

Academic Directorate of Gastroenterology & Hepatology

Research Strategy

2018-2021

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1) Executive Summary

During the 2016/2017 performance review at Sheffield Teaching Hospitals NHS Foundation Trust, Gastroenterology achieved Academic Directorate status. This was achieved through our continual growth and success when delivering research. The Academic Directorate of Gastroenterology and Hepatology is a nationally and internationally recognised premier unit. The directorate has cultivated four main themes and established significant cross cutting themes and important areas of clinical research interest, including inflammatory bowel disease, small bowel endoscopy, coeliac disease, pancreatic exocrine insufficiency, percutaneous endoscopic gastrostomy (PEG) feeding, irritable bowel syndrome and gastrointestinal bleeding. Although the directorates' strengths have been in clinical research there are continued and sustained links with basic science collaborators, most notably through collaboration with Dr Bernard Corfe in the University Department of Oncology and Dr Simon Hufton at the National Institute for Biological Standards and Control (IBD theme), the Bardhan Research and Education Trust and Wellcome Trust (Hugo Penny).

Researchers and clinicians within the department have received the European Rising Star Award in GI research (2010), the UK Nutrition Society Cuthbertson Medal (2011) and the British Society of Gastroenterology Hopkins Endoscopy Research Award (2012). In 2017 Professor Mark McAlindon was also awarded the BSG Hopkins Endoscopy award. This represents a significant achievement as this is the second time a Gastroenterologist from Sheffield Teaching Hospitals NHS FT has won this award; no other centre has ever received this award more than once. The clinical services are integrated with research programmes and have been equally recognised with the Coeliac UK Healthcare Award (2010), the inaugural British Society of Gastroenterology National GI Care awards (2011) and the Medipex Award (2013) for the Sheffield Small Bowel Endoscopy Service. The Department was a winner of the Shire awards for excellence and runner up in the BMJ awards in 2014 for services in gastrointestinal haemorrhage, ambulatory care and community IBD services. The directorate has strong links to the Department of Infection and Immunity and the Sheffield Institute of Gluten-Related Disorders (SIGReD), which involves pioneering work into coeliac disease.

2) Research Themes

Through careful development and cultivation, the directorate has progressed 4 key and fundamental research themes. Each theme has subsequently grown sub-themes to strengthen and enhance the Directorate's overall capacity and capability to conduct high quality research. The infrastructure which has been developed within the directorate ensures we have a raft of senior investigators with a wealth of experience who are supported by an influx of junior researchers who are coming through the ranks. We have ensured those researchers who are new to research act as sub-investigators in NIHR portfolio studies and commercial studies. This model has ensured developing researchers are given prime opportunities to enhance their clinical research skills and also affords strength in depth within the directorate.

2.1 – Coeliac – IBS Theme (Professor David Sanders)

Professor Sanders has continued his delivery of prolific recruitment through portfolio studies. The Pre-endoscopy serological testing for coeliac disease project was the highest recruiting portfolio study in STH over the 2016/2017 financial year. This work has also been supplemented with

commercial work (STH19201 – Pbad) and also through further Point of Care Testing in Pharmacies (STH19172 - 502 recruited). Further strides forward within the directorate have been made through the successful grant application to NIHR EME for a randomised, placebo controlled trial to determine the efficacy and mode of action of ondansetron in the treatment of irritable bowel syndrome with diarrhoea (STH19222) for the value of £2,564,272. The theme continues to submit large scale grants to further develop this key research area, notably two NIHR HTA grants submitted with the exploratory aim of effective detection of adult coeliac disease. The Coeliac – IBS Theme has been strengthened through the work of Clinical Fellows (Michelle Lau, Matt Kurien, Peter Mooney). Further consultant appointments within Gastroenterology has enabled a depth of clinical and research input, most notably in the form of John Hebden and Lam Ching who will support David Sanders in the NIHR EME funded study due to commence in early 2018.

2.2 – Inflammatory Bowel Disease Theme (Professor Alan Lobo)

The IBD Theme is supported by Professors Alan Lobo, Mark McAlindon, Consultant Gastroenterologists Dr Alenka Brooks, Dr Melissa Hale, Dr Josh Chew and Dr Gloria Tun (Research Fellow) –reflecting the importance of interdisciplinary management of people with IBD .

In keeping with scientific and therapeutic developments in this sub-speciality, the IBD theme at STH has been the largest growing area over recent years. Opportunities for portfolio and commercial studies have been grasped by the IBD Team, such that the unit at STH now has the most varied research in Yorkshire and Humber. This has been facilitated by the size of our IBD population and the reputation of the service.

In order to succeed in the delivery of a large set of trials it has been of vital importance to ensure close links between the CRF and clinical services. Currently we have CRF Research Nurse presence in key clinical meetings with consultants and in meetings with IBD Specialist Nurse teams. This integration of research and clinical services has helped with the identification of participants for key trials.

In addition to these commercial and national portfolio studies, the IBD theme now encompasses a wide range of other research sub-themes and projects:

- Biologic therapies:
 - Antibodies to infliximab: in collaboration with the NIBSC at Mill Hill, Dr Gloria Tun, Clinical Fellow is undertaking laboratory work to identify important epitopes on infliximab molecules. This follows establishment of a carefully phenotyped bio-bank of samples from patients with differing clinical outcomes and antibodies to infliximab
 - Predicting treatment failure with Vedolizumab: data currently being collected by an ACF
 - NIHR HTA grant submitted for management of steroid resistant ulcerative colitis

- We are working with a pharmacy database company to utilise national data to understand the budget impact of bio-similar introduction in England.
- Joint medicosurgical management of inflammatory bowel disease in collaboration with Department of Colorectal Surgery (Prof SR Brown and Mr MJ Lee, Clinical Fellow).
 - Decision making and treatment variation in perianal Crohn's disease (see also ENiGMA collaboration below)
 - Information sources and preferences for patients with ulcerative colitis facing surgery
- Service delivery for patients with IBD
 - Prof Lobo is currently co-supervising an M.Res student in SchARR, with Dr Dan Hind to undertake a systematic review of existing guidance on service delivery
 - This topic will be the basis for Prof Lobo's work within the Sheffield CRA.
- Psychological morbidity in young people with IBD (In collaboration with the University Department of Psychology)
 - Dr AJ Brooks is currently writing up her PhD
 - A BMed Sci project is currently running on predicting psychological morbidity in this group.

The STH IBD team also linked with national research initiatives including the ENiGMA perianal Crohn's group – with Prof Lobo on the steering committee of this group and which has already published a series of papers on variation in medical and surgical management and developed a core outcome set for research.

2.3 – Endoscopy Theme (Professor Mark McAlindon)

We have been conducting research into remote gastrointestinal (GI) imaging using small bowel capsule endoscopy for over 10 years, with clinical studies sponsored by Given Imaging (Yoqneam, Israel; now subsidiary of Medtronic, Dublin, Ireland) and Intramedic (Seoul, S Korea). Our focus recently has been on the development of capsules to image the upper GI tract. Current studies include the use of a capsule with imaging devices at either end propelled around the stomach in ingested water using positional changes of the patient, a device which has been released to our unit (one of a handful of centres worldwide) by Medtronic for the purpose of feasibility studies. Further studies will address whether or not external control of capsule movement might enhance diagnostic capability or ease of use. A robot magnet developed in China (Ankon Technologies, Wuhan, China) offers considerably greater control of capsule movement; we are in the process of taking delivery of a system (costing £300K) funded by a grant from Ankon for the purpose of clinical trials. This will be the first such system outside of China. Collaboration with colleagues in the Automated Control and

Systems Engineering Department in the University of Sheffield using a small project grant from Insigneo allowed us to develop simple gastric mapping software which we hope to develop further, with an aim to automate pathology detection by gastric capsule endoscopy in the future. Other collaborations being discussed locally include work with the Medical Physics Department (Dr John Fenner) to study the use of virtual reality in capsule endoscopy reading and with Dr Sule Yildirim (Dept of Computer Science, Gjovik University College, Norway) to develop automatic lesion recognition software. This theme is further supported through the contributions of Reena Sidhu and Melissa Hale.

2.4 – Hepatology Theme (Professor Dermot Gleeson)

Professor Gleeson leads our field and theme of Hepatology. At present Professor Gleeson has two commercial studies in set-up and continues to attract the interest of further commercial studies. The research theme has continued to contribute to the directorates overall portfolio success over recent years with numerous high recruiting portfolio studies proving a success. Professor Gleeson has also been chosen by the UK-AIH Steering group to lead on an application for NIHR funding to develop a disease-specific quality of life measure for autoimmune hepatitis. Success in this will see a national collaboration to develop a tool which is lacking at present for this patient cohort.

3) Research Infrastructure

Directorate members are considered to be key opinion leaders in research in their field. Prof Alan Lobo is a member of the national Inflammatory Bowel Disease Research Group, developing individual studies and a national research strategy, and has leadership roles in two UK collaborative research groups (perianal Crohn's, with the Association of Coloproctology) and Stem Cell transplantation. Professor Gleeson is a nationally recognised opinion leader in Hepatology and his work in Autoimmune Hepatitis has changed international practice. Dr McAlindon and Dr Sidhu are nationally recognised for their clinical work in small bowel endoscopy (Dr Sidhu is the first female doctor to win the British Society of Gastroenterology Hopkins Endoscopy research award 2010). Prof Sanders is an International researcher in the field of coeliac, gluten and small bowel disease. He is the current President of the International Society for the Study of Coeliac Disease.

It is also worth noting that over the last 2 years our research staff who are either active, function in a contributory role, or form part of the infrastructure has risen from 20 to 35. This represents a significant increase and has ensured the directorate has continued to further grow its portfolio of research. The infrastructure which has been developed within the directorate ensures we have a raft of senior investigators with a wealth of experience who are supported by an influx of junior researchers who are coming through the ranks. We have ensured those researchers who are new to research act as sub-investigators in NIHR portfolio studies and commercial studies. This model has ensured developing researchers are given prime opportunities to enhance their clinical research skills and also affords strength in depth within the directorate.

4) Research Landscape and Current Projects

4.1 Coeliac – IBS Theme

4.1.1 Participation in studies:

Through 2018 – 2021 we will aim to continue to develop this theme with regards to participation in NIHR Portfolio studies and also continue the commercial development of this theme. Key studies which we are participating in during this period include:

STH19222 - *TRITON: A randomised, placebo controlled trial to determine the efficacy and mode of action of ondansetron in the treatment of irritable bowel syndrome with diarrhoea.* This is an NIHR-EME funded study which Professor Sanders was a co-applicant on. This study is due to open to recruitment in the first quarter of 2018.

STH19201 - *A double blind, randomized placebo controlled crossover multiple dose study of LYN452 to assess safety, tolerability and efficacy in patients with primary bile acid diarrhea (pBAD).* This is a commercially sponsored study which remains open to recruitment and has been supported by the CRF at the Royal Hallamshire Hospital.

4.1.2 Grant Submissions:

- A large scale NIHR-HTA grant has been submitted entitled '*Reducing biopsies and missed diagnoses in patients with suspected coeliac disease*'. The proposed project intends to recruit up to 5000 participants if successful.

4.2 Inflammatory Bowel Disease Theme

4.2.1 Participation in studies:

STH16287 - Predicting Serious Drug Side Effects in Gastroenterology (PRED4): a Portfolio, multicentre study assessing genetic predisposition to drugs used in IBD. This study has recently been extended for a further 2 years.

STH18546 - PASS: a portfolio-adopted commercially sponsored, post-marketing study of the new biological agent, vedolizumab in inflammatory bowel disease.

STH18547 – SPARE – a portfolio adopted multi-centre study comparing infliximab-thiopurine combination therapy to Thiopurine immunosuppression alone in patients with Crohn's disease.

STH19351 – APRICOT – a portfolio adopted, multi-centre study comparing Combination Antibiotic Therapy (Ciprofloxacin, DoxyCycline and Hydroxychloroquine) with standard therapy (Budesonide) in the treatment Of active Crohn's disease.

STH19356 – BioResource – a large recruiting UK multi-centre portfolio study assessing how genes and environmental factors influence disease and response to therapy.

STH19364 – I-CARE – a large scale, European study assessing Cancer and Serious Infections in IBD Patients in Europe.

STH19563 – An STH sponsored, multi-centre study aiming to develop a risk assessment index to identify young people with Inflammatory Bowel Disease at risk of psychological morbidity

STH19579 – ASTIC-Lite – an NIHR-EME funded project using low intensity stem cell transplantation to treat patients with refractory Crohn’s disease

STH19624 – TRIDENT – a commercially sponsored study assessing an experimental drug in patients with Moderate to Severe Crohn’s disease.

STH19765 – VH-Squared – a commercially sponsored study assessing a new oral anti-TNF treatment in patients with Moderate to Severe Crohn’s disease.

STH19802 – Food QoL – a large recruiting, national portfolio study examining the prevalence and nature of the burden of food-related quality of life in people with IBD

STH19954 – VEST – a portfolio adopted observational study examining real life experiences of patients with IBD who are prescribed Vedolizumab.

4.2.2 Planned participation in future studies:

STH20149 – Profile – a Portfolio adopted study using a molecular biomarker to predict outcomes in patients with Crohn’s disease.

STH20183 – Enterprise – a commercially funded study comparing a new experimental drug with Vedolizumab in patients with Ulcerative Colitis.

STH20263 – Accure Trial – a portfolio adopted trial of therapeutic appendicectomy for the treatment of Ulcerative Colitis

4.2.3 Grants awarded and currently held

£2,564,272 - Lindsay JO (PI), Snowden J, Lobo AJ, Emsley R, Pockley G, Parkes M, Satsangi J, Travis S, Barnet D, Gribben J, Hawkey CJ, Mahida, Y, Moran G, Hind D. Autologous Stem Cell Transplantation In refractory Crohn’s disease - Low Intensity Therapy Evaluation (ASTIC-LITE). Efficacy and Mechanism Evaluation Programme, National Institute for Health Research. 2017

£56,589 - ACP Delphi perianal Crohn’s Disease Fistula group. ‘Optimising management of fistulating perianal Crohn’s’. Bowel Disease Research Foundation of The Association of Coloproctology of Great Britain and Ireland, 2017

£10,000 - Lee MJ, Lobo AJ, Brown SR. Optimisation of multimodal management of fistulating perianal Crohn's disease. Bowel Disease Research Foundation, 2016

4.2.4 Grant Submissions – outcome pending

- 'PoPSTER' – AJ Lobo (PI), £125,000. NIHR-HTA grant submitted to assess current practice and patient preferences for adults with steroid resistant ulcerative colitis. Invitation for stage 2 submission.
- Development and pilot testing of a patient decision aid to better support patients with ulcerative colitis choosing between on-going medical treatment and surgical treatment options: Crohn's and Colitis UK, £120,000. Selected for interview – AJ Lobo (PI), 2.3.18
- Nick Peake and AJ Lobo - Extracellular Vesicles: drivers of disease and biomarkers of progression in IBD: Crohn's and Colitis UK, £ 115,146. Selected for interview
- 'BIONIC' - Best medical therapy or resectiON for Ileocaecal Crohn's (BIONIC) SR Brown and AJ Lobo (Joint PIs)
- A commercial grant submitted to Pfizer to assess the effect of antibodies to infliximab on the pharmacokinetic profile of infliximab

4.3 Endoscopy Theme

4.3.1 Participation in studies

STH19785 – a portfolio adopted device trial using a new colonoscopic cuff (Endocuff Vision®) with the aim of improving visualisation of colonic mucosa by flattening colonic folds and manipulating them away from the field of forward view.

STH20061 – An STH sponsored, international clinical trial exploring whether bowel preparation (either as a single or divided dose) produces better cleansing and diagnostic yield than no preparation at all in small bowel capsule endoscopy

STH19107 – An STH sponsored clinical trial to compare magnetically assisted capsule endoscopy against conventional upper gastrointestinal endoscopy in upper GI bleeding

STH19595 – An STH sponsored device trial to assess the acceptability and tolerability of magnetic assisted capsule endoscopy compared to gastroscopy in patients with dyspepsia.

STH19998 – An STH sponsored, commercially funded study assessing the severity and quantification of villous atrophy on video capsule endoscopy in patients with coeliac disease using computer imaging processing algorithms.

4.4 Hepatology Theme

4.4.1 Participation in studies

STH14924 – a portfolio adopted study investigating genetic and molecular pathogenesis of primary biliary cirrhosis. This study is now being supported by the CRF in order to boost recruitment.

STH18866 – a portfolio study aiming to assess whether detailed phenotype characterisation can improve treatment for people with autoimmune hepatitis.

STH19737 – a commercially sponsored assessing the efficacy of GSK2330672 for the treatment of pruritus in patients with primary biliary cholangitis.

4.4.2 Grant Submissions

As discussed above, Professor Gleeson has also been chosen by the UK-AIH Steering group to lead on an application for NIHR funding to develop a disease-specific quality of life measure for autoimmune hepatitis. Success in this will see a national collaboration to develop a tool which is lacking at present for this patient cohort

5) Research Forums

Our research forums allow for networking and dissemination of leading edge research to Gastroenterologists from across the UK. The forums we devise and deliver are supported by commercial sponsors who also deliver bespoke sessions and tutorials on the latest advancements within the medical speciality. The forums actively provide the opportunity for patients, researchers, clinicians, academics and industry liaisons to discuss and build research awareness and capability.

The Sheffield Gastroenterology Symposium – Professor David Sanders

This is the largest regional Gut meeting in the UK with more than 300 delegates. The delegate feedback suggests 95% good to excellent rating. The meeting showcases Sheffield Gastroenterology and attracts delegates from a 70-100 mile radius.

National Dietetic Gastroenterology Symposium, Sheffield

This was a unique standalone meeting for dieticians. The meeting attracted more than 200 dieticians, making it the largest dietetic UK meeting. The meeting showcased one of the strengths of the department which is small bowel and nutrition.

6) Patient and Public Involvement

Patients are at the heart of the service and are regularly involved in the development of our services. Our research themes incorporate patient and public involvement through White Rose grants with the School of Health and Related Research (University of Sheffield). We have a patient meeting annually in March at the St Mary's Church. In addition to this through collaboration with Sheffield CTRU we will also be holding PPI's groups focussed on the NIHR Grant submitted project 'POPSTER'.

7) Barriers to achievement

Consistent with many other research active directorates there are barriers which exist when striving for research excellence. The Academic Directorate of Gastroenterology continually strives to address, evaluate and surpass these in order to achieve the aims and objectives set each year. Such barriers which have been noted and addressed include:

7.1 Principal Investigator time:

Due to widespread clinical pressure we experienced difficulty with factoring research time for our PI's in the directorate. In order to address this issue we have developed plans whereby our investigators have managed to use generated funding through grants, CRN allocations and commercial work to fund research PA's. This technique has led to our directorates' expansive portfolio of work and ensured we are delivering to our studies.

7.2 Research Coordination:

We currently have a directorate research coordinator fixed within the Clinical Research and Innovation Office who is able to support the capture of studies and the set-up. This has relieved administrative burden on the directorate and ensured investigators are in a position to deliver research both as lead and as a participating site. This administrative support has also proven useful in our attempts to further develop our commercial portfolio of research and NIHR Portfolio range of studies.

7.3 Research Nurse Support:

We have developed an exemplary and effective relationship with the CRF which has contributed to our recent success when delivering studies. Our CRF Research Nurse regularly attends meetings with Consultants and Clinical Nurse Specialists which has ensured that research has become embedded within our clinical services. This process has subsequently ensured participants have been picked up in our more complex studies. We do feel it is vital for further support to be positioned within the CRF for Gastroenterology studies. Regionally and Nationally Sheffield Teaching Hospitals NHS FT competes with other large centres but we have significant less research nurse support than our counterparts across the UK.

7.4 UK Research

It can be argued that some of our strong areas of research are not a top priority for government and grant funding bodies, continued effort, drive and focus is maintained within the directorate to counter this to some success (for example co-applicant success on ASTIC Lite and TRITON – NIHR EME).

8) Research Aims and Objectives

The Academic Directorate of Gastroenterology has developed a robust infrastructure whereby Clinical Fellows and Consultant Gastroenterologists & Hepatologist provide key support, expertise and knowledge for research growth. The directorate has gained research strength from delivering

basic science through to complex clinical trials by utilizing this model which is supported by our Research Lead.

8.1 Aims

- Current research and academic staffing: 1 Clinical Lecturer, 5 MD fellows, 1 Post CCT fellow, 1 International Fellow, 1 ACF & 1 BmedSci
- Prof Sanders application to Sheffield Clinical Research Academy (SCHARR) was successful and since that time a further successful application by Prof Lobo. The subsequent aim of Prof Lobo's application is to increase significant grant capture
- Creation of 2 Senior lecturers
- 4th Personal Chair has been awarded
- HTA application ~400K – submissions are on-going with focus on coeliac patient group which is under represented within clinical research
- Portfolio Badged Endoscopy study n=2000 completed. Develop a significant grant to gain portfolio adoption for an endoscopy study. This is key as in the UK there is a dearth of endoscopy research.
- Continued fellows from DSS research/agency funding providing Clinical Service and development of research projects
- NIHR Professorship or Senior Fellow
- Successful Creation and unification of both an Academic Directorate & University Department of Gastroenterology
- A continuing and consistent aim with the directorate relates to the on-going development of our infrastructure. The tactic employed whereby our senior investigators work closely with more junior investigators in order to develop their skills will continue. As such we will continue to encourage our junior investigators to act as sub-investigators and co-investigators on portfolio and commercial studies before taking over leadership as Principal Investigators.
- Continue to succeed in meeting NIHR Metrics for recruitment to time and target and 70 day target. In order to achieve this we will ensure:
 - 1) All recruitment targets are set in the same challenging yet realistic manner.
 - 2) All consultants are aware of recruiting studies and can assist in the identification of patients. Current practice is for this to be discussed in regular meetings with PI teams and through dissemination of communications via the Directorate Coordinator.
 - 3) Our clinics are staffed by Research Nurses/Clinical Trials Assistants from the CRF.

4) We maintain strong communication links with Clinical Services and Endoscopy team to ensure patients are identified for research before commencing standard of care treatment and routine investigations (colonoscopy)

5) Studies and targets are regularly reviewed in our R&T and also in our IBD Speciality meeting (where applicable)

6) Continue to take advantage of commercial research opportunities in order to generate further research income. This has been an on-going method adopted which has seen our researchers successfully deliver industry studies and use the income generated to further develop our infrastructure and capacity. Commercial research is integral to both our development and the treatment options we can provide our patients.

To summarise, our focus and aims are geared directly towards using our strength in depth and our established and developing infrastructure to deliver leading edge research to our clinical population. We aim to deliver on NIHR performance metrics such as RTT & 70 day PPFV. The Directorate strives to be a leading hub in Yorkshire and Humber and to compete both nationally and internationally to retain our status as a recognised premier unit. Key to this is enhancing our research income through commercial and portfolio studies and reinvesting this responsibly to ensure the directorate continues to attract, develop and retain the best research professionals. Furthermore, a key aspiration is to contribute to the on-going improvement to healthcare whilst increasing the opportunities for our patients to benefit from research. Ultimately and fundamentally we aim to deliver research which is directly for the benefit of our clinical population, we see continued growth as a directorate vital in achieving this.