**Mental Health and Clinical Neuroscience**

**Project 1-** Personalisation of transcranial direct current stimulation (tDCS) for the treatment of tinnitus [Magdalena.Sereda@nottingham.ac.uk](mailto:Magdalena.Sereda@nottingham.ac.uk)

**Rationale:**

Tinnitus is the perception or sensation of sound in the absence of an external physical stimulus, thought to affect around 15% of adults in the UK. The impact of tinnitus in an individual can range from minimal to extremely invasive. About 20% of people with tinnitus experience symptoms that negatively affect their quality of life including sleep disturbances, difficulties with hearing and concentration, social isolation, anxiety, depression, irritation or stress. Most common clinical management strategies for tinnitus include education and advice combined with some form of sound therapy. The effects of these management options are however variable. Currently the exact aetiology of tinnitus is unknown; however maladaptive plasticity due to sensorineural hearing loss is thought to play a big role. Neuroimaging studies have pointed to overactivation or excessive spontaneous activity within the central auditory cortex (1). Furthermore, electrophysiological techniques have confirmed the frontal cortex’s role tinnitus through dysfunctional top-down modulation (2).

A new treatment approach for tinnitus - transcranial Direct Current Stimulation (tDCS) is a non-invasive neurostimulation technique in which small currents (1-2mA’s) are delivered to the brain, thereby depolarising or hyperpolarising neurons within the desired region of cortex. tDCS is a non-invasive and easy to apply tool, delivered by applying two surface electrodes to a patient’s head. It has previously been used as a treatment for depression, stroke rehabilitation and cognitive enhancement. Some studies pointed to the potential benefit of tDCS in tinnitus patients, however the results are variable and only proportion of patients seem to benefit from the stimulation (3,4,5).

Typically, tDCS studies use a fixed-dose of tDCS approach, where all patients receive the same stimulation protocol (3,4,5). However, such approach does not account for inter-individual differences in anatomy, such as skull thickness (5,6) and gyrification (cortical folding) patterns. Those anatomical differences can result in variable amount of current reaching the brain in individual participants, with some studies showing that electric field intensity at the cortical target site can vary by more than 100% across individuals (6,7,8). This can lead to variable therapeutic effect for tinnitus. However, individualised stimulation approach has not yet been investigated in individuals with tinnitus.

**Aims and methodology:**

The aim of the project is to develop an individualised tDCS protocol for people with tinnitus and explore acceptability, feasibility and efficacy of individualised stimulation for tinnitus.

In particular the project will involve:

1. Literature review of methods and stimulation parameters in current modelling studies for tDCS.
2. Application of current modelling to existing MRI brain scans using software package for the Stimulation of Non-invasive Brain Stimulation (SimNIBS) and exploring the association between the amount of current reaching the brain and changes in tinnitus loudness before-after the tDCS stimulation in tinnitus patients.
3. Feasibility, safety and acceptability of personalised stimulation in healthy volunteers, including the effectiveness of blinding (participants and researchers) and any adverse effects during the individualised active and sham stimulation.
4. Effects of personalised stimulation in tinnitus patients (pilot study). The effects of personalised tDCS on tinnitus symptom severity, tinnitus loudness, depression, anxiety, and neurophysiological changes in the brain, as measured using MEG (specifically, changes in oscillatory power in different frequency bands and changes in functional connectivity between and within frequency bands) will be investigated and compared with the conventional fixed-dose stimulation and/or sham stimulation.

This will be the first study to investigate the feasibility and efficacy of the individualised tDCS for tinnitus.

**Project 2-** Designing an online intervention to improve GPs knowledge of tic disorders: an exploratory investigation and feasibility randomised control trial [Charlotte.hall@nottingham.ac.uk](mailto:Charlotte.hall@nottingham.ac.uk)

Tic disorders, including Tourette syndrome, are common conditions. Tics are sudden involuntary movements or vocalisations that can lead to significant impairment, including poor mental and physical health and reduced educational attainment. If untreated, tic-related impairments continue into adulthood, increasing the risk of poor long-term outcomes. Early intervention improves outcomes (1). However, only about 12% of Children and young people (CYP) with tics receive treatment. In England, CYP seeking support for tics must first attend an appointment with a General Practitioner (GP) in National Health Service (NHS) primary care, where they may be referred to a specialist service for treatment. The GP is therefore a “gatekeeper” to specialist care/treatment.

Families report being extremely dissatisfied with their GPs tic knowledge and awareness and having to fight for their specialist referral (2,3). A quote highlighting the impact of tics:

“*…our daughter was acting like a chicken, kissing everything, swearing, throwing herself on the floor…it’s very scary then to be pushed away by the doctors. Our lives changed forever that day.*” (parent quote)

GPs also indicate that they feel under-equipped to identify tics or appropriate referral pathways. Thus, there is a need to develop an easy-to-use resource to improve GPs knowledge of tics. We have conducted a similar PhD developing and testing an intervention to improve GPs knowledge of ADHD. The project was extremely successful, experiencing no issues with recruitment, and the intervention is now hosted on the Royal College of GPs website. The project resulted in several academic publications and real-world national and international impact. We will follow this tried-and-tested format for this proposal.

**Aims**

The overarching aim of this project is to raise GPs’ awareness and knowledge of tics through a targeted online training resource. This will be achieved through three sub-aims:

1. Investigate gaps and barriers in GPs’ understanding of tic disorders.
2. Develop an online psycho-education intervention tailored to GPs.
3. Evaluate the acceptability and feasibility of the intervention.

**Methodology**

This project involves three stages, using mixed methodologies and co-production. Each stage forms a thesis chapter. The student will be supported to publish as an iterative process. The project forms part of a larger programme of research led by Groom and Hall, and which is supported by a steering group including patients and clinical experts in tics, who will provide expert guidance.

*Stage 1*:

1. A systematic review will identify barriers and facilitators to GPs understanding of tics and care pathways in the existing literature. The findings will inform questions for part B.
2. Qualitative interviews with GP trainees, GPs, service providers/managers and patients will be conducted to investigate barriers in GPs’ understanding of tics. We will recruit participants via NHS healthcare services and through our existing contacts (including third-sector organisations). Interviews will be online to minimise cost/time and increase national participation. We will purposefully sample from ethnic minority and under-served groups. The interviews will be transcribed and thematically analysed.

*Stage 2:*

Based on knowledge gained from stage 1 and our prior experience in developing a similar intervention (for ADHD), in the second stage the student will develop a brief online psychoeducation intervention for GPs. This intervention will be co-produced with GPs and patients through a series of workshops. We will link with national charity ‘Tourette’s Action’ and our existing contacts to develop/host the intervention.

A usability study will be conducted with 10 GPs to assess the accessibility of the intervention. GPs will provide feedback on technical errors, learnability, and satisfaction via an online questionnaire. Any changes to the intervention will be implemented before Stage 3.

*Stage 3:*

A pilot/feasibility Randomised Control Trial (RCT) will be conducted.

Design

***Participants****:* approximatelyn=80 GPs

***Design****:* parallel-group, single-blind feasibility/pilot RCT

***Setting*:** Participant recruitment will be via the NHS, facilitated by the Clinical Research Networks in England.

***Interventions****:* participants will be randomised to one of two arms: one will receive the online psychoeducation (intervention group) and the other an online video without tic education materials (control group).

***Follow-up****:* participants will be followed-up immediately after completing the intervention and two-weeks later.

***Measures***: Baseline and follow-up online questionnaires of tic knowledge, confidence in identifying tics, and awareness of tics. Additional measures of acceptability/feasibility will be recorded. A sub-sample of participants will be invited to an interview to gain further feedback.

The quantitative findings will be analysed descriptively, with inferential statistics where appropriate. Qualitative findings will be thematically analysed.

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**Translation Medicine**

**Project 3**- Immune characterization to discover new biomarkers for diagnosis of drug-induced liver injury (DILI) in patients. [Jane.grove@nottingham.ac.uk](mailto:Jane.grove@nottingham.ac.uk)

**Rationale:**

***The problem:***

Drug-induced liver injury (DILI) is an unpredictable, serious adverse effect occurring occasionally in response to taking common medications or dietary supplements. Although rare, its severity and potential consequences such as liver failure and death make it an important issue during drug-development as well as in clinical practice. However, it can be initially indistinguishable from other liver diseases and it is impossible to predict whether an individual will develop severe effects [1]. Also, when patients develop liver injury they are advised to stop taking all their medications, as one may be the cause, but this means their original illness may worsen while not being treated. This is a particular problem if the drugs are needed to treat urgent life threatening conditions e.g. infections or cancer.

***What is needed:***

Tests to quickly identify when drugs are causing liver injury, and predict whether this is likely to develop into a severe effect, are needed so that individuals get appropriate advice and treatments. Determining how drugs and their metabolites interact with the immune system and how this leads to liver injury in certain patients will inform better drug design.

***Progress so far:***

Previous studies have attempted to identify possible non-invasive diagnostic biomarkers [2], but further investigation is necessary to establish tests enabling the stratification of patients for appropriate care. Our initial experiments using mass cytometry and immune profiling have identified some cell types that may be potential markers of liver injury due to cancer immunotherapy drugs [3]; immune cell signatures associated with other causes of liver injury have not yet been explored.

**Aims and Methodology**:

The studentship will build on current projects (e.g. [www.TransBioLine.com](http://www.TransBioLine.com)), which have highlighted the potential of molecular biomarkers (microRNA, bile acids, cytokines) and circulating immune cell signatures, to establish specific indicators of DILI.

The goal is to identify new non-invasive biomarkers that can be used in clinical practice to improve patient care and for monitoring participants in drug trials.

The project will involve 3 aspects:

1. **Exploration of the molecular mechanisms and links between tissue and blood biomarkers of liver injury.**

First, immune cell signatures associated with specific disease types will be identified by data mining using bioinformatics. This will utilise a mass cytometry dataset of immune markers in blood samples from >100 individuals, including healthy volunteers, patients with drug-induced liver injury and control groups taking medications or with autoimmune hepatitis [3,4]. Cell profiles from mass cytometry will also be compared to linked bulk and single-cell RNA sequencing data generated by Pfizer collaborators.

The mass cytometry and RNAseq findings will be validated by targeted flow cytometryexperimentsusing stored blood samples and isolated blood monocytes available from on-going research projects (<https://proeurodilinet.eu/about-us>; and ClinicalTrials.gov NCT04476563). By evaluating peripheral cell subtypes and cytokines in conjunction with clinical information available, putative mechanistic models underlying drug-induced liver injury can be developed.

Next, potential mechanisms of liver damage will be explored in liver tissue samples from hospital biobank archives using immunofluorescence microscopy techniques. This will characterise immune cell subsets in liver tissue associated with disease to establish mechanistic links between circulating immune cell populations and the liver populations.

**b) Determination of circulating molecular biomarkers using multiplex immuno-assays.** Following evaluation of the hypotheses generated from the mechanistic exploration, candidate molecular biomarkers linked to the disease pathways will be selected. Immuno-assays will be used to quantify protein biomarkers in our patient sample repository, building upon our ongoing collaboration with Pfizer. This will assess the potential of circulating molecules as a non-invasive diagnostic test to distinguish DILI from other liver diseases, or to stratify patients for specific clinical care pathways.

1. **Design and delivery of a patient study to investigate the association between symptoms and disease biomarkers.**

In partnership with Nottingham University Hospitals NHS Trust and other stakeholders, an observational study will be developed to understand how rare genetic variants in cellular transporters and molecular biomarkers (e.g. hyocholic acid and IL-31) are linked to symptoms such as itching, which is a key determinant of quality of life in patients with drug-induced liver injury [5]. Alongside recruitment of patients to current research studies in the NIHR Nottingham Biomedical Research Centre, a new study will be set-up within the multidisciplinary team entailing consultation with patient advisors, project design, and ethical application. Enrolled patients will be monitored with blood sampling and regular questionnaires about symptoms, treatments and quality of life. Candidate biomarkers will be determined and associations with disease features explored to provide additional information about disease mechanisms. Also, since new treatments are becoming available for some symptoms, it is expected that this study could provide the basis for future clinical trials to improve clinical care.

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[5] Fontana RJ: Am J Gastroenterol ,2015:110(10):1450-9.

**Project 4**- Identification of cell persistence mechanisms after chemotherapy in colorectal cancer patients. [Paloma.ordonezmoran@nottingham.ac.uk](mailto:Paloma.ordonezmoran@nottingham.ac.uk)

Team

It is an inter-disciplinary project lead by an early-career biochemist and a senior bioengineer. The team is also composed of Dr. Austin Acheson (colorectal cancer surgeon at Queen’s Medical Centre) and two Senior gastrointestinal pathologists Dr. William Dalleywater and Dr. Abhik Mukherjee (School of Medicine, University of Nottingham, Queen’s Medical Centre). Finally, Dr. Carmen Pin (AstraZeneca, Cambridge) expert in Drug discovery & Pharmacology will be involved in the study of drugs effect in normal and cancer cells.

Rationale

Cancer is the second leading cause of death globally. At advanced stages of disease, conventional therapies are ineffective due to a small population of **drug-resistant cells** that can reform the tumour after anti-cancer treatment. Indeed, the spread of these cells to distant organs accounts for over 90% of patient deaths. The cells responsible to form metastasis are a sub-population of cancer cells with stem cell properties (self-renewal and potential of multiple differentiation) that are not being totally eliminated by current therapies. For metastatic colorectal cancer, the antimetabolite 5-fluorouracil has been the backbone of treatments for many years with addition of leucovorin in the 1990s. The past two decades have seen improvements in median survival from 10–14 months to only 16–23 months with addition of oxaliplatin or irinotecan. Since 2004, targeted therapies in combination with standard chemotherapies have provided more treatment options and better results. However, these treatments are still not able to decrease substantially the number of deaths of colorectal cancer patients and one of the reasons is that we did not have very good in vivo or in vitro models for testing drug-resistant cancer cells mechanisms.

In the last years, the development of in vitro 3D organoids to study these **drug-resistant cells** has been a major breakthrough in cancer research (Ootani et al., 2009; Sato et al., 2009). The Ordóñez-Morán’s lab has extensively used 3D patient derived colorectal cancer organoids to study tumour progression and drug response (Ordóñez-Morán et al., 2015, Gjorevski et al., 2016). Still this new technology can be improved as currently relies on heterogenous animal-derives matrices which cannot reproduce the complexity of the tumour microenvironment.

Aims and Hypothesis

It is evident that more research is urgently needed for patients that present advanced colon cancer. We propose here to study the cancer stem cells or drug-resistant cells that are responsible of tumour re-growth. So, the main objective of this PhD studentship is to understand which **mechanisms are behind drug-resistant cells behaviour** by using patient-derived organoids surrounded by a modified synthetic niche/scaffold that acts as a more realistic tumour microenvironment. To overcome limitations of previous approaches that have not mimic well the tumour niche, we will optimize and integrate a 3D matrix technology to engineer 3D in vitro models that aim to identify what features of the tumour microenvironment are critical to affect (i.e., enhance or reduce) cancer drug resistance. We aim to validate our 3D in vitro cancer cell methodology and transfer these skills to study mechanism of persistent cells after treatment with anticancer compounds. We hypothesize that this model would be possible to translate into the clinic to improve clinical drug targeting studies.

Research plan

The project will be composed of three main aspects:

1. We will optimize an in vitro 3D culture system that would enable recreation of key features of the complexity of colorectal cancer TME and study its effectiveness to drug responses.
2. We will treat the 3D organoids established from fresh samples (healthy and cancer) with different available compounds that are currently being used in the clinics. In order to understand the pathways involved, we will perform RNA-seq analysis of cells surviving the treatment and control cells. We will test stemness and drug-resistant parameters. Our ethics approval is: 17/EM/0126.
3. We will model drug sensitivity in healthy and tumoral cells The results obtained will be quantified and analyzed by the AstraZeneca team. They will develop an approach to model the spatio-temporal stem cell dynamics by an individual based computational model.

Methodology

The student will use **3D organoid technology, bioinformatics, and molecular biology approaches. In addition, the student will be trained in bioengineering**. He/she will use a culture model that supports 3D human organoids derived from patient biopsies by using a versatile self-assembling platform where peptide amphiphiles (PAs) can organize key ECM components into nanofibrous matrixes (PA-ECM) cells (Hedegaard et al., 2019, Inostroza-Brito et al., 2015, Capito et al., 2008). Using this matrix, the cells maintain disease specific features as stem cell properties. The use of this synthetic niche enables rapid and simple fabrication that resembles features of the complex in vivo environment, which is known to be critical in cancer behaviour and its response to drugs. Therefore, the capacity to implement a controlled environment within cancer cell studies would be an important parameter required to properly study drug responses of cancer cells. The main advantages of our method compared to others is that we a) incorporate structural ECM components as structural elements of our hydrogel, b) the physical properties can be tailored by tuning PA-ECM affinity, and c) the chemical composition can also be tailored to identify optimum conditions. In addition, with this platform, we can substitute a poorly defined natural compound obtained from a mouse source required for most of the current 3D in vitro organoid culture and also has the capacity to tune these hydrogels to enable the culture of three types of cells simultaneously.

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**Injury, Recovery & Inflammation Sciences (IRIS)**

**Project 5**- Exploring the utility of OMICS to predict physiological responses to exercise-for-health interventions. [Philip.atherton@nottingham.ac.uk](mailto:Philip.atherton@nottingham.ac.uk)

**Rationale**

OMICS, encompassing interrogation of biological levels of DNA, RNA, protein, and metabolites is at the fore of biological discovery. As such, skill acquisition in this sphere in terms of sample processing, data analytics and application to physiological and clinical outcomes is highly sought after; and is the basis of this PhD. Specifically, this PhD will focus on analytical work in the areas of proteomics, metabolomics, and transcriptomics; with an overall aim of “exploring the utility of OMICS to predict physiological responses to exercise-for-health interventions”. This approach is, to date, uncommon yet we contend should become a standard approach for translational research advancement. Utilising valuable biobanks of human samples from both volunteer and patient studies (which represent significant prior investment), the successful student will develop high-end analytical and data processing skills in the context of translational research, whilst surrounded by multi-disciplinary peer and senior support networks, including the direct supervisory team. In addressing the specific aims outlined below, this PhD will also generate an OMICS-clinical data pipeline that can be readily adapted for future studies aiming to predict clinical outcomes from baseline multi-OMIC features.

**Aims**

1. To determine OMIC-based predictors (metabolomics and proteomics) for differential rates of muscle atrophy across different human lower limb muscles exposed to immobilisation (Bass et al., 2021), and links with integrated metabolic and molecular features (e.g., muscle protein synthesis, cell signalling).
2. To identify predictors (RNASeq) of physiologically and clinically relevant skeletal muscle and cardiorespiratory adaptation to different modalities (aerobic *versus* resistance) of exercise training.
3. To determine OMIC-based predictive links between different forms of (pre-surgical) exercise prehabilitation and clinical outcomes in cancer patients (Blackwell et al., 2021).

**Methodology**

State-of-the-art mass spectrometry will be adopted for untargeted proteomic and metabolomics as per our well-established and published protocols (Deane et al., 2022; Aldritt et al., 2021; Cegelski et al., 2021; Wilkinson et al., 2020). This approach will generate lists of OMIC features in baseline biological samples (following false discovery rate (FDR) cut-offs) in sample sets specific to each of the listed aims, and importantly will afford the successful student training in methodologies (i.e., analytical chemistry and mass spectrometry) with wide-reaching application beyond translational human physiology- the focus of this studentship.

Beyond this mass spectrometry, the successful student will (after comprehensive training and with ongoing support) apply contemporary bioinformatic approaches to examine the predictive ability of the identified OMIC variables. Prior to modelling, the data will be mean centred and examined for non-normality (and transformed as required) and multicollinearity, with these approaches violating linear modelling assumptions and increasing variability in model coefficients (Slinker and Glantz, 1985). If multicollinearity is identified we will either remove a variable if physiological principles inform us that variable provides the same information as another variable or we will combine collinear variables in a principled way (e.g., height & weight to body mass index (BMI)). Multi-model inference using, for example, Bayesian methods will then be used to calculate how much the data support each predictive model (Clyde et al., 2012), allowing efficient identification of a probabilistically principled set of variables to keep in a predictive model. Training in these bioinformatic approaches, as with the mass spectrometry, will provide the successful student with training in a research methodology with vast scope for future application, and will afford them upon graduation a research “tool-box” including translational and data sciences - a desired combination with growing recognition (<https://www.ukri.org/wp-content/uploads/2022/07/MRC-270722-BiomedicalDataScienceReview.pdf>).

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**Project 6-** Investigation of hypoxemia and hypercapnia during apnoea in children using a computer simulation. [marianna.laviola@nottingham.ac.uk](mailto:marianna.laviola@nottingham.ac.uk)

**Rationale**

General anaesthesia is common in delivering lifesaving medical interventions; however, it can suppress upper airway muscle activity and create upper airway obstruction. Failure to manage the airway may result in potentially lethal apnoea (i.e. the cessation of ventilation) which may cause hypoxaemia (i.e. low level of arterial oxygen in the blood) and hypercapnia (i.e. high level of carbon dioxide in the blood). During apnoea, oxygen supplies diminish, and carbon dioxide accumulates. These events are known, but the understanding of the physiology of apnoea and optimization of gas exchange are still expanding, especially in children.

Children develop hypoxaemia more quickly than adults develop during apnoea, due to their larger metabolic utilisation of oxygen and smaller oxygen store in the lungs. However, ethical limitations prevent research that would improve our understanding of hypoxaemia and hypercapnia, and their treatment in the clinical setting.

Because of the emergency nature of work in anaesthesia, it is difficult to recruit patients to studies examining crisis scenarios; it is also difficult to guarantee proper matching, blinding, stratification, and control of confounders. Computational modelling is a novel and effective alternative to human and animal trials, while avoiding the need to put patients at risk and replacing the use of animals in research. Computational modelling has minimal ethical issues; strong reproducibility and its results are widely considered valid and impactful. Finally, it is low-cost, highly flexible, and mechanistic (it is possible to look at any variables desired), assuring translation into human application.

**Aims & Methodology**

This project aims to investigate the safe prolongation of apnoea, improving the high-risk period of anaesthetic induction, and optimising gas exchange in virtual children.

Specifically, the objectives are:

* Aim1. Understanding the pathophysiological mechanisms occurring during apnoea and apnoeic oxygenation (the passive inflow of oxygen via an open airway during apnoea) which can delay/slow hypoxaemia and hypercapnia in children.
* Aim2. Assessment of the impact of sex, age and obesity on the development of hypoxaemia and hypercapnia.
* Aim3. Evaluation of various methods of providing apnoeic oxygenation, including low flow nasal oxygenation (LFNO) and high flow humidified nasal oxygenation (HFNO, i.e. Optiflow, a recently developed oxygen therapy device), to prolong safe apnoea time and optimize gas exchange, i.e. oxygen uptake and carbon dioxide clearance.

The student will use and will further develop the Interdisciplinary Computational Systems in Medicine (ICSM) simulation suite, a set of integrated, high fidelity, highly integrated cardio-pulmonary models, built in MATLAB. The ICSM suite has been developed by the supervisors, Dr Laviola and Prof Hardman [1-5] and has already been used in adults to investigate apnoea [4], rescue strategies in adults [6, 7] and pregnancy [8, 9].

The project has three interlinked work-packages (WP):

* WP1: Investigating the pathophysiological mechanisms occurring during apnoeic oxygenation. The student will further develop the ICSM suite, adding new modules to the current model, in order to simulate the key physiological mechanisms underlying of transport and exchange of gases in virtual children during classical apnoeic oxygenation (100% oxygen provided at the glottis), LFNO and HFNO. The new modules will be validated against existing, published clinical data.
* WP2. To investigate the impact of sex, age and weight on the development of hypoxaemia and hypercapnia, the student will build a bank of virtual children, modelling boys and girls, different ages (1-18 years old) and weight (lean, overweight and obese), using published physiological values pertaining to oxygen uptake, storage and distribution to the tissues. Each factor will be examined to determine how it impacts the time course of changes in arterial partial pressure of oxygen and oxygen haemoglobin saturation (SaO2) (to evaluate hypoxaemia) and arterial partial pressure carbon dioxide (to evaluate hypercapnia).
* WP3: The student will simulate, using the bank of virtual patients, various methods aimed to provide apnoeic oxygenation – classical, LFNO and HFNO, assessing, for example, different flow oxygen rates, oxygen fractions, cannula sizes. Comparisons will be made in terms of prolongation of safe apnoea time, i.e. the duration of time following apnoea until SaO2<90% and gas exchange optimisation.

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**Lifespan and Population Health**

**Project 7**- Exploring the experiences of lung cancer in never smokers. [Rachael.murray@nottingham.ac.uk](mailto:Rachael.murray@nottingham.ac.uk)

Rationale: Lung cancer is responsible for the largest number of cancer deaths worldwide (18.4%) (Bray et al 2018) and cigarette smoking is the main risk factor for developing the disease. Around 50,000 cases of lung cancer are diagnosed in the UK each year (Cancer Research UK 2022). Lung cancer incidence is characteristically highest in men from more disadvantaged background (largely mirroring historical patterns of smoking prevalence). Lung cancer is typically diagnosed at a late stage, which results in poorer treatment outcomes (Cancer Research UK 2022); however the National Screening Committee has recently recommended a screening programme for individuals at high risk of lung cancer which will aim to diagnose lung cancer at an earlier stage, thus increasing 5-year survival in this group. Eligibility for lung cancer screening is based, in part, on a balance of benefit and potential harm from the screening process itself and thus individuals without a history of smoking would currently be considered at more risk of harm than benefit from participation in lung cancer screening. However, the incidence of lung cancer in never smokers is rising (Bhopal et al 2019), possibly in more affluent women (Rait et al 2020). Relatively little is known about this population in terms of attitudes towards lung cancer screening, the stigma associated with diagnosis of a smoking-related cancer and difficulties and delays in diagnosis.

Aim: This PhD aims to explore experiences of never-smoking lung cancer, both from the patient and health care professional perspective in order to improve future practice and patient pathways.

Methodology: This PhD will consist of three components. Firstly, the successful candidate will undertake a qualitative systematic review of patient and healthcare professionals experience of the never-smoking lung cancer pathway (the majority of which will have been published before the National Screening Committee decision to recommend a lung cancer screening programme), including but not restricted to barriers and delays to diagnosis, experiences of stigma following a lung cancer diagnosis and attitudes towards a national screening programme for high risk individuals. The second component will comprise one to one interviews or focus groups with never smokers diagnosed with lung cancer to better understand their experiences from symptom development, diagnosis, managing stigma as a consequence of their diagnosis and also seeking their views on the national screening programme, decisions to not offer screening to low risk individuals and how messages around why screening is not offered be best communicated. Finally, one to one interviews or focus groups will be conducted with health care professionals (general practitioners, lung cancer clinicians and specialist nurses) and individuals working in cancer support services (for example Maggie’s) to explore their experiences of diagnosing and/or supporting never smoking individuals with lung cancer and their own views on and communication of eligibility for cancer screening.

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**Project 8-** Exploring the care pathway to diagnosis for people with bullous pemphigoid.[sonia.gran@nottingham.ac.uk](mailto:sonia.gran@nottingham.ac.uk)

**Rationale**

Bullous pemphigoid (BP) is a rare life-threatening blistering disease in older people. General Practitioners (GPs) are usually the first healthcare professionals to assess people with BP, but diagnosis is usually made by a dermatologist based on clinical features and immunopathological findings.

As BP is rare and can mimic other inflammatory dermatoses such as eczema, urticaria, nodular prurigo and scabies at the early stages of presentation before blistering develops, there is potential for delayed diagnosis and referral by GPs to dermatologists. As BP is associated with treatment related co-morbidity and high mortality, delayed diagnosis may impact prognosis.1

BP is under-researched, probably because it is a rare condition. A scoping review has shown that there is a paucity of studies that have attempted to explore the diagnostic pathway of BP and they have methodological limitations such as small sample size and selected populations.2,3 No systematic review or qualitative research have been undertaken in this field, to date.This work is important as a recent international survey reported that half of patients with pemphigoid diseases are unsatisfied with the diagnostic process mainly due to misdiagnosis and long diagnostic delay.4

By improving knowledge on the diagnostic pathway for BP in primary care, this proposed study will have key benefits for patients with BP such as responding to milder treatment if diagnosed earlier and not requiring hospitalisation.

**Aims**

The aim of the project is to explore the care pathway to diagnosis for people with BP**.** The objectives are:

1. To synthesise the current literature on what facilitates and delays diagnosis of BP
2. To determine the views of patients on the care pathway to diagnosis
3. To quantify conditions patients with BP may be misdiagnosed with and features that help distinguish BP at an early stage
4. To determine the average length of time for a diagnosis and impact of delay in diagnosis on prognosis

**Methodology**

This PhD project consists of a series of linked studies using a mixed-methods approach:

Study 1: A synthesis of the current evidence on average delay in diagnosis of BP

In this first part of the project, a systematic review will be conducted to synthesise data on average delay in diagnosis and to describe initial clinical features made in patients with BP.

Study design: Systematic review of observational studies

Output: Pooled average delay in diagnosis and a narrative of the clinical symptoms/conditions patients are often misdiagnosed with. These findings will inform Studies 3 and 4.

Study 2: The views and experiences of patients with BP of the care pathway to diagnosis.

In the second part of the project, qualitative methods will be used to describe the experiences of patients with BP with regards the diagnostic pathway.

Study design: Semi-structured online interviews with community-based sample of 15 patients with BP.

Output: Clinical symptoms/conditions patients have been misdiagnosed with. The impact of delay in diagnosis on patients’ lives and the perspective of patients on the care pathway to diagnosis. The findings will inform Study 3.

Study 3: Exploration of symptoms/conditions with which patients with BP could be misdiagnosed with and length of diagnostic delay

In this part of the study, the Clinical Practice Research Datalink (CPRD) and linked Hospital Episode Statistics (HES) will be used to identify patients with BP and explore symptoms/conditions with which patients may have been misdiagnosed with prior to their diagnosis of BP, and length of diagnostic delay. Diagnostic delay will be defined as the difference between first potential misclassification diagnosis and date for first BP diagnosis.

Study design: Case-control study

Output: Description of conditions patients with which BP may be misdiagnosed with, proportion and adjusted odds of diagnostic delay, and median delay in diagnosis. Findings will inform Study 4.

Study 4: How does mortality and risk of treatment related co-morbidity compare for those with and without a delay in diagnosis?

In the final study, the CPRD, HES, and Office for National Statistics will be used to compare mortality and treatment related co-morbidity in BP patients with and without a diagnostic delay based on the findings of Study 3.

Study design: Cohort study

Output: The risk of death or treatment related co-morbidity in those with a delay compared to those without a delay.

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**Medical Education Unit**

**Project 9-** Education for sustainable healthcare: what are the challenges for curriculum design and implementation in medical schools? [steven.agius@nottingham.ac.uk](mailto:steven.agius@nottingham.ac.uk)

Climate change is the greatest threat to public health in the 21st century. Despite growing awareness and concern about the climate and ecological emergency, as well as Government and NHS commitments on carbon reduction, there remains a gap in knowledge and skills for sustainable healthcare among health professionals.

In the UK, NHS staff will increasingly find themselves caring for patients who bear the burden of disease from the impact of climate change and ecologically irresponsible practices which harm ecosystems and contribute to climate change. There is a pressing need within medical education to emphasise the connection between the climate, ecosystems, sustainability and health, and the responsibility and capacity of medical and healthcare professionals in changing the status quo.

The AMEE Consensus Statement on Planetary health and education for sustainable healthcare defines Education for Sustainable Healthcare (ESH) as the process of equipping current and future health professionals with the knowledge, values, confidence and capacity to provide environmentally sustainable services through health professions education. It is vital for the prevention of adverse health outcomes due to the changing climate and environment.

ESH is a mandatory requirement of the medical regulator (the General Medical Council) in *Outcomes for graduates*. The recent publication of *Education for sustainable healthcare* (Tun & Martin, 2022) endorsed by the Medical Schools Council, has brought into clear view the obligation of UK medical schools to adapt their curricula whilst recognising the challenges in implementation including the need to develop the capacity and capability of medical educators to integrate ESH into their material, as well as determine where ESH should fit within an already overcrowded medical curriculum.

Aims

To map the international evidence base for curriculum design and implementation in order to embed sustainable healthcare in medical schools.

To identify effective models of curriculum design and implementation in order to optimise medical student learning in sustainable healthcare, including syllabi, teaching, assessment, learning environments and faculty development.

Methodology

Phase 1: To conduct a systematic scoping review of international academic and grey literature on sustainable healthcare curriculum design and implementation using [Arksey and O’Malley’s](https://www.tandfonline.com/doi/abs/10.1080/1364557032000119616) six step approach in combination with guidelines from the [Joanna Briggs Institute](https://jbi.global/scoping-review-network/resources).

Phase 2: Conduct a Mixed Methods study in order to gather quantitative and qualitative data on sustainable healthcare curriculum design and delivery. The study design will involve a one-phase project based on concurrent empirical data collection, combining results by merging two separate strands of data in order to generate a composite curriculum model. Quantitative data collection will be carried out using a survey instrument sent to all UK medical schools and a purposive sample of international medical schools. Qualitative data will be collected using a combination of semi-structured interviews and/or focus groups with medical school curriculum leads, medical and healthcare professional educators, sustainable healthcare experts, medical students and other stakeholders. Public and patient involvement will be in-built in the study design, with careful attention paid to principles of inclusive curriculum development.

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**Project 10-** Does widening participation status affect undergraduate medical student performance? A single centre, mixed methods study. David.O’Brien@nottingham.ac.uk

Rationale:

Widening participation (WP) is certainly not a new concept. In the broadest educational terms, it “helps underrepresented groups access further or higher education to continue their education” (1) In addition to improving access, it aims to improve graduate outcomes and employability (2). It is core to UK government educational policy (3) but is very much a global initiative (4), aiming for improved social mobility (5).

Medicine has fallen behind other subjects in progressing the WP agenda, although has reinvigorated the focus of widening access to medical school in selecting the best candidates to become doctors, irrespective of their background.(6)

Health Education England very much supports the drive to widen participation in Medicine, not only in its role of underpinning the NHS constitution of promoting a culture of equality, inclusion and opportunity (7) but also in terms of workforce planning, ultimately aiming to reduce health inequalities by training a more socially diverse workforce of future doctors. (8)

Whilst there has been a significant drive to widen access to Medical School from applicants of differing ethnic, cultural, and socioeconomic backgrounds, including the creation of various Gateway and Foundation courses, the continued performance of applicants once in medical school, and following qualification remains poorly understood. Numerous studies have tried to investigate this, with mixed findings due to marked heterogeneity. Concerns around the ‘attainment gap’ persist, particularly for ethnic minorities (9), care-experienced students (10) and those accessing medical courses via contextual offers as well as those entering via dedicated gateway programmes (11). A recent published qualitative systematic review of the experiences of WP students in undergraduate medical education in the UK (funded by the Joan Browne Legacy as part of their PhD thesis) concluded that in regard to WP students, “It remains from the aggregated evidence that the experience at medical school still is not an equal one.”(12)

Our own previously published 5-year metanalysis of both Applied Knowledge Test (AKA) and Objective Structured Clinical Examination (OSCE) data for WP and non-WP student performance highlighted a small but significant difference in performance between these two groups, albeit it one that is unlikely to have a major real-world consequence.(13)

Understanding why differences in performance exist is fundamental to seeking solutions to reduce any attainment gap, with educational establishments needing to recognise that they have an ongoing obligation to WP students above and beyond simply facilitating admission (12).

**Aims:**

1. Document the academic and clinical performance of WP students throughout medical school when compared to their non-WP counterparts.
2. Document the lived experience of WP students throughout medical school when compared to their non-WP counterparts.

**Objectives:**

1. Examine the results of academic and clinical performance of WP vs non-WP students based on the AKT and OSCE results over a 5-year period
2. Conduct individual student interviews with both WP and non-WP students in the final year of the 5-year MBBS programme at the University of Nottingham to document their lived experience whilst at medical school.
3. Conduct focus groups with both WP and non-WP students in their final year MBBS programme at the University of Nottingham to focus groups to further explore their lived experiences at medical school

**Methodology:**

This project will use a mixed-method approach to answer the research objectives set out above. Using a meta-analysis, results of multiple assessments over a five- year medical course will be combined to minimise uncertainty regarding the performance of students from a WP background. This meta-analysis will include over 41 assessments comprising both AKT and OSCEs from 2017 to 2022. Performance of students from both WP and Non-WP backgrounds will be measured across individual assessments using standardised mean differences (SMD). Forest plots will be generated to understand the differences in performance among individual assessments, for each and for overall performance.

A purposive sampling strategy of WP and non-WP students predominantly from the final year (year 5) of the MBBS programme will be used to explore the lived experience of those students in medical school with the most experience. If this yields insufficient subjects, then the next year down (year4) will then be interviewed, and a thematic analysis of all transcripts undertaken. It is intended to sample subjects using the principle of data saturation, with the expectation this will be most likely to require approximately 10 subject interviews per group. If data saturation is not reached, additional interviews will be undertaken up to a maximum of 15 subjects per group. The use of focus groups will also be considered to further embellish and capture relevant themes.

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**Clinical Trials Unit**

**Project 11-** Improvingrecruitment and retention in clinical trials: using a not-for-profit marketing approach [Eleanor.mitchell@nottingham.ac.uk](mailto:Eleanor.mitchell@nottingham.ac.uk)

**RATIONALE:**

Well-designed and conducted clinical trials provide high-quality evidence required to improve healthcare decision-making. However, many clinical trials fail to recruit and retain the required number of participants, impacting on data completeness, statistical power and diversity of representation (1, 2). Ultimately this can mean the research question is inadequately answered, failing to influence healthcare and policy, and leading to considerable resource waste (3).

A clinical trial is a scientific study, yet many of the techniques needed to engage patients and staff at recruiting sites can be found within the social science discipline. In particular, the study of people’s motivations, needs, values and experiences is a central feature of consumer psychology. A key component of this, in the context of clinical trials, is how far we consider the viewpoint of potential participants and how we might ensure they have a positive experience. Those working in the design and delivery of academic-led, non-commercial clinical trials are not necessarily skilled or knowledgeable about the potential impact of marketing techniques on clinical trial engagement, and yet are expected to ensure successful trial promotion, recruitment and retention.

A deeper understanding of why people choose to engage in clinical trials – motivations that differ and are not always obvious – would allow for better design of recruitment and retention methods. However, little is known about the application and potential of such theory in clinical trials (4). Indeed, many not-for-profit organisations use insights from consumer behaviour and marketing theory to be more cost-effective, efficient and minimise wastage. For example, trialists could use marketing theory when seeking to satisfy stakeholders’ different reasons for involvement, to ensure participants are given accurate descriptions of what they will be asked to do, to, or to craft interventions that help stakeholders feel appreciated throughout a trial. A marketing approach prioritises the point of view of an organization’s audience in order to understand what it is they *really* value.

However, clinical trials appear to have only made limited use of such techniques, despite literature that indicates considerable potential (5, 6). Research is urgently needed to gather evidence on current practice, develop tools to support trialists, and examine the impact of a marketing approach on recruitment and retention.

**AIMS AND METHODOLOGY**

**Overall Aim:** To develop and evaluate a clinical trial marketing toolkit, offering practical guidance for trialists to implement in the design and delivery of clinical trials.

**Methods:**

1. **Systematic review** to review existing evidence on marketing in clinical trials. Cochrane systematic review guidance will be followed. A range of databases and websites will be searched. Findings will be summarised narratively.
2. **National online survey of current practice** to understand what elements of marketing (formal and informal) are currently being adopted in clinical trials. Two key stakeholder groups will be invited to respond: 1) clinical trial teams (e.g. trialists, trial management) and 2) clinical investigators and research nurses. Dissemination will be via national groups with whom the supervisors have strong links (see ‘wider benefits’). Questions will include experiences of explicit/implicit use of marketing techniques. Data will be analysed and presented descriptively.
3. **Focus groups +/- 1:1 semi-structured interviews** to understand experiences and opinions of key stakeholders on the use and acceptability of marketing strategies in clinical trials, and ideas for resources to include in the toolkit. Individuals from stakeholder groups (described previously) will be invited to participate in a focus group or a 1:1 semi-structured interview. In addition, we will also engage with postgraduate marketing students and patient and public involvement (PPI) representatives, both of whom bring alternative perspectives. Marketing students, identified via the Business School, will bring a non-trial perspective, understanding marketing theory and therefore diversify the trialist perspective. PPI representatives from trials in different clinical areas will be identified through existing links. Their input, as potential trial participants, is crucial in understanding the use of marketing approaches in future trials.

One focus group for each stakeholder group will be conducted, with the exception of the clinical trial team group, where 2-3 focus groups will be held, since these are the stakeholders for whom the toolkit directly targets. Using topic guides, focus groups will be conducted remotely, via videoconference, to encourage participation from across the country and recorded with consent. Recordings will be transcribed and coded for emergent, recurrent and divergent themes in accordance with Braun and Clarke’s thematic analysis (7).

1. **Toolkit Development.** All previously collected data will be triangulated between stakeholder groups for convergence, discrepancy or complementary information. All components of the toolkit will be developed iteratively, inviting previous participants to review the draft toolkit and provide feedback, before finalising. It is anticipated that the toolkit will include practical worksheets and templates and may be developed using multi-media.
2. **Toolkit Evaluation.** The toolkit will be implemented into at least one clinical trial during its development and/or set-up stage. The trial team will be asked to provide feedback to enable further refinement of the toolkit.

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**Project 12**- Improving the generalisability of findings from randomised controlled trials[chris.partlett@nottingham.ac.uk](mailto:chris.partlett@nottingham.ac.uk)

**Rationale**

The issue of generalisability of findings from clinical research, especially from randomised controlled trials, has long been a prominent and hotly debated topic[1,2]. While there is a lack of consensus as to the extent to which generalisability invalidates or compromises trial findings or conclusions, it is nonetheless a frequently cited explanation for the widespread failure of routine clinical care to adopt interventions that have been shown to be beneficial in clinical trials[3].

Researchers have grappled with the issue of generalisability for over sixty years[4]. Recent reviews suggest that the problem persists and, in some respects, has been exacerbated over time[5]. The decline in generalisability of randomised controlled trials can be largely attributed to two separate issues. Firstly, the settings in which trials are conducted appear to increasingly fail to reflect the real world settings in which, and people in whom, they are intended to be used. Secondly, the continued failure to approach and recruit a diverse and therefore generalisable sample population of participants.

The former is driven by a research culture where trials are typically conducted in larger research-active sites, while smaller research-naïve sites are increasingly overlooked. There is evidence demonstrating that patients at research-active hospitals have improved survival rates, reduced morbidity, and better patient experience[6]. In response, the Department for Health and Social Care (DHSC) has outlined plans to make research more diverse and relevant to the whole UK population[7].

There is also evidence that the process of enrolling participants or the collection of data from participants disproportionately marginalises certain socioeconomic or ethnic groups[8]. This issue is more relevant than ever due to the growing disparity in health equality and a greater focus on improving equality, diversity, and inclusion within healthcare research. In recognition of this, the DHSC has identified three priority areas of research interest – a cross-cutting theme is delivering research and innovation that reduces health disparities[9].

Likewise, the National Institute for Health and Care Research (NIHR) have recently prioritised this as an area to be addressed – the INCLUDE project initiative aims to improve trial delivery for under-served groups[10]. In addition, Trial Forge have developed initiatives and practical guidance to improve the inclusion and participation of underserved groups[11].

While these initiatives represent important progress in rectifying the widespread problem of inclusivity in clinical research, and by extension, the generalisability of trial findings, there remains a substantial evidence gap that this research will fill. Firstly, uncertainty persists regarding the importance attributed to and the attention paid to generalisability by researchers and other stakeholders. Secondly, there is uncertainty regarding the impact of interventions, initiatives and policies on addressing the issue of generalisability.

**Aims and Methodology**

The overarching aim of this PhD is to contribute to the evidence base surrounding the issue of generalisability of randomised controlled trials. Specifically, it will aim to better understand the importance attached to generalisability, evaluate the effectiveness of existing interventions and initiatives that aim to address this issue, and quantitatively measure impact of a failure to achieve generalisable trial findings.

This can be achieved through (some or all of) the following work packages:

1. A literature review to explore and understand the definition(s), meaning and importance of the interlinked concepts of inclusivity, external validity, and generalisability.
2. Development of an index (or indices) of generalisability (IoG) to attempt to quantify the external validity of a trial. This could incorporate features of the trial design (e.g., those identified by the PRECIS-2 tool [12]) and the trial results (e.g., the diversity of the trial population).
3. A systematic review of evaluations of interventions aimed at improving the representativeness of participants in randomised controlled trials.
4. A review of published trial protocols/main result publications to investigate:
   1. How prevalent are interventions/initiatives to improve the representativeness of participants?
   2. Is there any evidence that the interventions/initiatives are effective?
   3. Where trial teams planned an intervention/initiative to improve representativeness within a trial, was this matched in their implementation?
5. A detailed investigation of case studies to:
   1. Compare the characteristics of participants recruited into the NCTU-led FAMOUS, FEED-1 and POP-I trials with routinely collected data
   2. Identify whether there is any evidence of a link between the generalisability of trial findings and subsequent uptake of effective treatments
6. A quantitative analysis to determine whether there is an association between the indices of generalisability (developed in WP2) and
   1. the number of eligibility criteria
   2. the use of ‘soft’ eligibility criteria (e.g., those relying on clinical judgement)
   3. single centre versus multicentre trials
   4. definitive versus pilot/feasibility trials
   5. no consent model versus individual consent model in cluster trials
7. A simulation study (underpinned with real clinical trial datasets e.g., The RECOVERY trial –almost 50,000 participants randomised across 200 sites) to quantitatively measure the impact on the estimated treatment effect of systematically excluding participants with certain characteristics

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