The University Of Sheffield.

Sheffield Teaching Hospitals NHS
NHS Foundation Trust

Academic Directorate of Diabetes and Endocrinology's

Research and Innovation Strategy for 2018-2021

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Executive Summary

The Academic Directorate of Diabetes and Endocrinology has built a national and international reputation in drug development and performing clinical studies, which have led to important benefits in the management of chronic diseases.

The diabetes and endocrinology research teams successfully deliver around 40 patient focussed clinical research projects at any one time to patients in Sheffield and the surrounding areas. These projects include phase 1 (experimental medicine), 2, 3 and 4 clinical trials in collaboration with pharmaceutical companies, large observational studies e.g. questionnaire based studies, and applied research involving development, refinement and evaluation of complex interventions to encourage more effective self-management.

Vision

The Directorate strives to maintain and strengthen its reputation of performing world-class, patient-focused clinical research to time and target by integrating research activities into daily working practices. This ensures clinical expertise are integrated with current research evidence to optimise health for life of people with diabetes and chronic endocrine conditions.

This document aims to set out the strategic direction of the research activities undertaken by the Academic Directorate of Diabetes and Endocrinology for the next 3 years and is aligned with the Sheffield Clinical Research and Innovation (CRIO) strategy.

Reflection - Achievements & Challenges

A review of the strategic objectives outlined in the previous strategy document (2015-2018) has shown that the research team has excelled in many areas, but continued attention is required in others.

Previous Research Objectives:

1. **To develop new treatments and management strategies that improve the health of patients**
   - The One-Stop Microvascular Screening Service (introduced in 2015) combines eye, foot and kidney screening tests in one appointment. This innovative service has high patient acceptability (92%) and immediate translation to patient benefit (Diabetic Medicine, 2018 in press).
2. **To recruit and retain the best researchers at all career stages**
   - Five former research fellows have successfully gained consultant posts within the department.
   - Clinical staff recruited to the department are required to actively engage with research (job planning).
   - With the ever nearing retirement of key researchers within the Directorate, it is imperative to attract eminent researchers to the team and continue to nurture our junior researchers.
3. **Allow flexible working practices that promote research time wherever possible**
   - Protected research time has been written into job plans and staff members have been released to perform specific research activities with their time backfilled by other staff to allow research activities to be undertaken.
   - Flexible working patterns are also permitted when the service allows, including condensed hours, part-time working and job-sharing.
4. **To support the Directorate's postgraduate research students and recognise their important role in the research conducted in the Directorate**
   - The Directorate continues to attract high calibre post-graduate students who deliver internationally relevant research.
   - Senior researchers support and encourage them to present their finding at local, national and international conferences to enhance their own research standing and promote Sheffield as a centre of research excellence.
   - BMedSci students and international clinical research fellows are supported in a similar manner.
   - The challenge remains, however, to maintain their engagement once they return to their clinical commitments.
5. **To provide training, as appropriate, to ensure a culture of research excellence and integrity**

- 75% of clinical trainees in Diabetes and Endocrinology have or are studying for higher degrees (MD and PhD) compared to the national average of 11%.
- All research staff are trained in Good Clinical Practice with the principles reinforced by interaction with the Directorate Research Coordinator and CRIO staff.
- A mentoring scheme is employed to ensure research clinicians/nurses are appropriately trained.
- Research Coordinator training was introduced by the CRIO following a proposal by our Directorate Research Coordinator to ensure consistency in advice and service across the Trust.

6. To increase the number of participants recruited to portfolio and commercial research studies

- Innovative recruitment strategies including social media campaigns have yielded exceptionally high recruitment to observational, portfolio diabetes studies.
- The Directorate was the highest recruiting directorate within the Trust in 2016/17 and 2017/18.
- A primary care collaboration initiated by the Directorate is now being expanded across other Directorates with the support of the CRIO.
- The Directorate was the first to appoint a Patient Research Ambassador (2015), who has spoken to >1000 diabetes and >500 endocrine patients in clinic waiting areas about research opportunities.

7. To utilise the Diabetes, Endocrinology and Retinal Screening Research Database to open research opportunities to the wider population of Sheffield

- Over the past 5 years the database has grown to include over 3000 patients (predominantly diabetes patients treated in primary care), >2000 of whom have been contacted about participating in research projects.

8. Develop and strengthen interdepartmental, national and international research activity

- The team consciously develops and engages with research opportunities requiring a collaborative approach to delivery to allow the expansion of our research portfolio without the requirement for additional resources.
- The team regularly engage with the Academic Directorate of Cardiology and Cardiothoracic Surgery, the Academic Directorate of Renal Services, and the Academic Unit of Radiology, University of Sheffield (UoS).
- National collaborations include King's College London, Imperial College London, and the Universities of Manchester and Oxford.
- International collaborations have been established with the Medical University of Vienna, Austria and Pharma companies such as Novartis, Ipsen and NovoNordisk.

9. **Develop a stronger web presence for the Directorate's research to ensure colleagues, potential collaborators, funders, service users and the wider public are aware of our research strengths and successes**
   - Despite updating the Directorate webpage hosted by the CRIO, this objective needs further attention.
10. **Promote activities that communicate our research strengths and successes in engagement with the wider public**
    - The Directorate has worked with the Trust and UoS communication teams to publicise the research achievements of the team.
    - Participation in Patient and Public Involvement events such as International Clinical Trials Day, engagement with local charity groups (e.g. Diabetes UK), and the development of promotions materials e.g. webpage, noticeboards and leaflets, have increased awareness locally.
11. **To utilise the Diabetes and Endocrine Lay Advisory Panel to ensure all research undertaken within the Directorate is patient focused**
    - The panel, rebranded as the Lay ADvice for Diabetes and Endocrine Research (LADDER) Panel, has developed into a valuable resource locally and for other centres and is beginning to attract its own funding.

Future Strategy & Initiatives

This document summarises the Directorates research and innovation strategies together with specific objectives for the next three years. We will focus our attention on extending successes of previous years and begin to generate new infrastructure and collaborations. Performance elements of the strategy will be implemented via the Performance Operating Framework annual plans.

Research Objectives:

1. **Strengthen Current Infrastructure** to enhance the effectiveness of the clinical research activity undertaken by the Directorate.
   a. Develop the capability of the Sheffield Clinical Research Facility (CRF) to undertake phase 1 and 2 clinical trials. This work is being undertaken by the UoS with plans for SOPs and support required to be in place in 2018.
   b. Integrate the research training of clinical fellows specialising in Diabetes and Endocrine within the CRF and investigate appropriate appointments to promote clinical research on the CRF.

   c. Extend the Neurosciences Biomedical Research Centre (BRC) bid to include components of Diabetes and Endocrinology at the next round.

2. **Reinforce and Develop Collaborations with Primary Care and Commercial Companies** to maximise the number of research opportunities provided to people in the locality in line with the NIHR and Trust research strategies.
   a. Develop a working model of study delivery with primary care colleagues that is mutually beneficial.
   b. Maximise commercial interests by developing partnerships with companies.

3. **Develop Clinical Registries** to increase our research output at minimal cost**.**
   a. Develop endocrine condition specific registries and promote to industry.
   b. Extend the use of the Diabetes, Endocrinology and Eye Screening Research Database to more complex clinical trials, expand its use from diabetes into endocrinology research, and utilise its potential to perform retrospective data analysis.

4. **Timely Succession Planning** to ensure continued research output.
   a. Recruit and retain the best researchers at all career stages.
   b. Continue to support in-house clinicians in independent research.

5. **Support Research Training** to allow all staff the opportunity to contribute to research and innovation activities.
   a. Clear structure to include training programme director within the Directorate.
   b. Develop regular academic meeting open to all staff.
   c. Away day for all research active staff to share best practice and disseminate findings.

6. **Enhance Communication and Publicity** to engagement with the wider public.
   a. Develop a stronger web presence for the Directorate's research to ensure colleagues, potential collaborators, funders, service users and the wider public are aware of our research strengths and successes.
   b. Disseminate research and innovation opportunities and findings to people in the locality via the Trust's Inspire Research and Innovation E-bulletin, newspapers, webpages and events.
   c. Collate information regarding newspaper/online articles, radio interviews etc to measure the impact of our research promotion.
   d. Present findings at local, national and international platforms.

Impact & Innovation

The Research Office has recently been renamed as the Clinical Research and Innovation Office (CRIO) with Prof Wendy Tindale appointed as Innovation Director. The Directorate will work with Prof Tindale and the CRIO to deliver the Sheffield Teaching Hospital NHS Foundation Trust (STH) Impact and Innovation strategy as follows:

1. The directorate in collaboration with the CRIO & UoS Healthcare Gateway will identify potential impact stories, commercial opportunities, licence deals and R&D contracts for both pharmaceuticals and devices. Start and maintain a list of opportunities reported to the research committee including:
    - The *Withcare+* System and Glucollector online computer application
    - Salivary cortisone as an alternative to synacthen testing
    - One-Stop Microvascular Screening Service
    - Chronocort for treatment of CAH (in Phase 3 on CRF)
    - New native testosterone (DITEST) for hypogonadism (in Phase 2a on CRF)
2. Support impact and innovation through grant pathways such as the Medical Research Council (MRC) Confidence in Concept scheme for which STH and UoS are partners and was awarded £600,000 in January 2018. This route, I4I and D4D all provide support for Impact and Innovation projects such as a new intranasal synacthen test being developed by endocrinology.
3. Support consultancy with industry to build the business network for example consultancy with NovoNordisk and Eli Lilly, major players in Diabetes, and Novartis and HRA Pharma in Endocrinology.
4. Build relationships with key partners including the UoS & Hallam, local industry e.g. Prospect Diagnostics Limited, and key companies such as Diurnal Plc, a spinout from UoS which currently has R&D contracts with the STH & UoS and has just received its first European Market Authorisation for Alkindi, a drug to treat paediatric adrenal insufficiency.

Risks to Delivery

A number of key factors have been identified as areas of risk to delivering the Directorate's research strategy over the next period. These risks will be monitored and appropriate action taken to avoid/minimise negative implications to the delivery of this research strategy.

1. Retirement of senior investigators
2. Failure to obtain grant funding
3. Lack of alignment between strategies of STH and UoS
4. Decreased funding for key infrastructure

Appendix 1 – Resource Summary

Facilities

The Diabetes and Endocrine Centre at the Northern General Hospital allows greater integration of the diabetes research team with the clinical staff. This facility houses a dedicated outpatient nursing team, podiatry rooms, eye screening, a phlebotomy room, consultation spaces and a patient education suite, but there is limited capacity to perform research visits here. As such the NIHR Sheffield Clinical Research Facility (CRF), NGH is often utilised on a room only basis for commercial and NIHR portfolio studies (link-studies) with nursing support provided by three diabetes specialist research nurses. The research team also utilises the contribution of CRF nursing and support staff at NGH for observational studies not requiring diabetes specialist nurse input in order to maximise our research output.

The location of the Diabetes Neuropathy Lab (M Floor, RHH) and the (UoS) MRI scanner (C Floor, RHH) necessitate that some diabetes research is conducted at the Royal Hallamshire Hospital; the NIHR Sheffield CRF, RHH provide outreach nursing support for these studies if required. The majority of the complex endocrine studies are conducted in the NIHR Sheffield CRF, RHH with observational studies conducted either in clinic or on the Endocrine Investigation Unit, B Floor, RHH.

Expertise

The clinical research team within the Directorate comprises four internationally renowned professors, nine consultant physicians/senior lecturers, eleven specialist registrars and international training fellowship registrars (Sri Lanka, China & Brazil), and >10 research active nurses, podiatrists, dietitians and engineers attracted to the unit by and opportunity to develop new techniques and research excellence.

Prof Solomon Tesfaye is the Directorate Research Director and delivered the prestigious Arnold Bloom lecture in 2017 at the Diabetes UK Professionals conference. Prof Simon Heller is the current R&D director for STH, diabetes speciality lead within the Yorkshire and Humber Clinical Research Network (CRN), and holds the respected role of an NIHR Senior Investigator (second term) in recognition of his outstanding contribution to diabetes research. Prof Richard Ross is the Director of Sheffield Health Innovation Centre and a founding Director of two university spin-out companies; Asterion Ltd and Diurnal Group Plc. Prof John Newell-Price is ex-chair of the Joint Speciality Committee for Diabetes and Endocrinology of the Royal College of Physicians, and is the 2018 Chair of the Program Organising Committee for the American Endocrine Society, being the first non-

American chair is a marker of the high esteem held by his international colleagues for his work, and has been elected as Chair (President) of the UK and Ireland Neuroendocrine Tumour Society in 2018.

The Directorate's research programme is supported by a Research Coordinator and two part-time Research Administrators (one at each site) who work with the Directorate Research Director and Directorate Research Executive to develop the directorate's clinical research programme by supporting current projects, improving research delivery systems and maximising research effectiveness.

In September 2013 with the assistance of the Clinical Research & Innovation Office, the Directorate developed the Lay ADvice for Diabetes and Endocrine Research (LADDER) panel. LADDER is comprised of patients, carers and members of the public with an interest in diabetes and/or endocrine conditions and overseen by the Directorate Research Coordinator. The panel is preferentially accessible to the directorate's investigators and service staff, but due to the quality of reviews, the panel is increasingly consulted by researchers from other institutions e.g. University of Leeds and Imperial College London. The panel meet regularly to review research proposals and study documentation to ensure that research carried out within the directorate is patient focused and presented in lay terms where appropriate.

The Directorate was the first within the Trust to appoint a Patient Research Ambassador under the NIHR Patient Research Ambassador Initiative that is aimed at improving how NHS patients can find out about and participate in research. Since July 2015 our PRA has spoken to nearly 1000 diabetes patients and 500 endocrine patients in clinic waiting areas about clinical research in general and specific opportunities within our directorate.

Strengths

The Academic Directorate of Diabetes and Endocrinology has an active Research Executive Committee that meets quarterly to evaluate its performance (using a RAG rating system in line the National Institute for Health Research (NIHR) criteria) and finances, and discuss the future direction of its research.

The Directorate embraces the NIHR Performance in Initiating and Delivering Clinical Research exercise and utilises monthly research group meetings to carefully evaluate the feasibility and delivery of every study it hosts to ensure it can deliver the agreed recruitment target within the specified timeframe. Since the implementation of the NIHR 70-day benchmark to recruit first patients into clinical trials (2013) the Directorate has performed well and achieved this target for all of its measurable clinical trials (100%) exceeding the national target of 80%.

Appendix 2 – Research Themes

Diabetes Research:

1. Hypoglycaemia (Prof Simon Heller, Dr Peter Novodvorsky, Dr Ahmed Iqbal)
2. Complex educational interventions in diabetes (Prof Simon Heller, Dr Jackie Elliott)
3. Economic evaluation of Health and Self-Management In Diabetes (Dr Jackie Elliott)
4. CNS Imaging and diabetes (Prof Solomon Tesfaye, Dr Dinesh Selvarajah, Dr Marni Greig)
5. Peripheral biomarkers of painful diabetic neuropathy (Prof S Tesfaye, Dr D Selvarajah)
6. Biomarkers of diabetic autonomic neuropathy (Prof Solomon Tesfaye, Dr Rajiv Gandhi, Dr Dinesh Selvarajah)
7. Early Detection of Diabetic Peripheral Neuropathy (Prof Solomon Tesfaye, Dr Dinesh Selvarajah)

Endocrine Research:

8. Adrenal (Prof Richard Ross, Prof John Newell-Price, Dr Miguel Debono)
9. Pituitary (Prof Richard Ross, Prof John Newell-Price, Dr Miguel Debono)
10. Endocrine disorders as late effects of childhood cancer survivors (Prof Richard Ross, Dr Jennie Walsh)
11. Neuroendocrine tumours (Prof John Newell-Price, Dr Alia Munir)
12. Parathyroid disease (Prof John Newell-Price, Prof Richard Eastell, Mr Saba)

Diabetes Themes

1. Hypoglycaemia: This research is currently concerned with exploring mechanisms of morbidity and mortality. We have undertaken mechanistic studies which may underlie the rare syndrome of sudden death in young patients with Type 1 diabetes overnight, attributed to hypoglycaemia. We explored the contribution of autonomic neuropathy and sought a simple screening test which may identify individuals worthy of further detailed ECG monitoring. We have also explored the contribution of autonomic neuropathy to hypoglycaemia unawareness as part of our participation in the Hypo-Compass Trial.

As part of an NIHR Biomedical Research Fellowship, Dr Elaine Chow, one of our Academic Clinical Fellows (ACFs) undertook mechanistic studies in collaboration with Dr Paul Sheridan of the Dept. of Cardiology, UoS that revealed an increased risk of cardiac arrhythmias during nocturnal hypoglycaemia in patients with type 2 diabetes at increased cardiovascular risk (Chow, 2014). Dr Novodvorsky, another of our ACFs, undertook a similar study in young and otherwise healthy people with type 1 diabetes which was aimed at gaining insights into aetiology of the 'dead-in-bed' syndrome. This work found increased relative risk of bradycardia during nocturnal hypoglycaemia

and confirmed pro-arrhythmogenic potential of spontaneous hypoglycaemia (Novodvorsky, 2017). In an experimental project involving inhalation of a β2-mimetic salbutamol and subsequent hypoglycaemic clamp in young people with type 1 diabetes, we showed that salbutamol inhalation cannot be used as a non-invasive test to predict electrophysiological responses to hypoglycaemia (Novodvorsky, 2018). We are currently analysing other studies which have explored these and other potential mechanisms (thrombosis/inflammation) during experimental hypoglycaemia involving hypoglycaemic clamps.

Dr Novodvorsky is currently writing a BHF grant for a project that uses modern cardiac MRI techniques to scan people with type 1 diabetes in order to assess subclinical changes in cardiac function behind diabetic cardiomyopathy and to examine possible anatomic and pro-arrhythmogenic substrates behind the 'dead-in-bed' syndrome. This project will involve collaboration with the Department of Infection, Immunity & Cardiovascular Science and the Academic Unit of Radiology MRI research facility at the UoS.

Another Diabetes/Endo Academic Fellow (Dr Ahmed Iqbal) is nearing completion of an MRC clinical fellowship PhD. This collaborative project brings together University Departments of Infection, Immunity & Cardiovascular Science (supervisor Prof Ian Sabroe, co-supervisor Prof Sheila Francis) and Human Metabolism (co-supervisor Prof Simon Heller). The project involves an exploration of the contribution of inflammatory mechanisms in both non-diabetic human subjects (utilising endotoxin challenge and hypoglycaemic clamps) and mouse models.

2. Diabetes Education and other approaches to improving diabetes self-management: We have adapted structured educational approaches developed in Europe in Type 1 diabetes by translating these curricula and testing them successfully in the UK in a randomised controlled trial (RCT). We built on this success by securing an NIHR programme grant to explore factors determining success and 'failure' of these courses in promoting effective diabetes self-management.

We used the programme grant to pilot a trial involving DAFNE and the use of insulin pumps, which led to a £2m NIHR Health Technology Assessment (HTA) grant to lead a 2 year, a multi-centre RCT. The Relative Effectiveness of Pumps over multiple daily injections (MDI) and Structured Education for Type 1 diabetes (REPOSE) trial compared DAFNE plus MDI vs DAFNE plus insulin pumps (CSII) thereby comparing new technology while controlling for the structured training.

We have since secured additional NIHR programme funding to progress research involving self-management in Type 1 diabetes. The DAFNE*plus* project is attempting to improve the DAFNE educational intervention by incorporating emerging theories of behaviour change and technological support to enable more adults with type 1 diabetes to self-manage their diabetes effectively. Led by

Prof Simon Heller, the experienced team includes clinical investigators from Sheffield and Kings, investigators from the School of Health and Related Research (ScHARR), health psychologists from University College, University of Southampton and University of Edinburgh. This project has been running since April 2016 with a national multi-centre clinical trial planned to start in Q4 2018.

Funding from the NIHR Collaboration for Leadership in Applied Health Research and Care (CLAHRC) initiative was used to participate in a clustered RCT of the Diabetes Education for Self Management for Ongoing and Newly Diagnosed (DESMOND) educational intervention for patients with established diabetes led by investigators in Leicester. Unfortunately, it proved impossible to recruit patients in Sheffield to this trial which eventually proceeded only in Leicester.

The funding was also used to improve the care and diabetes self-management of adolescents with Type 1 diabetes. We worked with the Dept. of Psychology, UoS to assess our current approaches and then develop a complex educational intervention to provide both structured skills training (Working with Insulin Carbs, Ketones and Exercise to manage Diabetes (WICKED), 1 week course) and individualised support from key diabetes professionals (nurses and dietitians). We have used additional funding from the Yorkshire and Humber CLAHRC to explore the feasibility of delivering WICKED educational courses to young adults in Leeds and Harrogate prior to an application to HTA for a national multi-centre trial. These pilots have been delivered successfully and we are currently collecting the biomedical data before submitting two papers, one qualitative and one quantitative on this project.

We continue to attract commercial research income by undertaking clinical trials of insulin analogues, new treatments for type 2 diabetes including cardiovascular outcome trials. We also participate in multicentre trials of agents to treat painful peripheral neuropathy.

3. Economic Evaluation of Health and Self-Management in Diabetes: Patient self-management is crucial for the successful control of blood glucose, which largely determines the chances of developing diabetes-related complications. Self-management interventions vary widely, and a method is required for assessing the impact of self-management. Current questionnaires are not able to do this, and so interventions are valued only in terms of biomedical measures and very blunt measures of quality of life, e.g., EQ-5DL.

Through funding obtained from The Health Foundation, the attributes involved in self-management were determined through qualitative research, and subsequently the value of each of these attributes was determined through use of a discrete choice experiment. The attributes themselves have been validated through a further online and postal survey, the results of which are currently being analysed. The final outcome will be a Patient Reported Outcome Measure (PROM), consisting

of 8 questions, which will be able to value self-management in terms of QALYs, and therefore be utilised by NICE etc when valuing self-management interventions.

4. CNS Imaging and diabetes: We previously demonstrated central nervous system involvement in diabetes including spinal cord atrophy and thalamic neuronal dysfunction in diabetic "peripheral" neuropathy, and increased peripheral grey matter loss in the brain in patients with diabetic neuropathy. These studies opened a new area for further research in a condition hitherto considered confined to the peripheral nervous system. In a set of studies funded by the JDRF, we have also shown increased thalamic vascularity and abnormal central pain processing in painful diabetic neuropathy.

Based on these novel findings we secured a 3 year grant from the European Foundation for the Study of Diabetes (EFSD) and Novo Nordisk to perform an observational study to determine: 1) the microvascular perfusion characteristics of the thalamus and other areas of the pain matrix in type 1 diabetic subjects with painful diabetic neuropathy, both at the resting state and in response to acute pain, and 2) the effect of improvement in the intensity of painful symptoms on microvascular perfusion of the thalamus and other areas of the pain matrix in subjects with painful diabetic neuropathy and 3) the effect of improvement in the intensity of painful symptoms on fMRI correlates of painful diabetic neuropathy. The data are currently undergoing extensive analysis (Dr Marni Greig) prior to publication. We a have also obtained another 3 year EFSD Novo Nordisk grant to examine the resting state networks in patients with painful neuropathy.

5. Peripheral biomarkers of painful diabetic neuropathy: Currently, lower-limb skin punch biopsy for Intra Epidermal Nerve Fibre Density (IENFD) measurements is the gold standard to diagnose small fibre diabetic polyneuropathy. A group of IENF known as "peptidergic", expressing neuropeptides, substance P (SP) and calcitonin gene related peptide (CGRP) are considered to be more involved in the mediation of nociception. The development of these fibres is dependent on Nerve Growth Factor (NGF) and hence these fibres are positive for the high affinity NGF receptor, tropomyosin-receptor-kinase A (Trk A). Recent evidence from animal models suggest that peptidergic IENFD level may be a potential biomarker of painful diabetic neuropathy.

Other recent reports, again from clinical and experimental diabetic neuropathy studies, suggest that Capsaicin-sensitive, TRPV1 (transient receptor potential vanilloid-1) receptor activity, Poly ADP-ribose polymerase (PARP) activation, the level of Nitrotyrosine, Growth Associated Protein (GAP) 43 (nerve regeneration marker) levels and increased IENF axonal swellings may be other potential biomarkers of painful diabetic neuropathy. These findings now need confirmation in carefully phenotyped patients with and without painful diabetic neuropathy.

In collaboration with Department of Neurology at Imperial College, London, we have conducted a study in very carefully phenotyped subjects (healthy volunteers, non- neuropathic diabetic and diabetic patients with painful and painless neuropathy) undergoing lower limb skin biopsy for potential molecular biomarkers of neuropathy/painful neuropathy followed by detailed CNS magnetic resonance (MR) imaging. We found IENFD was severely decreased in both neuropathy groups, with no differences for GAP43 and CGRP. However, there was evidence of dermal microvascular proliferation suggesting “painful vaso-neuropathy". Further research is now taking place by taking skin biopsy more proximally in the thigh and in patients with early painful neuropathy looking for earlier changes. The identification of objective biomarkers of painful-DPN is likely to lead to the development of novel, mechanism-based treatments.

6. Biomarkers of diabetic autonomic neuropathy: Autonomic neuropathy is one of the most common and serious complications of diabetes. Early detection of this disorder might lead to a better prognosis for people with diabetes, by the deployment of interventions which will slow or possibly even reverse its progression. However, unlike other microvascular complications, there is currently no simple test or biomarker that would allow for screening large numbers of people. It has also limited the study of the natural history of the disorder and the impact of interventions in large-scale prospective trials. Spectral analysis of Heart Rate Variability (SHRV) is a safe, non-invasive, quick and easy technique that may allow for more widespread assessment and earlier detection of autonomic dysfunction both in the research and clinical setting. It results in a variety of different measures that may act as novel biomarkers for different types and stages of autonomic neuropathy.

We have previously demonstrated that SHRV is a sensitive tool to detect autonomic dysfunction. In addition a model incorporating many of the parameters measured has shown a high level of internal validity at being able to discriminate between different levels of autonomic dysfunction, when compared to current gold standard tests.

The aim of this study is initially to validate this model in an independent population with diabetes. This population will then be followed up prospectively over 6 years, to gain insights the natural history of the process and to determine whether detecting subclinical cardiac autonomic neuropathy (CAN) using this simple technique predicts for the development of clinically significant CAN and other adverse diabetes related outcomes.

7. Early Detection of Diabetic Peripheral Neuropathy: In the UK, diabetic peripheral neuropathy is being diagnosed late and amputations are increasing year-on-year. The feasibility of a one-stop microvascular screening service for the early diagnosis of early DPN, painful DPN and the at-risk diabetic foot was evaluated. Patients with diabetes attending retinal-screening in hospital and community settings had their feet examined by a podiatrist including two validated, state of the art,

objective and quick measures of neuropathy: DPN-Check, a hand-held device that measures sural nerve conduction velocity and amplitude, and Sudoscan that measures sudomotor function. We found that combined, eye, foot and renal screening is feasible, has high uptake, reduces clinic visits, unmasks painful DPN and the at-risk foot. Combined large and small nerve-fiber assessment using non-invasive, quantitative and quick point-of-care devices may be an effective model for the early diagnosis of DPN. We now plan to further pilot work to investigate if subclinical neuropathy is reversible or can be halted by multifactorial risk reduction and if this is the case we will apply for NIHR funding for a multicentre trial to replicate our findings in the one-stop service.

Endocrine Research Themes

8. Adrenal: The thrust here is cortisol excess and deficiency. In cortisol deficiency we have led on developing a UK registry study of congenital adrenal hyperplasia (CAH; http://www.i-cah.org/) launched in 2014. We are developing new endocrine therapies for CAH including Infacort and Chronocort both of which are entering phase 3 studies in EU and USA in 2015 and in which studies the UoS will participate. This work is funded by a 5.6MEuro EU grant and a UoS spinout company Diurnal Ltd which separately raised £6m in 2014 to support clinical studies. Diurnal is also developing a novel oral formulation of testosterone and phase 1 studies are planned to be undertaken as part of the experimental medicine programme in the CRF at UoS and STH starting in June 2015. A separate programme is looking at developing an emergency treatment for adrenal insufficiency through a TSB grant, ACEspray. If successful clinical development will be taken through the UoS and STH CRF in 2016.

In cortisol excess we have established patient cohorts with the common condition of adrenal incidentaloma and low grade of cortisol excess (1-2 % of the population aged 70y) and our recent publication demonstrates an increased mortality. We have performed investigator-led studies using a novel approach to stratify patients to intervention by antagonising cortisol, and this has led to IP filing, and data that has recently been published. We have done this in collaboration with industry, and now plan a major multicentre UK study using this approach to stratify patients to intervention.

We have set up a Chronobiology Research Group and using our knowledge of circadian rhythms, especially that of cortisol, we are looking at the impact on health of shift work in collaboration with the Department of Automatic Control and Systems Engineering of the UoS and ScHARR. An exploratory programme is in development with plans to look at nursing shifts at STH funded by NIHR and EU applications with the potential for major impact on occupational health.

Other research involves the development of novel ways of monitoring the hypothalamopituitaryadrenal axis. We are investigating the use of salivary cortisone to assess the

physiological cortisol rhythm, monitor patients on hydrocortisone replacement and for diagnosis of hypercortisolism. In addition we are also planning to apply for an NIHR RfPB grant to assess the usefulness of salivary cortisone to diagnose adrenal insufficiency as opposed to using a Short Synacthen test.

9. Pituitary: We have developed a fusion technology for making long acting biologicals which underpinned the formation of the UoS spinout company Asterion Ltd. The lead product is a growth hormone antagonist for the treatment of acromegaly. We were successful in being awarded a £2.4M MRC Developmental Pathway Funding Scheme/Developmental Clinical Studies (DPFS/DCS) grant in December 2014 to take our fusion growth hormone antagonist to being phase 1 ready in 3 years. It is then planned to raise money for an experimental medicine programme in patients through a joint programme between the UoS CRF and Asterion Ltd.

We have worked with Novartis global and UK to initiate a multicentre study in Nelson's syndrome, and are working on the set up of a multicentre study in Cushing's. Our basic science work has successfully led to orphan drug designation from the European Medicines Agency (EMA) for our RNA interference approach for Cushing's disease. We have worked closely with Pfzier and Lilly on pituitary, and with NIHR-portfolio, Society of Endocrinology (SFE) funded Acromegaly databases. We are seeking industrial partnerships for our RNA interference and growth hormone studies and will seek to apply to MRC DPFS/Welcome to develop this further.

We have achieved a Medical Education Goods and Services grant from Ipsen Limited to carry out a qualitative research study in patients with acromegaly where we will be investigating quality of life post-surgery.

10. Endocrine disorders as late effects of childhood cancer survivors: This programme of research being undertaken jointly with oncology looking at survivorship and cancer survivors and the late effects of cancer therapy. Sheffield is a leading player with a multi-professional and multi-disciplinary team with impressive research metrics. The research has helped drive local service developments, has strong links with Macmillan and National Cancer Survivorship Initiative (NCSI) and a highly successful biannual conference. Sheffield has led on a CRUK funded (£0.5M) clinical trial looking at testosterone replacement in young male cancer survivors (TRYMS). The clinical trial finishes recruitment in January 2015 and will report outcomes in Q4 2015. The strategy is to increase NIHR and CRUK funding.

11. Neuroendocrine tumours: We have been involved in two commercial studies in this area assessing somatostatin analogues. There is a major pipeline of new industry agents in development. Our strategy will be to ensure that we are well placed to work with industry in this area, specifically

Novartis and Pfzier. Databases are developed for UK and Europe with Prof John Newell-Price on the boards for each.

12. Parathyroid disease: In collaboration with the Department of Chemistry and Imanova Centre of Imaging Sciences, we are developing novel means of parathyroid imaging. We have been successful in gaining UoS and MRC Confidence in Concept (CiC) monies for the initial work and further development will be by targeting the MRC Development Pathway Funding Scheme (DPFS).