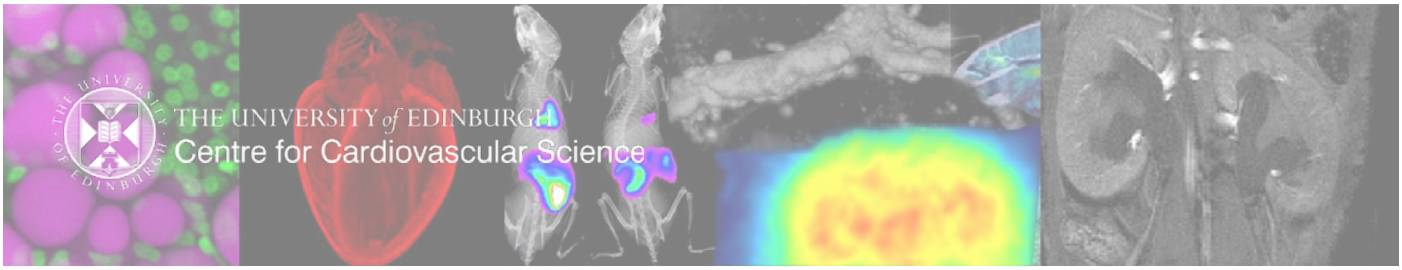
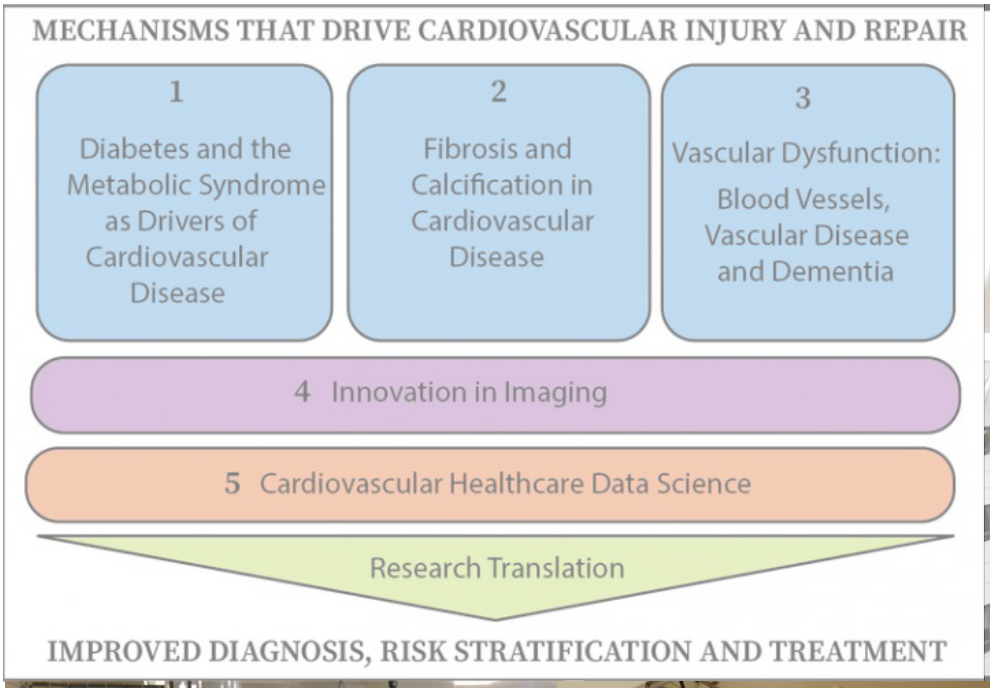


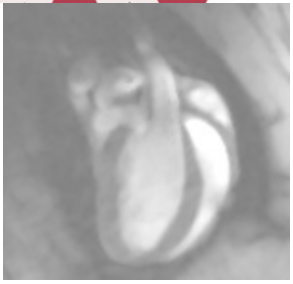
REA3 BIMONTHLY NEWSLETTER

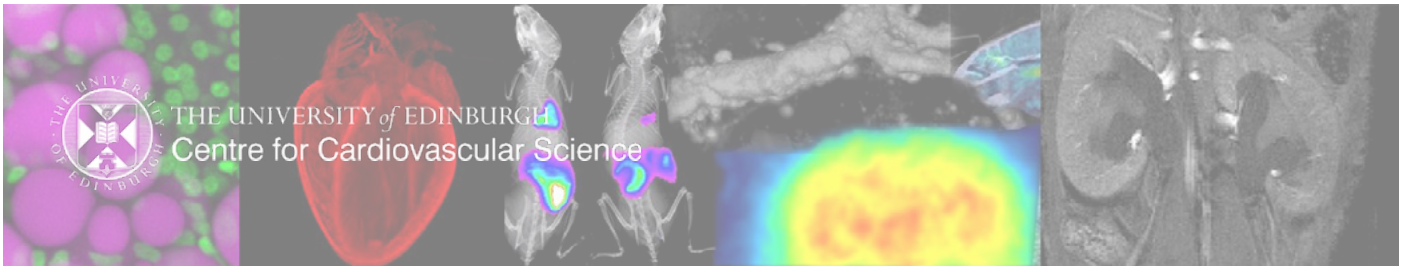
May 2021



THE UNIVERSITY of EDINBURGH

BHF Research Excellence Award University of Edinburgh





INTRODUCTION

Welcome to the May 2021 edition of the REA3 Newsletter.

Since our last edition the speed of the vaccination programme has gathered pace across the UK. Certain parts of our life are able to return to some kind of normality. However, everyone remains cautious as we observe and evaluate the data concerning the spread of the B.1617.2 variant. It is looking positive from many quarters that the vaccinations on offer provide highly effective protection after 2 doses. However, the increase in numbers in some areas shows that COVID-19 is still having an impact on people's lives and the freedoms we are used to.


Dr Shruti Joshi

REA3 continues to plough on successfully during this time with our team of dedicated staff, students and collaborators navigating the restrictions placed upon them in the labs to continue with their funded research. We have 3 contributors in this issue providing an overview of their work. This includes Dr Shruti Joshi who received a clinicial fellowship from REA3, which provided some short term support before securing her pre-doctoral clinical research training fellowship. We find out more about her study regarding Type 1 diabetes.


Dr Catherine Stables

One of our postdoctoral researchers, Dr Catherine Stables, who is funded partly by REA3, has given us an insight into her time as a Data Manager with DataLoch, the repository of the health and social care data for Edinburgh and South East of Scotland. This project was developed to help provide a solution to the health and social care challenges that these areas face.

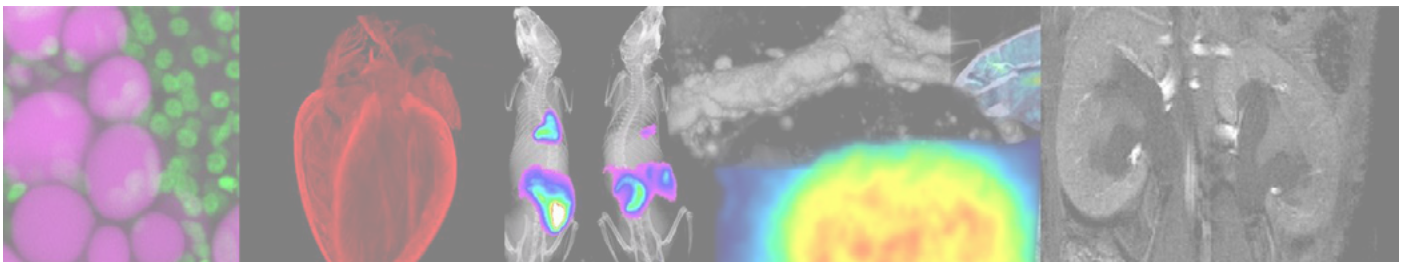

Dr Steven Williams

Finally, Dr Steven Williams, who we welcomed into the REA3 sphere in the latter part of 2020, updates us regarding his move from London and his research interests while working as a consultant cardiologist and electrophysiologist.

Gillian Joyce is always looking for any interesting bits of news to be added in and you can email her directly if you wish to have any work/achievements featured: Gillian.Joyce@ed.ac.uk

The next newsletter will be issued towards the end of July and until then, we extend our thanks again to everyone across the REA3 community and beyond.

Professor Andrew H Baker, Director REA3
Professor David Newby, Deputy Director REA3



Dr Shruti Joshi - Clinical Research Fellow

Non-invasive quantification of pancreatic islet beta cell mass and function in people with type 1 diabetes

Approximately 400,000 people are living with type 1 diabetes in the United Kingdom: one of the highest rates in the world. It is characterised by autoimmune loss of pancreatic beta cell mass leading to metabolic dysregulation, requiring lifelong insulin therapy. It is now recognised that there are micro-secretors of insulin and that preservation of insulin secretion in these cases is associated with decreased complications. Therefore, recent research has focused on using immunomodulation to preserve pancreatic beta cell mass. Emerging evidence suggests a potential role for sodium glucose co-transporter 2 (SGLT2) inhibition in improving glycaemic control in type 1 diabetes at diagnosis by preserving beta cell mass via reduction in apoptosis and reactive oxygen species.

There are currently no non-invasive imaging modalities available to assess and to quantify the functional mass of pancreatic beta cells. Development and implementation of non-invasive techniques for quantitative measurement and spatial localisation of the functional beta cell mass would help in early diagnosis of beta cell loss or dysfunction in sub-clinical phases of diabetes. Moreover, it would enable evaluation of emerging therapeutic approaches which specifically focus on preservation or regeneration of beta cells including early intervention with immunomodulatory therapies.

To address this unmet need, we have developed a magnetic resonance imaging (MRI) technique using a manganese-based contrast medium that is combined with quantitative T1 mapping of the pancreas **(Figures 1 and 2)**. Like gadolinium, manganese has paramagnetic properties and shortens T1- relaxation. In contrast to gadolinium, manganese acts a calcium analogue and is taken up into pancreatic beta cells during insulin secretion via voltage gated calcium channels, serving as an intracellular contrast agent that represents active insulin secretion. This imaging technique has the potential to provide a safe and reproducible method of assessing pancreatic beta cell mass and function that can track disease progression and monitor response to therapy.

We plan to conduct a proof-of-concept study to investigate manganese-enhanced MRI of the pancreas in people with type 1 diabetes and a sub-study to investigate the effects of SGLT2 inhibition on pancreatic beta cell mass. We are currently recruiting participants for the first phase of this study.

I am very grateful to the British Heart Foundation Research excellence award for supporting me whilst I was applying for my pre-doc clinical research training fellowship, which I was able to secure (FS/CRTF/20/24087).

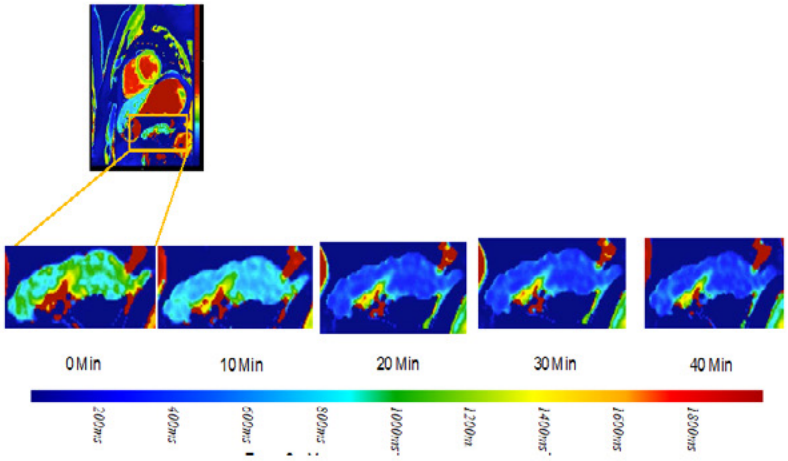


Figure 1. Manganese enhanced MRI T1 Mapping in a healthy volunteer (Note the colour change in pancreas at different time points after Manganese administration)

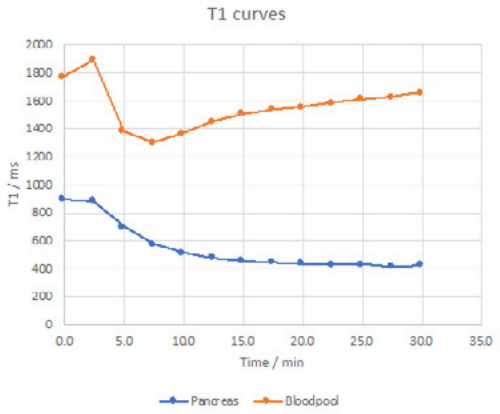
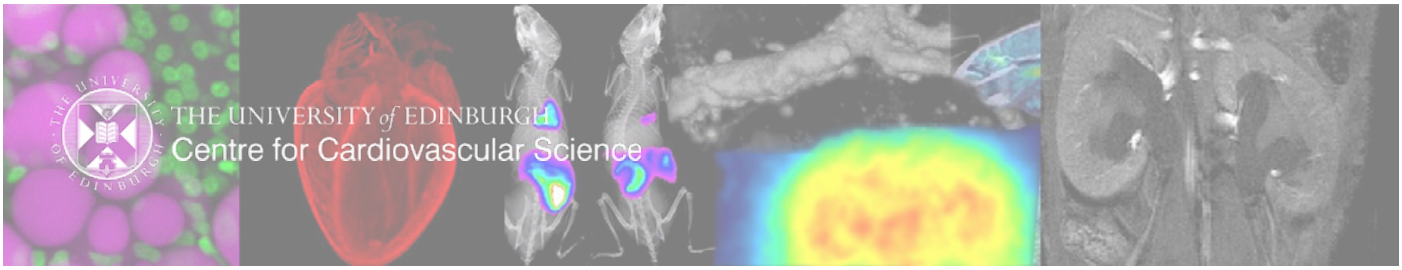


Figure 2. Rate of Manganese uptake in pancreas vs Blood pool in a healthy volunteer



Dr Catherine Stables – Postdoctoral Researcher & Data Manager DataLoch

As both a postdoctoral researcher in CVS and the Data Manager for DataLoch I am in a unique position to be able to talk about what DataLoch is, what it will evolve into, and how researchers from CVS and beyond will be able to use DataLoch to do truly impactful research. I'm also on quite an unusual career trajectory, so I'll share a bit about my role and how I got here. Here goes…

What is DataLoch?

This is often the first question I get asked, and the answer really depends on whether you want to know what it is right now, or what we're moving towards. The simple answer is that DataLoch is delivering health and social care data to researchers and analysts in a way that removes many of the existing barriers to such data, while maintaining protection of individuals' privacy. By providing this world-leading service, DataLoch will enable data-driven improvements in health and social care outcomes for our region.

We are currently in the middle of building a "beta version" of DataLoch. We are doing this in an agile way (in fact we're in the middle of a training/coaching programme on how to use "Agile" methodology properly, and it's a steep learning curve!). This means that we will deliver a minimal product in the next few months, but it will improve iteratively after that.

The goal is to create something that is more than a simple data repository. The diagram below shows how DataLoch will add value to the data by documenting metadata in a consistent way, doing QC checks, validating data and metadata with clinical experts, and pre-processing certain variables to make them more "research ready" for users. This will include creation of specialist collections of data relevant to specific conditions such as heart disease. The process of creating and validating these "research ready" views is very much a collaborative effort. We need to work closely with experts: front-line clinical staff and researchers who understand what the data means in "real-life" and how it can be presented in the most useful way.

As well as innovating in the linkage of data and addition of valuable processing and metadata, we are also innovating across the whole service being provided. We have partnered closely with the Lothian Research Safe Haven from the start and have now officially merged into one service. Our new innovative approach includes an online application portal that streamlines processes and covers both research and service management projects. We are also working with the ACCORD team and the NHS Lothian Data Protection Officer and Board to define a data governance framework that is both robust and agile. And finally, we are working closely with eDRIS and EPCC, who provide vital aspects of the Safe Haven structure, to improve the user experience.

My role

My role as Data Manager has been evolving along with DataLoch. I was originally doing this role part time alongside my postdoc in Nick Mills' group, where I was managing data from the HighSTEACS trial (an innovative data-enabled trial with over 48,000 participants with suspected acute coronary syndrome) and making it more research-ready for our team and our collaborators.

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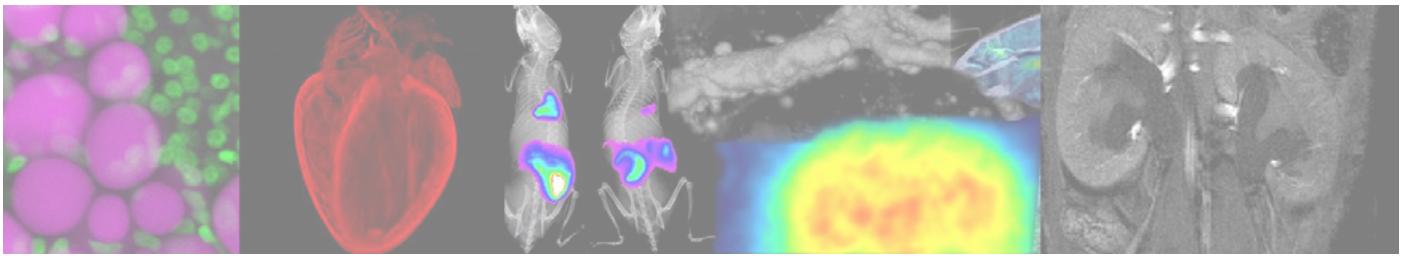
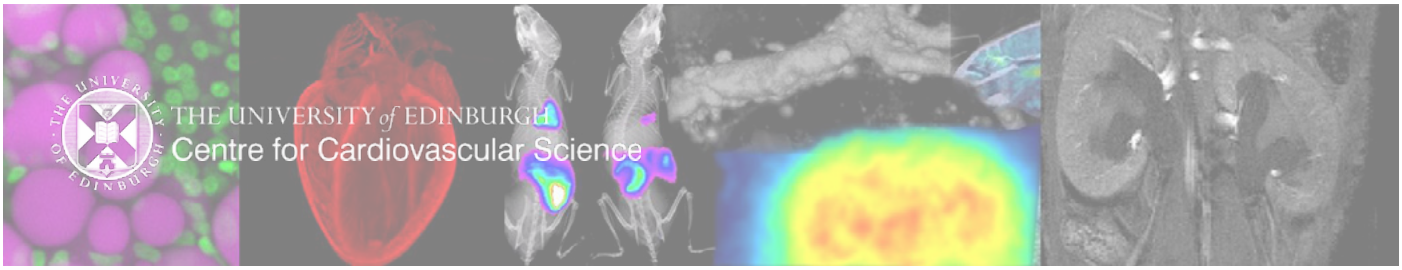


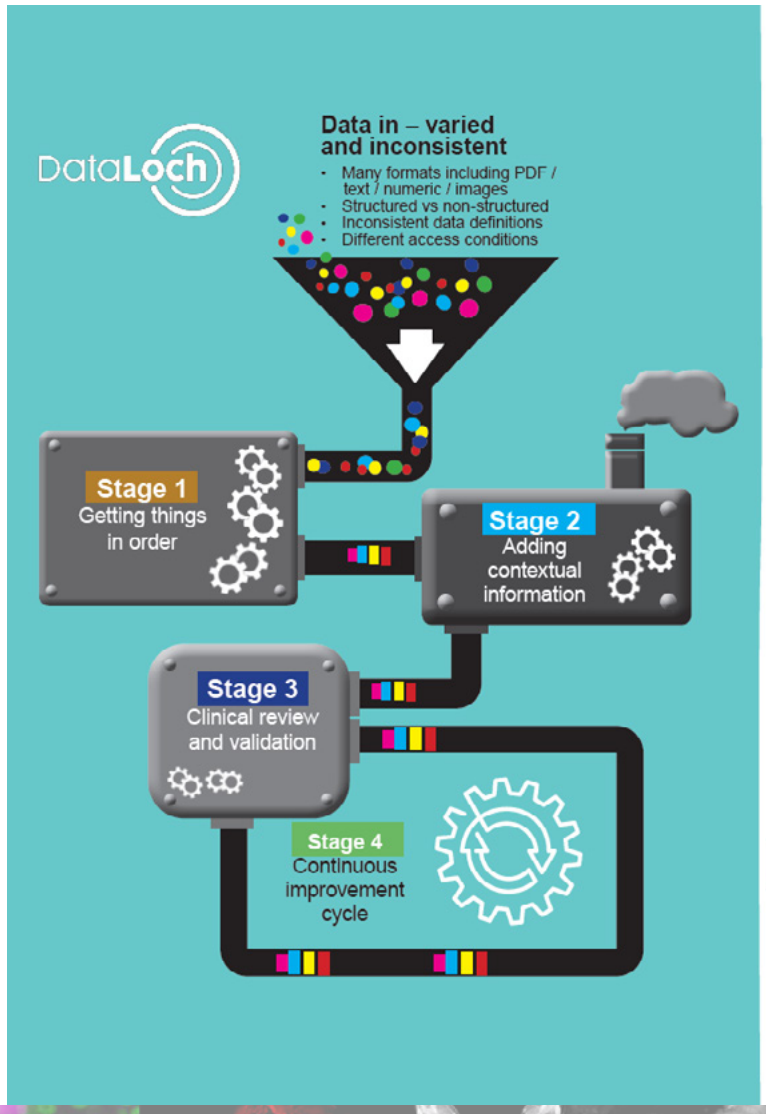


Dr Catherine Stables – Postdoctoral Researcher & Data Manager DataLoch

However, when the pandemic hit, I moved over to work full time on the rapid development and delivery of our Covid19 database. This was a huge amount of work and I'm incredibly proud of our team's achievement (it was a massive collaborative effort with input from many individuals across NHS Lothian and UoE https://www.ed.ac.uk/usher/dataloch/covid-19-collaborative/contributors). So far, we have delivered data to around 30 projects, including both research and service management within NHS Lothian.

Now that we are working on the beta version of the DataLoch offering and have expanded the development team from 3 to around 10 members, my role is one of "product owner" (using our new "scrum agile" terminology). This means that I control the to-do list for the development team and determine what bit gets built next. This involves a lot of engagement with stakeholders, users and developers, and requires a deep understanding of both the data and the processes required to deliver it to projects. Luckily, since I had to build the processes from scratch during the early phase of the pandemic I know them inside out!

DataLoch will help to realise a key goal of the REA3 in using world-class data science to improve the diagnosis, risk stratification and targeting of treatments in patients with cardiovascular and cerebrovascular disease. I am proud to be part of the team that is making that happen.



Stage 1

What does DataLoch do?

We check for:

- Existence: do the data exist and are they accessible?
- Missingness: what proportion of fields with expected data are either incomplete or have no data?
- Consistency: is data similarly represented and/or structured?
- Type: structured/unstructured, if free text (how many characters in each extract), values – report range
- Access conditions: what conditions have we been set in terms of how/when/where data is used?

What is available at this stage as a result?

- Data available for qualified and trained researchers who would be able to work with the data to validate
- Any data documentation of metadata will come from the data source and will not have been validated with DataLoch.
- DataLoch will provide a basic data summary statistics report

Stage 2

What does DataLoch do?

We add

- Contextual details (ie. date/time stamp, document author, document contributors)
- Document data definition, meta data and processing steps

What is available at this stage as a result?

- Basic quality checks complete
- Data available for research work with basic documentation

Stage 3

What does DataLoch do?

We add clinical review and improve

- Credibility: clinical view of believability/credibility of data and therefore its usability
- Validity: data accurately represents reality

What is available at this stage as a result?

- DataLoch may at this stage process the data further by adding derived variables to add research value to data.

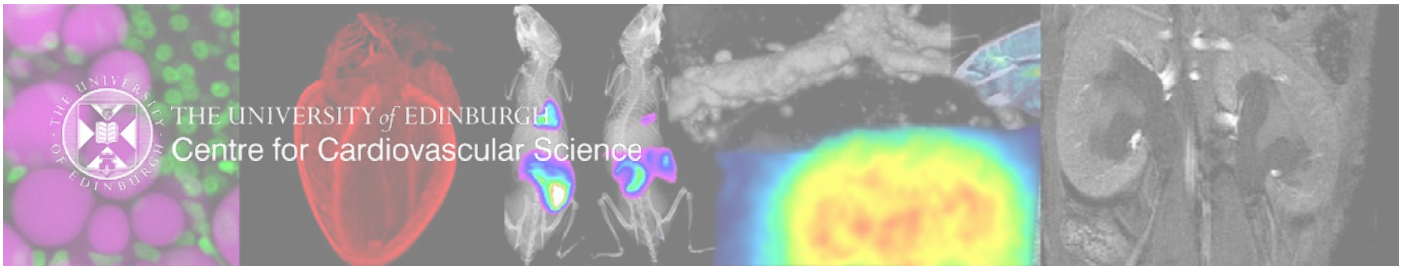
Stage 4

What does DataLoch do?

We take on board feedback from Clinicians and Researchers

- As part of the continuous improvement of data through research access, work is validated and improved with input from researchers and clinicians
- Researchers tell us where there are inaccuracies and improve data as a case of continuous improvement.
- Gold standard validated through clinical experts who have used the data in their service areas.

CONTINUOUS IMPROVEMENT CYCLE



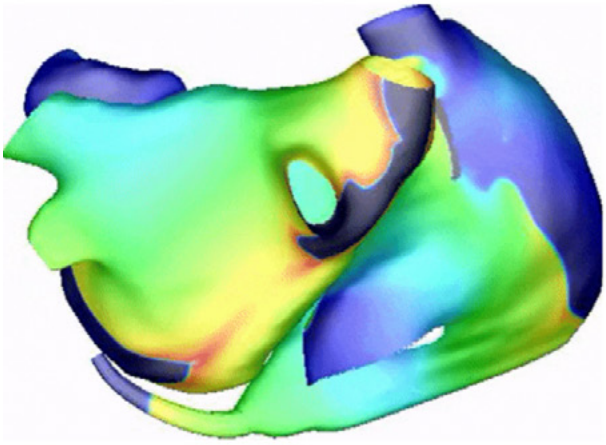
Dr Steven Williams – BHF Intermediate Clinical Research Fellow

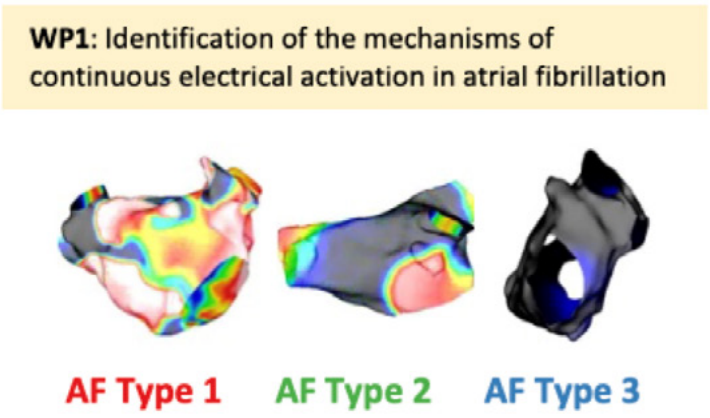
I joined the Centre for Cardiovascular Science in November 2020 and moved with my family from London to Edinburgh in December 2020. I am extremely grateful to the British Heart Foundation Research Excellence Award programme for supporting me during this move which would not have been possible otherwise.

I am a consultant cardiologist and electrophysiologist and am also accredited in cardiac magnetic resonance imaging. My research interest lies at the interface of clinical electrophysiology, imaging sciences and computational modelling. The aim of my Intermediate Fellowship is to use these techniques to investigate the mechanisms of atrial fibrillation in individual patients.

Although recognised for over 100 years, the mechanisms sustaining atrial fibrillation in patients are poorly understood. The multiple wavelet theory proposes that propagation of multiple random wavefronts sustains fibrillation. Other data suggests that re-entry of one or more spiral waves sustains fibrillation. Alternatively, focal sources can repetitively trigger fibrillation. All these mechanisms result in the clinical symptoms of palpitations, breathlessness, lethargy or complications such as heart failure or stroke. The distinction is important however since patients with different mechanisms will respond differently to existing treatments (drugs and ablation). This unrecognised heterogeneity in mechanisms between patients may be a major cause of the current difficulties in treating atrial fibrillation in patients.

In order to classify patients as having a particular mechanistic 'type' of atrial fibrillation, I am using computational modelling where the anatomy of a patient's atria is combined with a cellular model of the cardiac action potential to create realistic simulations of electrical propagation during atrial fibrillation. An example 'still image' from one such simulation is shown below, together with an image shown how simulations could be used to classify atrial fibrillation as dependent on multiple wavelets (Type 1), a single rotor (Type 2) or dependent on focal triggers (Type 3).





Once we have established the technique for classifying atrial fibrillation, the next step is to determine which atrial properties (anatomical or functional) are critical to continued fibrillation. To do this I am using a combination of magnetic resonance imaging and invasive electrical assessment

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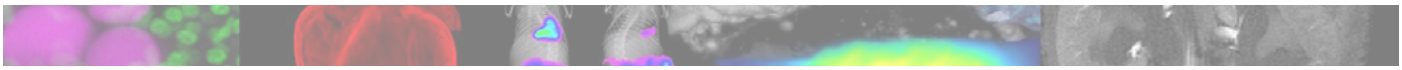
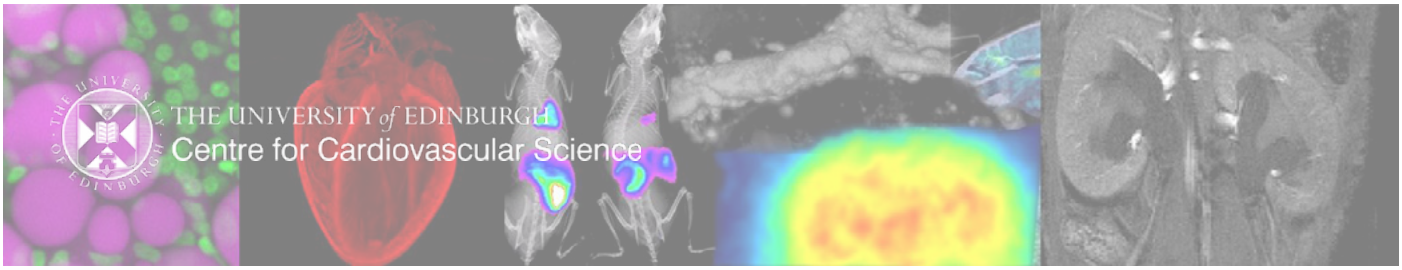
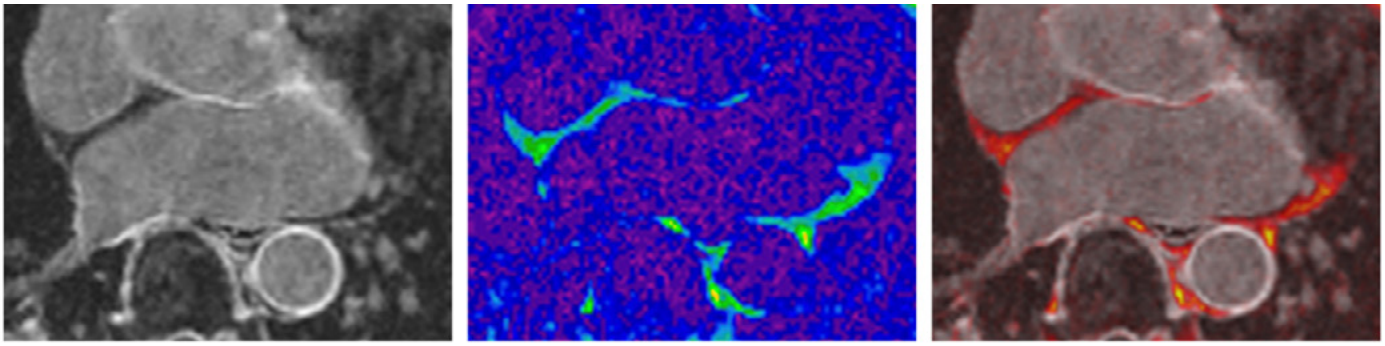




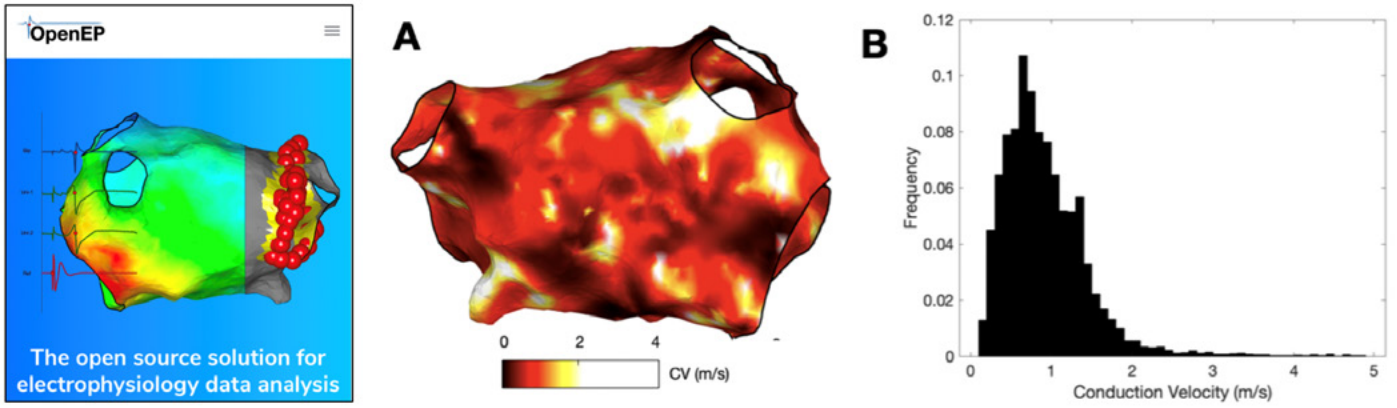
Dr Steven Williams – BHF Intermediate Clinical Research Fellow

My colleagues at King's College London previously developed a technique to perform simultaneous atrial scar and fat imaging which we will use in this project. One of the challenges of imaging the atrium is performing motion correction during the respiratory cycle, and the key to this imaging is a new method of doing this called 'image navigation'. To analysis the electrical data from patients we will use software from an open-source project that I run called 'OpenEP' (https://openep.io). Modern clinical techniques for assessing atrial electrophysiology produce many GB of data, and OpenEP allows this data to be easily manipulated. Some example images from both atrial MRI and OpenEP are shown below. Ultimately, we hope that identifying important atrial properties for the continuation of atrial fibrillation in patients will allow new, patient-specific, treatment targets to be identified.

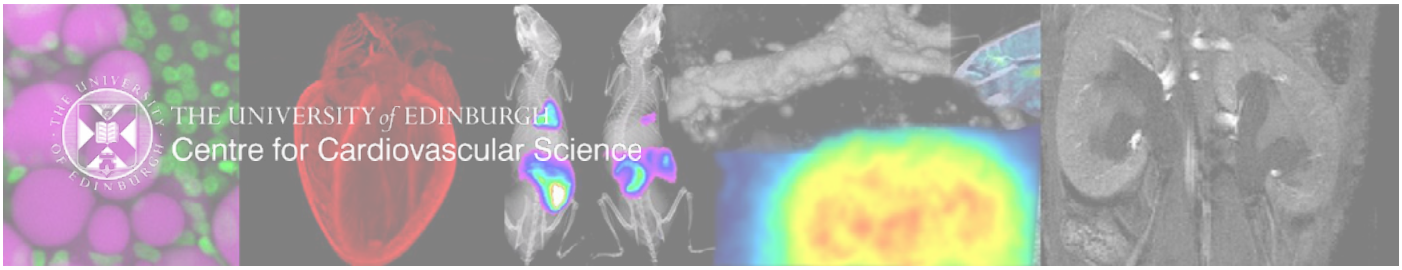
Atrial MRI:



OpenEP (conduction velocity (CV) assessment):



Finally I wanted to say a few words about the move to Edinburgh. Having spent the last 10 years in London it is now very exciting to have moved to a new city with the opportunity to make new contacts and collaborators. The move to Edinburgh has allowed me to already make many wonderful new contacts and there are two infrastructures in Edinburgh (DataLoch and the Large Animal Research Imaging Facility) which I am particularly excited about. Indeed, I had no idea that I would be thinking about atrial fibrillation in athletic horses when I moved in December! For obvious reasons it has not been the easiest time to meet people during the last six months, but I am hoping – like everyone – that that will become easier over the next period. I am always open to new ideas and collaborations so please do get in touch if something here is of interest!



BHF Reflections of Research - Image Competition

BHF's Reflections of Research image competition has returned for 2021. They are looking for entries of your most striking and engaging research images. There is also a new category, "Historical Images" which has been added to help celebrate BHF's 60th Birthday in July 2021!

Further information and how to enter can be found on the BHF website:
https://www.bhf.org.uk/what-we-do/our-research/reflections-of-research

FINALLY.....

Seemingly the 1980s could be considered "retro" Who'd have thought? Gillian Joyce has recently unearthed some handheld gaming consoles originally lost in the vault of time. Since their discovery, these now take up much of her day, trying to outwit ghosts, Charlie Brown and falling blocks: