another NextSeq2000 in late 2021 to allow a higher throughput - we have seen a large increase in single cell projects as these technologies improve, allowing greater insight into tissue biology. The extra platform also allows quicker turn-around times that are especially appreciated by our NHS colleagues when we sequence their patient diagnostic exome samples.

Mass Spectrometry

Steroid measurement in Edinburgh CRFs Mass Spectrometry Core has further advanced in the past year and we are now enrolled in the national equivalency quality assurance scheme (NEQAS) for 9 different steroids including cortisol, estradiol, testosterone and progesterone, giving us confidence in the concentrations measured in clinical samples. Recent publications measuring steroids include salivary cortisol in two studies in preterm infants with Dr David Stoye (Stoye et al. Arch Dis Child Fetal Neonatal Ed. (2022) doi: 10.1136/archdischild-2021-321593). Reproductive and metabolic adaptation to multistressor training in women with Dr Rob Gifford and Prof Rebecca Reynolds (Gifford et al, Am J Phys Endo Metab doi: 10.1152/ajpendo.00019.2021). ABCC1 modulates negative feedback control of the hypothalamic-pituitary-adrenal axis in vivo in humans, measuring cortisol and corticosterone with Dr Catriona Kyle (Kyle et al, Metabolism, 2022, DOI: 10.1016/j.metabol.2021.155118) and effects of obesity and insulin on tissue-specific recycling between cortisol and cortisone in men with Dr Anna Anderson (Anderson et al, JCEM, 2021, DOI: 10.1210/clinem/dgaa896).

Development of new methods and applications continue, including derivatisation of androgens for increased sensitivity with Dr Abdullah Faqehi (Faqehi et al, 2021, J Chrom A, DOI: 10.1016/j.chroma.2021.461933), measurement of cyclohexanone and cyclohexanol by different techniques with Prof Michael Eddleston (Hastie et al, ACS Omega, 2021, DOI: 10.1021/acsomega.1c03827) and paracetamol measurement in a study of dimethyl fumarate in hepatocytes (Meseguer-Ripolles, 2021, iScience, DOI: 10.1016/j.isci.2021.102552)

Another key publication in the BMJ Open resulted from expertise and practical work carried out in the Mass Spec Core from the ISARIC study in collaboration with Prof Tim Walsh.

Trisha Lee, Lab Technician preparing samples for analysis in the Mass Spectronomy Lab

There has been a huge amount of academic and public interest in the relationship between vitamin D and COVID-19 infections and outcomes. In a recent paper, the relationship between vitamin D status, as assessed by the measurement of plasma 25(OH)D concentrations, and clinical outcomes in a novel manner through the measurement of both total and free 25(OH)D in a large cohort of well phenotyped COVID-19 patients was investigated (1).
Total Vitamin D was measured in our Mass Spectrometry Core using a method validated and accredited by DEQAS.
The study revealed that patients with more severe disease, notably requiring invasive mechanical ventilation, had lower total 25(OH)D concentrations than COVID-19 patients who did not require ventilation. Importantly, it was observed that patients with more severe illness had lower free 25(OH)D, thereby further demonstrating the severity of the derangements in vitamin D metabolism in many COVID-19 patients and the link between increased disease severity and lower vitamin D status.
Similar observations were made in samples from influenza patients. Finally, the team demonstrated that vitamin D deficiency was commonplace in ICU survivors from a wide range of illnesses.

1. Hurst EA, Mellanby RJ, Handel I, Griffith DM, Rossi AG, Walsh TS, et al. Vitamin D insufficiency in COVID-19 and influenza A, and critical illness survivors: a cross-sectional study. BMJ Open. 2021;11(10):e055435.

Epidemiology & Statistics Core

Edinburgh CRF stats team have completed the analysis on the PATH-BP trial with Prof David Webb and Dr Iain MacIntyre. This trial, recently reported in Circulation. (2022 Feb 8; 145(6):416-423). They randomised 110 participants with hypertension in a cross over design trial to 2 weeks of 4g daily acetaminophen (paracetamol) or matched placebo. Their results showed that regular daily intake of 4 g acetaminophen increases systolic BP in individuals with hypertension by ≈5 mm Hg when compared with placebo; this increases cardiovascular risk and calls into question the safety of regular acetaminophen use in this situation.

Image Analysis Core

The IA Core is leading on a sub study of retinal imaging and analysis in the Edinburgh arm of the main PREVENT Dementia study. That team, led by Prof Craig Ritchie, successfully recruited their 700th & final baseline patient in March 2021.

The IA Core team recruited, imaged and analysed baseline data from 125 participants and are continuing to collected and analyse 2/3 year follow up image data. This data is being analysed as part of a funding award from the Alzheimer's Drug Discovery Foundation to investigate novel imaging biomarkers of dementia.

Rugby legends have also signed up to a University of Edinburgh study to investigate links between the sport & dementia. One of Welsh rugby's all-time greats, Shane Williams MBE, & former English World Cup winner Ben Kay MBE are among 50 former elite rugby players enrolling in the Edinburgh-led study.

The research – known as PREVENT: RFC – is funded by the Alzheimer's Society & will look at whether elite rugby players show more early warning signs of dementia than the general population. These former professionals are invited to participate in a sub study of retinal imaging that the IA Core is leading.

The Image Analysis Core also received media attention when Core Manager Tom MacGillivray contributed to an article in the Telegraph (Oct 2021) about the translation of eye research.

The IA Core is involved in the Scottish Collaborative Optometry-Ophthalmology Network e-research (SCONEe) project that is currently working towards the creation and curation of a retinal image research database by bringing together millions of images that have been acquired at routine eye exams in Scotland over the last 10 years. The IA Core is leading a work package on developing artificial intelligence techniques for identifying early signs of eye disease such as age-related macular degeneration. This project is in the process of creating what will become one of the largest datasets of its type in the world, helping to foster novel clinical research featuring retinal and ophthalmic data and the translation of Artificial Intelligence for healthcare.

Administration Team

The Edinburgh CRF Administration Team play a crucial role within the facility and are unique in the fact that they work in collaboration with all of the CRF Cores. Our contribution to the CRF may not always be visible, but the team work hard in the background to support the continued delivery of high-quality research.
We are a team of five, working in varied roles. We provide administrative, HR and financial support to the Cores, research governance and data management for studies being carried out in the CRF, and overall health and safety and facilities management.

After a long period of working from home, the team have been making a welcome return to the office to provide more in-person support. Our recent main focus had been the MHRA re-accreditation inspection, with our Admin Manager and Study Information Manager playing key roles in supporting the Nursing & Clinical and QA Teams with preparations for the inspection.

Looking ahead to this year, the Admin Team will be focusing on various transitions as the University of Edinburgh transform their Finance and HR systems, and we will be working hard to minimise the impact of these changes for our Cores. We are also embarking on a new collaboration with the Education and Nursing & Clinical Cores to deliver new education sessions. Firstly, we are working on a new and improved induction programme for newly recruited Research Nurses. This is an exciting piece of work and will involve the delivery of training sessions as part of the induction programme, covering the use of our CRFManager® system and the basics of the research application and approvals process. We will also be rolling out some additional training for current staff, which will help to build on existing knowledge and improve our study management processes.

Selected Developments and Partners

DataLoch – enabling improvements in health and social care through a secure, pioneering data service

The DataLoch approach aims to put data at the heart of responses to health and social care challenges and improve decision-making, research, and support for colleagues on the front line.

We do this by:

- Bringing together health and social care data for the South-East Scotland region;
- Working with experts in health and social care to understand and improve this data; and
- Providing safe and timely access to data for researchers.

Through bringing together key health and social care data, our service will allow a holistic data-driven approach to the prevention and treatment of different conditions, as well as the broader provision of health and social care services.

The DataLoch team

Our close-knit team of clinical experts, data analysts, service managers, and governance specialists enable improvements in health and social care that will make a real difference to the everyday lives of residents in South-East Scotland. The team is led by Professor Nick Mills, an experienced clinician and health data researcher.

Incorporating public value

Formed in DataLoch's early days, our Public Reference Group provides important insights for our operation and how to communicate our work. We are now revising our project-review processes to include our Public Reference Group in order to include an assessment of public value for the applications we receive. This input ensures that the projects we enable are aligned with the priorities of wider society.

Our beta phase

During the current beta phase of our development, we have invited applications from academics and clinicians in the South-East Scotland region. As part of this work, we have tested and improved our initial set-up in light of user feedback.

We have also:

- Further integrated primary and secondary care data within our main DataLoch-Core dataset.
- Improved the data structure and released a new Metadata Catalogue in which we have TrakCare, SMR, and WardWatcher data, with more datasets regularly being added. Applicants can access both primary and secondary care data through our service.
- Involved GPs within our Operational Delivery Board to embed primary care perspectives in our approach.

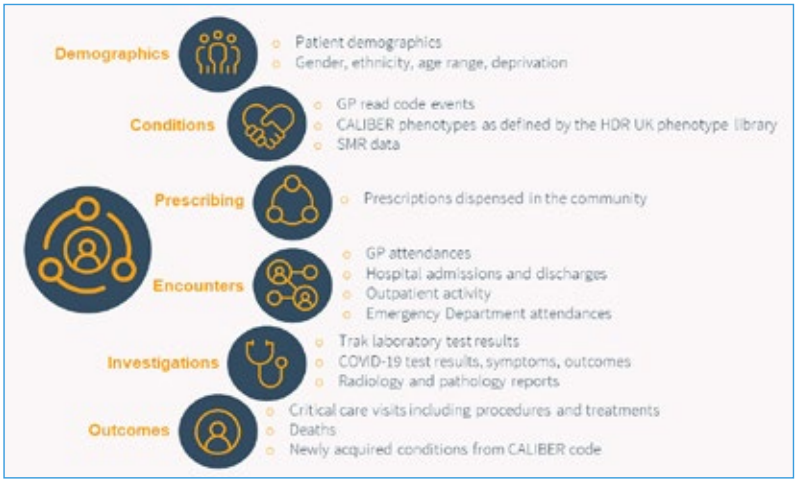
- Developed a new online application portal for applicants to submit proposals, communicate with the service team, and see the real-time progression of their proposal through the review process.
- Revised our project-review process to incorporate public-value assessments of proposals from our Public Reference Group.
- Joined the UK Health Data Research Alliance to better develop the adoption of standards, tools, and technologies for trustworthy health data research.

At the time of writing, to expand our understanding of public perspectives, we are working on a survey and deliberative workshops to explore ideas around non-traditional researcher (e.g. private-sector organisations, software specialists, AI developers) access to health data. This work will inform how we extend our service to enable non-traditional researchers to gain access to health data in an equivalent way to academics and clinicians within an appropriate information governance framework.

Our plans for 2022/23

Our full launch takes place in July 2022. This significant milestone means that we will open to applications from academics and clinicians not only in the South-East Scotland area, but throughout the UK and abroad. We will have also established our governance framework that will be applicable to researchers from private-, third- and public-sector organisations.

Our repository will also have its first intake of social care data from the Lothian region. This will begin the process of presenting a more holistic picture of the health and wellbeing of the local



Case study: Data-driven personalised-recovery care pathways after COVID-19

People who survive COVID-19-related critical illness have complex care needs, and it is essential to develop data-driven solutions to support care-transitions and recovery.

In collaboration with University and Health and Social Care stakeholders, we worked with DataLoch to identify NHS data sources related to recovery and rehabilitation, and translated these into new data assets. These included a rehabilitation-specific database, TrakCare, primary care data, comprehensive information relating to long-term health conditions, and a detailed critical-care extract. Following a meeting with PPI partners, we identified person-centred outcomes linked to these data resources. We then used artificial intelligence methods to develop a triage decision-support tool. The first version of the model correctly allocated patients around 28% of the time to one of six care pathways.

Looking forward, our novel research-ready data asset in DataLoch combines diverse data sources for new research and innovation opportunities. In addition, we are further developing and evaluating the triage assessment tool and developing the processes for automated outcome reporting. We will continue to engage with patients and the public to ensure data are relevant to their care needs and our priorities align with patient and family expectations.

Project Lead: Dr Nazir Lone, Senior Clinical Lecturer / Honorary Consultant

population, and allow projects to explore questions beyond those exclusively founded in health care.

In collaboration with the Edinburgh Cancer Informatics team, we will release the DataLoch-Cancer dataset to provide improved support for research and innovation around cancer. In association with Usher Innovation, we will provide the Frailty Collection: a bespoke view of data that will support the nascent community of researchers and innovators who are focusing their work on frailty and frailty-related issues.

The DataLoch Partnership

DataLoch is funded by the ten-year Data-Driven Innovation (DDI) programme, which involves NHS Borders, NHS Fife, NHS Lothian, as well as the six local authorities in South-East Scotland. To date, DataLoch has been developed by the University of Edinburgh and NHS Lothian with the other DDI partners to formally join the partnership in due course.

Case study: Investigating the utility of C-Reactive Protein tests for patients with COVID-19

We're working with DataLoch to help us understand the diagnostic value of specific biochemical tests in our treatment of patients with COVID-19. Whilst the obvious question many people asked when faced with a new disease is "how can we treat this?", an equally important question is about how we investigate and diagnose COVID-19 and associated complications. Our project examines the use of procalcitonin and C-Reactive Protein tests in patients presenting to hospital with COVID-19.

The real strength of our project comes with the breadth and depth of information hosted by DataLoch: using anything but the routinely collected data within the DataLoch repository would make our work much more arduous, more prone to error, and potentially even untenable. We've also benefited from the support and expertise of the DataLoch team in our preparation for ethical review and data request, as well as working within the analytic environment. Once complete, our goal is to equip clinicians with better evidence so that the way we investigate patients with COVID-19 is accurate and resource efficient.

Project Lead: Dr Jack Cafferkey, ACCS CT2 Trainee, NHS Lothian

Get in touch

Discover more about DataLoch through our website: dataloch.org

If you are looking for data to support a research or service-development question, or you wish to register as a user and access our Metadata Catalogue, then contact the DataLoch team: dataloch.org/connect-with-us

Selected Developments and Partners

Lothian NRS Biorepository

Human tissue samples are a valuable resource in medical and scientific research, enabling development of new medicines and treatments, improving detection of many different diseases, and developing a greater understanding of disease processes, prognosis and underlying mechanisms.

Lothian NRS Biorepository continues to provide managed access to this by providing an infrastructure to support local and national tissue research either directly or indirectly, in accordance with the appropriate governance and regulatory requirements.

The Biorepository is a REC-approved Research Tissue Bank (Ref: 20/ES/0061), which allows for the collection, storage, provision and use of tissue for research, subject to certain conditions. The approval allows for the support of a broad and diverse range of studies from both academic and commercial researchers. This approval also allows the Biorepository to grant delegated ethics to this research where applicable. The Biorepository is also accredited under the NRS-CMT Accreditation Scheme for Biorepositories. This is an independent accreditation scheme set up on behalf of the Chief Scientist Office to ensure that the collection and provision of tissue from NHS Scotland is in accordance with the governance standards for the rest of the UK. This accreditation also extends to sub-collections registered with the Biorepository that demonstrate they meet these standards.

Tissue and services

The Lothian NRS Biorepository provides access to a wide range of human tissue samples including surplus materials from diagnostic and surgical procedures. The Biorepository can also provide access to pathology archive specimens, with appropriate governance and approvals in place.
Our experienced staff are based within NHS Pathology labs and have close links with the department, allowing the Biorepository to utilise the services and expertise available within the department. As a result, we can offer pathology, technical and histological support as required.

The Biorepository also works closely with Laboratory Medicine Blood Sciences to provide surplus diagnostic samples collected via the main hospital sites. We are currently working with Lab management and other local stakeholders to establish a process to meet the increasing research demand for access to such samples.

Material released by the Biorepository to date has been used in a wide range of studies including; in vitro pharmacology, cell culture, digital imaging, diagnostic and prognostic assay development, proteomic studies, DNA analysis and genome sequencing.

Services include:

- Expert advice
- Processing tissue
- Processing bloods into serum or plasma
- Slide or section preparation from paraffin/frozen blocks
- Hematoxylin and Eosin (H&E) and Immunohistochemistry (IHC) staining
- Specialist stains
- Slide Scanning
- DNA and RNA extraction
- Tissue homogenisation for protein extraction
- Production of tissue micro arrays (TMAs)
- Liquid biopsies via surplus bloods.

Key developments during the past year

Biorepository support for clinical research has been ongoing through the difficult circumstances of past year, and the pandemic has not had a significant impact on our activity to date. The Biorepository has continued to support requests from a diverse range of clinical projects during this time, both academic and commercial.
While the majority of requests received were for FFPE tissue, we have also noted an increase in requests for prospectively collected fresh surplus material and previously collected ex-diagnostic samples. Staff have also assisted with sample retrieval for local service evaluation projects, which could ultimately influence the patient pathway. The Biorepository has also continued to support the retrieval and provision of archival diagnostic samples for patients enrolled into clinical trials.

COVID-19

During this period, we have also continued to support numerous projects related to COVID-19. Biorepository staff have been directly involved in the provision of material to studies ranging from large national surveillance projects to local pilot projects. The types of COVID projects supported include public health studies; diagnostic development; and pathology, virology, infectious disease and medicine, cardiovascular, respiratory and oncology-related research. The Biorepository have also supported ICECAP, a local tissue bank established specifically for the collection of post-mortem material from consented COVID-19 cases.

iCAIRD

The Biorepository has also engaged fully with iCAIRD (The Industrial Centre for AI Research in Digital Diagnostics) during the past year. This is one of five UK centres of excellence funded by Innovate UK, and established in Scotland by Prof. Harrison. Although this is primarily based in Aberdeen and Glasgow, Lothian in collaboration with the University of St. Andrews now leads on several work packages. Many of the projects are at the forefront of AI research in pathology rather than directly related to pathology digitisation. An added benefit is to provide consultant pathologists access to AI tools without having to navigate the hurdles of being an early adopter of full digitisation, making Lothian a major pathology research node for this pan-Scotland initiative.

Improving access to surplus samples

The excess from clinical samples routinely submitted to Labs can provide a wealth of information supporting research. These samples are often collected at initial presentation, prior to treatment, so are of significant research value. Consequently, there continues to be growing interest in access to these, but this has previously proved difficult to do on a large scale. During the past year we have established a working group involving various stakeholders from Tissue Governance, Laboratory Medicine and the local research community to address this and take this forward. This group are working to create a single, identified route for the provision of samples that ensures they are released in the appropriate manner, in accordance with all regulatory and legal requirements

The past year has seen Biorepository staff facilitate several collections for ongoing projects such as Code-HF, COVIRNA and TWITCH, which have acted as pilot studies for this process. This has allowed researchers to access these surplus samples without placing an additional requirement on the diagnostic service. We will look to develop this further and effectively embed this over the coming year. This will also enable NHS Lothian to participate in the national SHARE blood collection.

Data

Tissue samples are more valuable for research when linked to clinical data. The Biorepository approval allows for the provision of associated de-identified data.

During the past year, the Biorepository has continued to strengthen links with DataLoch and both have been working to establish a process for provision of tissue-associated data. The Biorepository will continue to provide a limited set of clinical and demographic data where required. If necessary, the scope of this can be expanded through our close collaboration with Dataloch, who can facilitate access to larger, more extensive or complex datasets within their platform. The aim of this is to ensure that researchers can access linked data as promptly as possible via the appropriate means, access and governance. We will continue to work closely over the coming year to refine this process.

Scottish biorepository network

Lothian Biorepository is a key member of the national NRS Biorepository network established by the Chief Scientist Office (CSO) and NHS Research Scotland (NRS) in partnership with the other health boards in Scotland.
The Lothian Biorepository continues to work closely with colleagues in NHS Greater Glasgow & Clyde, Grampian and Tayside to develop the network and provide streamlined means of access to tissue from across Scotland for the research community. This national approach is designed to encourage the use of tissue in research and boost the availability of tissue, ending the need for researchers to source tissue from more than one Board.

Tissue governance

The Biorepository also has the responsibility of providing a 'tissue governance' function for the health board. The remit of this is to help the board fulfil the role as 'custodian' and ensure that the local collection and storage of tissue from NHS Lothian complies with all applicable regulatory, legal and ethical requirements.

Collections of patient samples held or stored for research purposes within NHS Lothian and the University of Edinburgh should register with the Biorepository, particularly where there is no current project-specific REC or R&D approval.

The Biorepository will be establishing a new electronic management system during the next year (previously delayed due to the pandemic) that will allow researchers to register their collections and provide a database of those that are available for use to other researchers.

The management group can also assist with legal, ethical and regulatory requirements regarding the use of human tissue or patient samples in research.

Streamlined Pathway

Feasibility

- One application across Scotland
- Collated feedback to applicant
- National coordinated costs to reflect project requirements

Assessment

- Clinical and pathology support
- Scientific and technical review
- Accredited tissue governance and ethics provided

Delivery

- Wide range of tissue services
- National coordination of tissue acquisition
- National Material /Data Transfer Agreement

Any researchers interested in using patient samples from NHS Lothian should contact the Biorepository management team, Craig Marshall (craig.marshall@nhslothian.scot.nhs.uk) or Vishad Patel (vishad.patel@nhslothian.scot.nhs.uk) at the earliest opportunity to discuss the services and support the Biorepository can offer to facilitate their research.

Selected Developments and Partners

Edinburgh Clinical Trials Unit (ECTU)

Throughout 2021 and early 2022 the Edinburgh Clinical Trials Unit (ECTU) continued to respond to an expanding portfolio of clinical trials.

We welcomed new staff to our Data Management & Programming, Health Economics, Statistics and Trial Management teams to ensure that we continue to develop, design and deliver world-class clinical trials. In this year's update, we would like to share some examples of trials and methodological research the unit is involved in.

SoSTART - The Start or STop Anticoagulants Randomised Trial (NCT03153150)

A pilot phase trial run in a collaboration between ECTU (providing data management, programming, and statistics) and the Centre for Clinical Brain Sciences 2016-2021. SoSTART was an investigator-led, multicentre, randomised, open, assessor-masked, parallel group, clinical trial of two oral anticoagulant prescribing strategies. It was a pilot phase trial with a non-inferiority hypothesis to determine whether to proceed to a main phase trial. Published in The Lancet Neurology, it was the first published trial of its kind and was presented at the 7th European Stroke Organisation Conference in 2021.

Why did we do SoSTART?

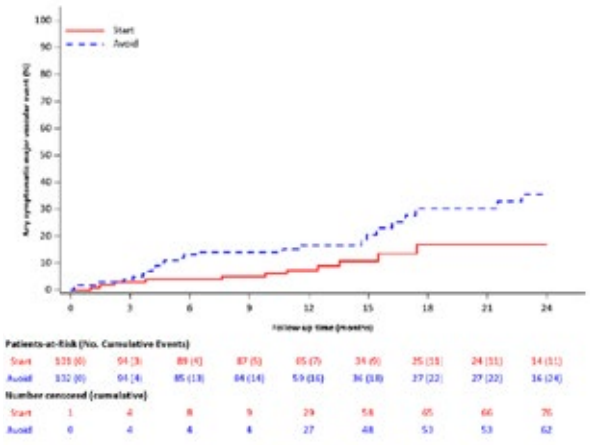
We wanted to find out whether starting or not starting an anticoagulant drug is better for people who have had a bleed within the skull (known as a "brain haemorrhage") as well as an irregular heartbeat (known as "atrial fibrillation" or "AF"). Blood-thinning drugs known as "anticoagulants" are taken by people with AF to prevent blood clots forming. Anticoagulants reduce the risk of clots a lot despite increasing the risk of bleeding.

What was SoSTART?

SoSTART was a randomised controlled trial involving 203 survivors of brain haemorrhage who had atrial fibrillation in the UK. SoSTART split the participants into two groups: half were allocated to start an anticoagulant drug, and half were allocated to stay off these drugs. Over the course of 3 years, we kept track of everyone to learn how they got on and who had recurrent bleeding or any major event involving the blockage of blood flow, like stroke or heart attack.

What did SoSTART show?

- We had 203 participants in total. 101 participants started taking an anticoagulant drug. 102 participants did not.
- 8 of the 101 participants who took an anticoagulant drug had another brain haemorrhage. 4 had a major event involving blockage of blood flow.
- 4 of the 102 participants who avoided these drugs had another brain haemorrhage. 23 had a major event involving blockage of blood flow.
- We could not prove that starting an anticoagulant drug was not worse than avoiding these drugs.
- However, starting an anticoagulant drug might be better than avoiding these drugs for reducing the overall risk of any major event due to blood vessel blockage or bleeding (as you can see in the survival curves below).



- These promising findings are now being investigated in larger trials to be sure about the effects of anticoagulant drugs for people with brain haemorrhage and atrial fibrillation.

RESULT-NOF - The impact of Restrictive versus Liberal Transfusion strategy on cardiac injury in patients undergoing surgery for fracture Neck Of Femur (NCT03407573)

RESULT-NOF was a feasibility randomised controlled trial run by ECTU between 2017 and 2019 with Professor Michael Gillies as Chief Investigator. It was published in the British Journal of Anaesthesia in 2021 (https://doi.org/10.1016/j.bja.2020.06.048).
The trial investigated two transfusion strategies in people undergoing surgery for fracture neck of femur (NOF) and was conducted in the Royal Infirmary of Edinburgh.
This research was important as there are many frail and elderly patients who undergo surgery for hip fracture each year, many of whom have anaemia in addition to other health problems. Patients are commonly prescribed a blood transfusion around the time of surgery, but there can be uncertainty about how low the blood count should be before a blood transfusion is ordered. Current guidelines suggest that prescribing at a lower haemoglobin count is better, but there is research which suggests that this level is too low if the patient has a history of heart disease.
Therefore, RESULT-NOF was planned as a small study of blood transfusion in order to use the data and results to plan a bigger study involving more hospitals and more patients.

Trial Design

The objectives of the trial were two-fold:

1. To investigate the feasibility of conducting a randomised trial of liberal versus restrictive transfusion in terms of recruitment, protocol compliance and red cell transfusion.
2. To investigate the effect of transfusion strategy on clinical outcomes (myocardial injury, postoperative complications, mortality, duration of hospitalisation, quality of life).

Patients were enrolled before surgery and were randomised to a restrictive (haemoglobin 70-90 $g.L^{-1}$) or liberal (Haemoglobin 90-110 $g.L^{-1}$) transfusion strategy for the duration of their hospital stay. In total, 62 patients were randomised into the trial with 26 allocated to the liberal transfusion group and 36 to the restrictive transfusion group.

Key findings

This small trial demonstrated that a study of two transfusion strategies is feasible in terms of protocol compliance and the assessment of clinical outcomes.

Further research

The results and learnings from RESULT-NOF have led to the establishment of the RESULT-Hip trial, a large multi-centre, randomised controlled clinical trial.
This large trial will be conducted across 30 NHS hospitals and will address the same objectives of RESULT-NOF. Its overall aim is to add to the clinical evidence for the most appropriate transfusion strategy (liberal or restrictive) in patients undergoing hip surgery.

Clinical trials methodology research

Alongside delivery of its portfolio of trials, ECTU continues to undertake clinical trials methodology research to improve trial design, conduct, analysis and reporting. ECTU colleagues contribute to working groups in the MRC-NIHR Trials Methodology Research Partnership, including co-leadership of its Outcomes Working Group. The ECTU Studies Within A Trial (SWAT) interdisciplinary group, linked to the Trial Forge collaboration, promotes SWAT development and implementation in ECTU to support enhanced methods of conducting trials. Other current methodological research topics include developing extensions to reporting guidance for clinical trials and statistical analysis plans; promoting effective data visualisation techniques; and deriving new methods to evaluate potential surrogate (substitute) outcome measures for use in clinical trials.

Methodology publications 2021-22 (selected)

Current recommendations/practices for anonymising data from clinical trials in order to make it available for sharing: A scoping review. Rodriguez, A., Lewis, S. C., Tuck, C., Murray, A., Dozier, M., Jackson, T., Eldridge, S. & Weir, C. J., 11 Feb 2022, (Accepted/In press) In: Clinical Trials.

Early phase clinical trials extension to the guidelines for the content of statistical analysis plans. Homer, V., Yap, C., Bond, S., Holmes, J., Stocken, D., Walker, K., Robinson, E. J., Wheeler, G., Brown, S., Hinsley, S., Schipper, M., Weir, C. J., Rantell, K., Prior, T., Yu, L-M., Kirkpatrick, J., Bedding, A., Gamble, C. & Gaunt, P., 7 Feb 2022, In: British Medical Journal. 376, e068177.

Multiple secondary outcome analyses: precise interpretation is important. Parker, R. A. & Weir, C. J., 10 Jan 2022, In: Trials. 23, 4 p., 27.

The need for reporting guidelines for early phase dose-finding trials: Dose-Finding CONSORT Extension. Yap, C., Bedding, A. W., de Bono, J., Dimairo, M., Espinasse, A., Evans, T. R. J., Hopewell, S., Jaki, T., Kightley, A., Lee, S., Liu, R., Mander, A. P., Solovyeva, O. & Weir, C. J., 6 Jan 2022, In: Nature Medicine. 28, p. 6-7

Density strips: visualisation of uncertainty in clinical data summaries and research findings. Weir, C. J. & Bowman, A., 21 Dec 2021, (E-pub ahead of print) In: BMJ Evidence-Based Medicine.

Costs and Staffing Resource Requirements for Adaptive Clinical Trials: Quantitative and qualitative results from the Costing Adaptive Trials Project. Wilson, N., Biggs, K., Bowden, S., Brown, J., Dimairo, M., Flight, L., Hall, J., Hockaday, A., Jaki, T., Lowe, R., Murphy, C., Pallmann, P., Pilling, M., Snowdon, C., Sydes, M. R., Villar, S. S., Weir, C. J., Welburn, J., Yap, C., Maier, R., Hancock, H. & Wason, J., 26 Oct 2021, In: BMC Medicine. 19, 251.

Separation and the information theory surrogate evaluation approach: a penalized likelihood solution Ensor, H. & Weir, C. J., 2 Aug 2021, (E-pub ahead of print) In: Pharmaceutical Statistics.

In Memoriam

Professor Fiona Denison: 22nd July 1970 – 8th January 2022

We wish to pay tribute to Professor Fiona Denison who died on Saturday the 8th of January 2022.

Fiona was a highly respected clinician and a talented researcher, whose research focussed on improving maternal and fetal health. She is greatly missed.

www.ed.ac.uk/centre-reproductive-health/news/2022-news/prof-denison-obituary

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