Mental Health and Clinical Neuroscience

Project 1 - **Understanding and improving participant diversity in multiple sclerosis rehabilitation research**. roshan.dasnair@nottingham.ac.uk

Rationale: Multiple Sclerosis (MS), a neurological condition with several symptoms adversely affecting quality of life, has long been seen as a disease primarily of White people, but recent research has shown that this is clearly not the case[1]. In fact, MS may affect ethnic minorities differently than it does White people, and the reasons for this are yet unknown, primarily because ethnic minorities are underrepresented in research[2]. Such omissions from research not only relate to ethnic minorities, but also to those from lower income and other marginalised/socially excluded groups. Furthermore, access to services, even in social healthcare systems, is unequal for different minoritised groups, and rehabilitation services are no exception[3]. Therefore, we are disadvantaging minoritised groups by failing to include them in our research and by extension, providing them with reduced access and care. Given that it is only recently that we have fully begun to understand the extent to which minoritised groups are affected by MS, it is vital we find ways to make our research and clinical services inclusive.

Aims: To understand which groups of people with MS (pwMS) are underrepresented in rehabilitation research and how to improve representation and engagement.

Methods: The specific research questions will be co-developed with the PhD candidate. However, we envisage that these will focus on:

1. Which groups of people are underrepresented in MS rehabilitation research, and what is the effectiveness of "inclusion interventions"?

We will use two different methods to answer this question.

1a. A *systematic review*. "Inclusion interventions" are strategies to improve participant representation in clinical studies. We have already conducted a scoping review of this area and know that there are potentially eligible papers that can be included in such a review, and a comprehensive review has not been conducted with pwMS and in rehabilitation settings.

1b. Using preexisting data from our clinical trials in MS rehabilitation (including some of the largest trials in the area), and using data being collected through the aforementioned NEuRoMS programme, we will undertake a *quantitative analysis* of which groups of people are underrepresented. Based on our preliminary work on a small dataset, we hypothesise that ethnic minorities, lower income families, and older adults may be underrepresented. We will compare these research data with demographic features of a clinical sample (i.e., those who are seen in MS clinics – although, even this may be limited by issues of access to care mentioned earlier).

2. Why are minoritised/underrepresented groups not included in MS research, and what can be done to improve representation/inclusion?

We will use two research methods to answer this question.

2a. We will use *qualitative methods* (interviews and focus groups) with (i) pwMS (those who have and have not participated in MS rehabilitation research) (ii) experts in healthcare inclusion. We will develop interview and discussion schedules with our MS-PPI group, focusing on understanding the barriers to participation and what can be done to remove them. Data will be audio recorded, transcribed verbatim and analysed using framework analysis.

2b. Using a *nominal group technique*[4], we will develop an "inclusiveness intervention" to improve inclusivity in MS rehabilitation research, with input from the preceding work and with minoritised groups and experts in healthcare inclusion.

3. Does an "inclusiveness intervention" reduce underrepresentation in MS rehabilitation research?

The intervention developed in 2b will be applied to the NEuRoMS trial (across 7 UK centres, randomising 478 participants). Because the intervention will be introduced mid-way through the data-collection period for this trial, we will be able to examine the impact of the intervention on diversity of

the participants recruited and whether we have better outcome completion than pre-intervention. We will introduce the intervention sequentially across the different centres, so we can also compare between centres and how each centre deviates from their "normal" monthly recruitment figures. This will be an exploratory analysis forming the basis for a larger trial evaluating the intervention in a new grant application.

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Project 2 - **Understanding self-harm and suicide in autistic girls to improve identification and assessment** Maddie.groom@nottingham.ac.uk

Rationale:

Autistic traits in girls are being missed and underdiagnosed for a number of complex reasons including: i) potential bias in diagnostic criteria and assessment tools (which have been based on studies involving boys) ii) a high degree of successful masking of difficulties by girls which can lead them to appear 'neurotypical'. We need to develop a more accurate and inclusive understanding of gender-specific patterns in autism presentations. Studying characteristics of autism in autistic girls and those with suspected autism will support more accurate and timely diagnosis, and a better understanding of how to tailor support and interventions in healthcare, education and community settings.

Presence of self-harm and suicidal ideation and behaviour may be an important component of autism identification in girls and therefore of relevance in improving understanding and assessment, especially where traits are suspected but undiagnosed. Self-harm is defined as any act of self-injury or self-poisoning regardless of the motivation (i.e. degree of suicidal intent associated with the act). Self-harm and suicidal ideation and behaviour are prevalent issues for autistic youth. Although findings are limited, some data suggest that autistic girls are more likely to present with a history of self-harm than autistic boys. The likelihood of death by suicide is also higher in autistic females than males (and notably this is contrary to the pattern of findings in non-neurodiverse populations). This PhD will aim to clarify how self-harm and suicide ideation and behaviour in youth manifests and progresses in autistic girls.

Recent work calls for a nuanced focus on the mechanisms which underlie heightened risk of self-harm/suicidality in autistic youth. Key factors critically implicated in self-harm and suicide-related behaviour in neurotypical girls include difficulties regulating emotion, and a drive to alleviate emotional distress through impulsive behaviour. For example, findings suggest that impulsive behaviour contributes to risk for self-harm and suicidality when an emotional tipping point is reached. These factors have not been explored specifically in autistic girls, or those with suspected autism. Exploring *how* and *when* difficulties with emotion regulation and impulsivity become manifest in girls and link to maladaptive behaviour (such as self-harm, and other emotion-based outcomes potentially associated with autism in girls such as burn-out, exhaustion and emotion-based school refusal) will support improved understanding, identification and assessment of autism presentation in girls.

Aims:

1. Understanding of self-harm/suicide ideation and behaviour risk in autistic girls and those with suspected/undiagnosed autism (e.g. waitlist for assessment) – prevalence, characteristics, trajectory
2. Understanding of the contribution of impulsivity and emotion dysregulation in these groups to heightening risk for self-harm and suicidality and other potential outcomes (including burn out, exhaustion, school-refusal) – triggers and tipping points
3. Early engagement work (with young people, families, schools) to contribute to the development of self-harm assessment and intervention approaches for autistic girls and those with suspected/undiagnosed autism which take particular account of emotion-based impulsivity and dysregulation - participatory focus
4. Understanding of the contribution of an emotional dysregulation and heightened risk profile for identification of autism in girls – translational impact

Methodology:

PPI group established at the outset to advise and provide oversight and direction and sensitivity check. The supervisory team have considerable experience of participatory working and share the view that participatory approaches are essential throughout the research cycle.

Year 1 Literature reviews / scoping landscape re self-harm prevalence, characteristics, trajectory in autistic girls and those with undiagnosed autism; assessment, identification and intervention in autistic youth; associations with impulsivity and emotion dysregulation

Year 2 Mapping studies to understand life course of self-harm/suicidality, and other outcomes (e.g. burn out, emotion-based school refusal) in autistic girls and those with suspected autism. Using surveys, interviews, focus groups, card-sorting methodologies to allow for the complexity and temporal nature of risk/protective factors to be explored with young people.

Year 3 Translational work to identify characteristics and risk profile using participatory focus through workshops/interviews. Writing up and dissemination at networks and events.

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Translation Medicine

Project 3- Precision oncology targeting of drug-resistant ovarian cancer.

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Background: Advanced high-grade serous ovarian carcinoma (HGSOC) is the commonest cause of gynaecological cancer death [1]. Despite advances in surgery, platinum-based chemotherapy, and targeted therapies (PARP inhibitors), most patients will develop resistance, recurrence and succumb to the disease [2]. Therefore, the development of novel biomarkers and therapeutic targets is a high priority in HGSOC. DNA helicases unwind DNA, a process essential during DNA replication and DNA repair. Human RecQ family of DNA helicases includes RECQL (RECQL1, RECQ1), RECQL4, RECQL5, BLM and WRN. Germ-line mutations in RecQ helicases cause cancer predisposing syndromes. RECQL is the most abundant of RecQ helicases. RECQL is an integral component of the replication complex. RECQL is required for the maintenance of replication fork progression and homologous recombination (HR) repair of DNA double strand breaks (DSBs). RECQL interacts with PARP1 during DNA repair [3]. RECQL germ-line mutation increases breast cancer risk [3] and recently discovered to cause RECON syndrome [4]. We have previously shown clinicopathological significance of RECQL in sporadic breast cancers [5-9]. However, the role of RECQL in HGSOC is unknown.

Our Preliminary data: Immunohistochemical evaluation of RECQL in 262 clinical ovarian cancers revealed high nuclear expression in 109/262 (42%) tumours which as associated with HGSOC ($p<0.0001$), shorter progression free survival (PFS) ($p=0.011$) and worse overall survival (OS) ($p=0.044$). *RECQL* mRNA levels evaluations in publicly available clinical data sets showed that high *RECQL* mRNA was linked with poor PFS ($p<0.001$) and worse OS ($p<0.001$). These data provide the first clinical evidence that RECQL predicts platinum resistance in HGSOC. Chronic replication stress is a feature of HGSOC which can occur either due to homologous recombination deficiency (HRD, seen in 50% of HGSOC) or amplified oncogenes (e.g. *CCNE1* amplification seen in 30% of HGSOC). We have profiled RecQ helicase in a panel of HGSOC cell lines. RECQL was overexpressed in CCNE1 (Cyclin E) amplified [COV318, OVCAR3 cell lines] and in c-MYC amplified COV362 cells. In clinical cohort, nuclear cyclin E overexpression was seen in 20% (53/260) of tumours. High cyclin E/high RECQL co-expression was also significantly linked with poor PFS ($p=0.04$) and worse OS ($p=0.04$). These data suggests that high RECQL may be a feature of CCNE1 amplified HGSOC.

Using CRISPR-Cas9 gene editing, we have generated an isogenic pair of RECQL wildtype (WT) and RECQL knockout (KO) in MDA-MB-231 breast cancer cells and investigated cisplatin sensitivity. Our preliminary evaluation has shown that helicase activity of RECQL is required for repair of platinum induced DNA damage. The current PhD project will investigate in ovarian cancer models.

Hypothesis: RECQL based precision oncology strategy is an attractive approach in ovarian cancers.

Aims & Methods:

Aim 1 (1-12 months): Pre-clinical evaluation of RECQL as a predictor of platinum resistance in an panel of HGSOC [COV362(MYC amp, cisplatin resistant), COV318 (CCNE1 amp, cisplatin sensitive), OVCAR3 (CCNE1 amp and cisplatin resistant), PEO1 (BRCA2 mutant, cisplatin sensitive) & PEO4 (BRCA2 revertant, cisplatin resistant)] and endometrioid [A2780 (p53 mutant, cisplatin sensitive) & A2780cis (p53 mutant, cisplatin resistant)] ovarian cancer lines .

Methods

a) RECQL depletion by siRNAs (x 2 constructs)
b) RECQL knock out (KO) using CRISPR/Cas-9
c) Knock in (KI) of plasmid vector, pCB6: empty vector, full-length wildtype RECQL or helicase dead RECQL variant (K119R) into RECQL_KO platinum resistant cell lines.
d) Investigate cisplatin sensitivity in wildtype, KO, KI cell lines: Clonogenic assays, 3D-Spheroids & Bioengineered three-dimensional (3D) matrices [10].
e) Functional studies
    a. DNA damage response (DDR) response evaluation:
        i. γH2AX, 53BP1 and RPA immunofluorescence

ii. FACS for cell cycle progression and apoptosis

b. Replication stress evaluation:
   i. Pan-nuclear γH2AX nuclear staining
   ii. DNA fiber assay (fiber length, right-left asymmetry)
   iii. Western blots for CHK1 p345

Aim 2 (12-24 months): Test replication stress inducers (Topotecan, Gemcitabine, etoposide, ATR inhibitor (Berzosertib), Chk1 inhibitor (AZD7762) in RECQL proficient and deficient cells.

Methods: Same as Aim 1-methods d and e & treated with replication stress inducers.

Aim 3 (18-36 months): RECQL directly interacts with PARP1 and is involved in the regulation of DNA repair, telomere maintenance, and replicative stress [11]. We will test RECQL deficient ovarian cancer cell lines for synthetic lethality application using PARP inhibitors (Olaparib, Talazoparib, Niraparib or Rucaparib).

Methods: Same as Aim 1-methods d and e & treated with PARP inhibitors.

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Project 4 Using multi-omics to identify severe asthma patients that respond to mepolizumab. ian.sayers@nottingham.ac.uk

Rationale: Exacerbations are a major cause of morbidity and mortality, particularly in children with asthma taking maximal treatment. These events account for over 90,000 UK hospital admissions and are fatal in nearly 1500 people per year. Asthma is a heterogeneous disease and Type 2 inflammation is a feature of some but not all patients, characterised by elevated blood eosinophils and levels of cytokines in the airways such as interleukin 4, 5 and 13 (1). Biologics that block these inflammatory cytokines e.g. anti-IL5 (mepolizumab) have shown efficacy in decreasing exacerbations (2). Mepolizumab was recently introduced into the NHS for patients meeting criteria including severe asthma characterised by elevated blood eosinophils. However, there is a wide distribution of responses (based on exacerbations) even in this selected population. There are currently no early stopping rules for anti-IL5 therapy and injections are given for one year meaning there is a missed opportunity to switch the patient to an alternative management e.g. another biologic such as Dupilumab (anti-iL4/13). Transcriptomic and DNA methlylation signatures of blood cells have been used to identify specific patient subgroups in asthma, however, utility of these data, cell profiles and more recently developed proteomic platforms in identifying responder/non responder signatures to existing drugs is an area for development.

Aims: This studentship aims to identify a blood based early indicator of clinical response to mepolizumab at one year that has potential to impact patient care and management.

Key questions: Can we identify a gene, DNA methylation, protein and/or cell signature in the blood cells of asthma patients at a) baseline b) after 12 or 26 weeks treatment or c) change from a – b that can act as an early predictor of the response of the patient at one year, i.e. identify an early signature of responders/non-responders?

Methodology: We have completed a clinical translational study, Poor Response tO monoClonaL therApy In asthMa (PROCLAIM) that recruited 44 patients with asthma that meet NHS criteria for mepolizumab (3). We have collected extensive clinical data and biological samples including blood cells, serum and plasma samples at recruitment, 12, 26 and 52 weeks post mepolizumab treatment. Within this group we have designated responders and non-responders at one year based on reduction in exacerbation and/or steroid sparing effects. To date we have generated transcriptomic (RNA-seq) and DNA methylomic (Infinium Methylation EPIC array) data on these blood cell samples.

This studentship will take these datasets forward and in year 1 we will generate complementary flow cytometry data to identify in detail the numbers and different types of inflammatory cell subtypes present using banked cells. Similarly, we will generate a proteomic profile of 250+ serum proteins including a range of cytokines and growth factors (NULISAseq™ Inflammation Panel). The studentship will use bioinformatic analyses to quality control and interrogate these data for each data type to answer the key questions above. The studentship will also use data integration approaches to combine these data providing additional mechanistic understanding of the mode of action of mepolizumab. Novel findings will be interrogated in the latter part of the studentship in three ways; i) novel findings from serum based analyses will be replicated in an additional cohort of asthma patients treated with mepolizumab via collaboration; ii) selected identified serum biomarkers will be measured and assessed in a complementary cohort of asthma patients (n=100) when the patients were stable or at exacerbation to see if key drug responsive biomarkers are a feature of exacerbations and iii) *in vitro* cell culture experiments using banked inflammatory cells to explore the in vivo observations to identify cell mechanisms in responders and non-responder cells. Overall, this study will provide initial proof of concept that a blood based signature shows utility in predicting response to mepolizumab with associated clinical and financial benefits leading to the development of a simple point of care assay. This study also has scope to generate new understanding of the mechanism of action of mepolizumab and identify alternative drug targets.

This PhD studentship provides an unprecedented opportunity to work on a clinical translational study while developing highly transferable skills in respiratory medicine, flow cytometry, bioinformatics, statistical analyses, imaging, and cell and molecular biology. Nottingham is a centre of excellence for Respiratory Research having NIHR Biomedical Research Centre status. We have outstanding

infrastructure for undertaking translational research and the student will be based in the Nottingham Biodiscovery Institute, a complex of buildings with 800+ multidisciplinary researchers.

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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

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- Identifying biomarkers of pain mechanisms and muscle pathophysiology in individuals with osteoarthritis Stephanie.Smith2@Nottingham.ac.uk

Rationale: Pain is the leading symptom of osteoarthritis, affecting >10 million people in the UK and rising, half of whom do not respond to current treatments. Pain and osteoarthritis are amongst the ten most common causes of years lived with disability globally. Pain makes undertaking everyday activities unpleasant. Reciprocally, inactivity increases pain and disability. Pain fluctuates over time, intruding on everyday life and affecting an individual's ability to work, care for family, move, and live independently. Inactivity over time leads to disuse atrophy and associated histological and structural muscle deterioration[1, 2].

Signalling pathways in the central nervous system (CNS: brain, spinal cord) are pivotal in pain processing and in physical activity. Neuronal activity from the CNS modulates pain and motor control. Reciprocally, physical activity drives CNS plasticity[3, 4]. Pain and inactivity are associated with muscle weakness, muscle mass loss, impaired nervous system control over muscle activation[5-7], and homeostasis, with histological and structural pathological changes[8].

Osteoarthritis pathology research has predominantly focused on cartilage, meniscus, and ligaments or on animal models, and only now is beginning to explore molecular changes associated with muscle function (Dr Smith's paper in preparation). There is little research exploring the link between pain mechanisms and muscle function in humans. Understanding how muscle pathophysiology in individuals with osteoarthritis is linked with pain mechanisms has huge potential to improve treatment and prevent disability.

Aims:

- To systematically identify the optimal histological techniques and biomarkers for assessment of muscle pathophysiology in human osteoarthritis.
- To characterise the key histopathological and molecular changes in muscle in individuals with osteoarthritis compared to non-arthritic controls.
- To define biomarkers of pain mechanisms and muscle pathophysiology in individuals with osteoarthritis that will be targeted for developing therapeutic interventions.

Methods:

Year 1: Building on previous systematic reviews (Dr Smith) of molecular markers associated with muscle in osteoarthritis and sarcopenia[9], a systematic review will evaluate current evidence for histological and molecular biomarkers of muscle pathophysiology. Key themes will be taken forward into years 2 and 3. Year 1 will also include training for undertaking all the appropriate laboratory techniques.

Year 2 and 3: Histological and molecular analysis will compare serum, quadriceps and spinal samples between individuals with or without osteoarthritis. Within the unique Pain Centre Versus Arthritis Human Joint Tissue Repository (https://www.nottingham.ac.uk/paincentre/resources/joint-tissue-repository.aspx) post-mortem samples of ipsilateral matched quadriceps muscle, knee, dorsal root ganglia and spinal tissues from >100 people with or without osteoarthritis are available for analysis. . Histopathological and molecular biomarkers identified in Year 1, will be assessed in these samples, and are likely to include number, size and type of muscle fibres, intra-muscular fat, CD44+, creatine kinase. The relationships between muscle and tissues of the synovium and subchondral bone of the knee joint will also be explored. Potential pain mechanisms will be assessed by exploring cell populations (e.g. macrophages, satellite cells, glial cells), and biomarkers of sensitisation and neuronal activation, within the L4 dorsal root ganglia and spinal cords. The student will use their results from the year 2 and 3 studies to design a definitive clinical study to explore associations of identified biomarkers with pain severity and phenotype, and with disability.

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Lifespan and Population Health

Project 7- Implementing health informatics to improve quality of care and reduce inequality in the diagnosis and treatment of lymphoma. Matthew.Grainge@nottingham.ac.uk

Rationale

Lymphomas are malignancies derived from mature B- , T- and NK-cells, and are the 6th most common cancer in the UK with >14,000 new cases annually. T- and NK-cell lymphomas are a heterogeneous group of diseases that are highly aggressive and associated with poor prognosis and rapid death. The WHO divides T-cell lymphoma into >15 different subtypes based on histologic and immuno-phenotypic features, with modern diagnostic techniques meaning increasing numbers of specific disease subtypes have been defined over time(1). The sum of these diseases still comprises <10% of all lymphomas in western countries.

The rarity and heterogeneity of specific subtypes of T- and NK-cell lymphomas severely limits the ability to make conclusions regarding optimal treatments for most of these diseases. The more common subtypes are thought to have 5-year overall survival (OS) rates between 15-30%, with patients with relapsed or refractory disease having dismal prognoses. The socio-demographical characteristics of patients, underlying aetiologies and management of limited stage disease are unclear, and the benefit of autologous or allogeneic stem cell transplantation (SCT) remains controversial despite therapies being both toxic and expensive(2).

Despite these problems, there have been therapeutic breakthroughs with marked improvement in survival for specific disease subtypes(3,4). These data were obtained in multi-centre early phase trials with small patient numbers (NKT-cell lymphoma) and one randomised clinical trial conducted internationally.

Although registration of cancer diagnoses to the National Disease Registration Service (NDRS) is mandatory, large-scale UK/English data regarding demographics, delivered therapies, and their impact on OS and time to next treatment (TTNT) for T- and NK-cell lymphomas have never been published. We will use NCRAS data to describe, on an unbiased population level, baseline demographics, delivered therapies, treatment response and survival for these deadly diseases.

Aims

1. To describe each T/NK-cell lymphoma in terms of coding, diagnostic information, age, sex, comorbidities (including prior malignancies, HIV and viral hepatitis), deprivation quintile and geographical region in England.

2. To calculate incidence rates, both overall and by patient characteristics overall and by patient characteristics (age group, sex, ethnicity, calendar year 2013-2020, socioeconomic status, and region), using published data to apply a population denominator.

3. To carry out incidence and mortality analyses and calculate rates of new diagnoses, 30-day and case-fatality rates, 1- and 3-year OS and cause specific mortality rates (overall, by calendar year of diagnosis, by age [continuous variable], by deprivation quintile, by specific co-morbidities (including prior malignancies, HIV and disease specific factors).

4. To describe delivered lines of therapies, including SCT and options used for second line therapy and analyse the impact of treatment, on OS, cancer related survival and TTNT.

5. Analyse regional and socio-economic inequality using deprivation quintiles, and its relationships with disease incidence, treatments and survival.

6. To analyse all episodes of care prior to and diagnosis, and cancer waiting time data to assess if diagnoses could be made earlier.

Methodology

We already have obtained ethical approval and hold data from NCRAS for >7500 patients diagnosed 2013-2019 inclusive with follow up to end 2021. The data includes the Cancer Registry, systemic anti-cancer therapy and radiotherapy administered, Hospital Episode Statistics, cancer waiting times

treatments and OPCS coding data. Based on the progression of the project, we will consider the benefit of obtaining funding for complimentary primary care data for >15 million patients via CPRD-Aurum, allowing links to patient diagnoses made prior to 2013, as well as further submission to NCRAS for both updated data and new data focussing on all other lymphoma subtypes and plasma cell dyscrasias.

The following statistical analyses will be undertaken:

Incidence and prevalence analyses

1. Rates of new diagnoses (incidence) up to the latest available date of follow up, overall and by age group, sex, region and socioeconomic status (amalgamating groups or time periods as necessary to ensure the numbers of outcomes are not <5 in any group) will be calculated.

2. Point prevalence at the latest available calendar year with full follow up will be calculated.

3. To assess trends in calendar time and variation by socio-demographic characteristics, Poisson (or negative binomial) regression, with relevant adjustment for confounding and examination of possible interactions, will be used.

Mortality analyses

1. Crude all-cause mortality and cause specific mortality rates (events/person time) and Cox Proportional Hazards Regression for modelling variation in survival by age, sex, socioeconomic status and region will be calculated.

2. A Cox proportional hazards model will be fitted to the each of the lymphoma subtypes predicting risk of cause-specific death. From this, cumulative incidence functions will be derived to account for competing risks. Absolute risks will be reported overall and stratified where there is adequate power by co-morbidities described above.

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Project 8- Understanding the patient experience of isotretinoin for severe acne: informing better resources for patients and planning future clinical trials. Paul.leighton@nottingham.ac.uk

Rationale:

Isotretinoin is an effective but contentious treatment for acne vulgaris.

It is the final treatment option on the National Institute of Health and Care Excellence (NICE) acne guidance treatment ladder (https://www.nice.org.uk/guidance/ng198), and its licensed use is restricted by the Medicines and Healthcare products Regulatory Agency (MHRA) to people with severe acne only. Recent concerns from patients and their families about possible side-effects (in psychological health and sexual dysfunction) have led the MHRA to produce more stringent guidance on how isotretinoin should be prescribed and monitored (https://www.gov.uk/drug-safety-update/isotretinoin).

Despite these concerns many healthcare professionals consider isotretinoin to offer the best opportunity for cure or prolonged remission in severe acne. Severe acne can have significant impact on quality of life, can be stigmatising, can have consequences for mental health, and can cause physical symptoms such as pain and bleeding [1-3]. In the UK up to 30, 000 people per annum are prescribed isotretinoin for severe acne.

This dissonance between potential efficacy and perceived side-effects means that a first prescription for isotretinoin can be an anxious moment for an individual and their family. Previous research offers little insight about this moment, or about the support that patients and their families might require and how to effectively discuss this in clinical consultations. Previous research has stressed concerns and anxieties about isotretinoin, but little research has focused upon the experience of starting treatment and the treatment journey [4-6].

The Acne-ID trial is currently comparing standard and lower dose strategies in isotretinoin use (Acne-ID) (https://fundingawards.nihr.ac.uk/award/NIHR151318). It is an NIHR HTA funded large multicentre randomised controlled trial recruiting across 20 centres in the UK. Acne-ID is a unique opportunity to investigate the experience of initiating and being treated with isotreinoin from both the patient/family and healthcare professional perspective.

Acne, despite being a common skin disease, remains an under-researched topic [7].

Aims:

To generate insight that supports the initiation of isotretinoin for the treatment of severe acne.

Specific objectives include:

i) to summarise the published literature on the experience of isotretinoin treatment

ii) to investigate healthcare professionals' views on isotretinoin

iii) to record the experience of being prescribed isotretinoin for the first time

iv) to consider how patients and their families view different dose strategies

v) to generate recommendations (and resources) to support those receiving isotretinoin for severe acne

vi) to explore acceptability and interest in alternative treatment options to isotretinoin

Methodology:

This largely qualitative research will run alongside the Acne-ID trial benefiting from its research infrastructure and recruitment processes. The study will consist of four separate work streams.

Workstream 1 – addressing objective 1.

This will be a qualitative systematic review summarising and appraising the evidence on patient and healthcare experiences of isotretinoin treatment for severe acne. It will identify key themes about what is already known, and also identify strengths and limitations of existing studies.

Workstream 2 – addressing objectives 3, 4 and 6.

This will consist of a longitudinal interview study with individuals (and their families) who are receiving isotretinoin for the first time as part of the Acne-ID trial. This sample will include both individuals who are receiving standard dose and lower dose isotretinoin.

Participants will be interviewed when they first receive their prescription to establish their knowledge, views and concerns about isotretinoin; they will be interviewed for a second time after 6 months about their experiences of taking isotretinoin and any benefits / difficulties that they have experienced. Family members (parents or partners) may participate in these interviews if the participant wishes. Participants will also be encouraged to maintain a research diary, recording their experiences of taking isotretinoin.

Workstream 3 – addressing objective 2 and 6.

This will consist of a series of interviews with those healthcare professionals who are part of Acne-ID recruiting centres – these will be with clinicians responsible for initiating isotretinoin (primarily consultant dermatologists and but could also include specialist registrars pharmacists, specialist nurses, general practitioners with extended roles). These interviews will explore views on initiating isotretinoin, views on a low-dose strategy, and will consider how best to support effective consultations when starting isotretinoin.

Workstream 4 – addressing objective 5 and 6

A series of stakeholder workshops will consider the format and content of resources that will help those individuals who are being prescribed isotretinoin for the first time. These resources may be web-based or printed and will contain information about isotretinoin as well as outlining strategies for optimising consultations. The workshops will also explore the acceptability and interest in treatments which are currently not widely available in the NHS.

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Medical Education Unit

Project 9- : Social justice in the medical workforce: An exploratory study of the experiences of UK doctors from working-class backgrounds in pursuing a career in medicine

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Rationale

The most under-represented groups in medicine are those from lower socio-economic backgrounds [1].In 2019, the Sutton Trust found that only six per cent of UK doctors are from working-class backgrounds, although they make up 33 per cent of the workforce as a whole [2].

There are clear benefits to improving the diversity of the medical workforce. It allows doctors to be more representative of the populations they serve. Research has shown that general practitioners from less affluent backgrounds are more likely to work in practices serving the most deprived communities,[3] while other research suggests those from low socio-economic backgrounds are more likely to apply for specialties where there are particular shortages [4].

The exclusion of students with low socioeconomic status, a social group that often overlaps with racial minorities [5], prevents the medical profession from renewing itself and perpetuates a cycle of privilege incompatible with the principle of social justice [6]. To compensate for this selection bias, medical schools worldwide are creating inclusion policies to increase admissions from underrepresented socio-economic groups [7].

Whilst there is a growing body of evidence around the impact of widening participation to medical school, comparatively little is known about how socio-economic factors, both alone and when intersecting with other factors (e.g. race, gender, etc.), impact upon career selection and progression. Understanding how individuals from underrepresented socio-economic groups experience their professional identity development and their career trajectory within the medical workforce is essential for devising tailored educational and supportive practices for career development.

Aims

To conduct an exploratory study on the experiences of doctors from working class backgrounds in establishing their career within the profession of medicine.

To determine how existing policy and practice in relation to medical education and career development should be adapted to better support the principles of social justice.

Methodology

To conduct a systematic scoping review of international academic and grey literature on social justice in medical careers with a specific focus on the experience of doctors from working-class backgrounds using Arksey and O'Malley's six step approach in combination with guidelines from the Joanna Briggs Institute.

To conduct a qualitative study using Narrative Analysis to explore the medical career experiences of doctors from working class backgrounds. Qualitative data will be collected using semi-structured interviews with doctors at all career stages in both training and non-training posts.

Qualitative and quantitative data will also be gathered from other key stakeholders at national, regional and local levels (e.g. NHS workforce leads, Royal College Equity, Diversity and Inclusion (EDI) leads, General Medical Council, etc.).

A document analysis will capture key data on extant policy and practice relating to social justice in the medical workforce in order to inform future developments. Public and patient involvement will be built into the study design, with careful attention paid to principles of equity, diversity and inclusion.

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Project 10- **Geriatric oncology in medical education: optimising undergraduate curriculum design and implementation.** steven.agius@nottingham.ac.uk

Rationale

The population is ageing, which has significant implications for the provision of health services.[1] In the United Kingdom (UK) and worldwide, the incidence of cancer is higher in the older population.[2,3] Currently, those aged 75 and older account for 36% of new cancer cases in the UK, a figure which is expected to rise to 46% by 2034.[4]

Geriatric oncology is a field of medicine focused on the care of older adults with cancer. Almost all healthcare professionals have a role in caring for older adults with cancer at some point in their careers. This role may involve the diagnostic, treatment, or recovery stage of the disease trajectory.

With the ongoing advances in oncology and the increasing complexity of treating older adults with cancer, the geriatric oncology field must be a priority for healthcare systems in education, research and clinical practice. However, geriatric oncology is currently not formally taught in undergraduate education or postgraduate foundation and specialty training programmes in the United Kingdom (UK).[5]

The International Society of Geriatric Oncology (SIOG) has laid out clear goals for medical education.[5] The proposed strategies include integrating geriatric oncology into training programmes, promoting optimal clinical practice and meaningful research, providing focused educational materials, and organising formal educational activities for medical students and trainee doctors.[5] Collaboration with the geriatric oncology expert community is essential to help ensure that oncology educators and supervisors are adequately skilled in designing, delivering, and assessing geriatric oncology content.[6]

To date, considerable foundational work involving members of the supervisory team has been undertaken nationally which strongly supports the importance of this doctoral research. The SIOG UK Country Group (chaired by K L Cheung) has been exploring this subject as one of the pressing needs for the UK. The Group consists of geriatric oncology expertise in different disciplines (oncology, geriatrics, surgery, allied health professionals etc.) in the UK. The work resulted in the publication of a narrative review in *Cancers* (authors inc. Cheung and Parks).[6]

If successful, this PhD would allow for a critical review of the evidence base and enable the collection of empirical data to underpin vital curriculum developments as outlined here. It would also encompass engagement with key stakeholders, including the Medical Schools Council, so that research outputs might rapidly inform changes in the curriculum for approval by the General Medical Council. The research therefore has potential for significant translational impact and knowledge exchange.

The research team has been carefully composed in order to maximise subject and methodological expertise across geriatric oncology, medical education and Mixed Methods research.

The team would welcome applications from any suitably qualified candidates with an interest in developing or furthering a career in medical education and/or geriatric oncology.

Aims

To determine how best to embed geriatric oncology into the undergraduate medical curriculum in the UK.

To identify optimum syllabi, pedagogy and assessment strategies for geriatric oncology within the undergraduate medical curriculum.

Methodology

To conduct a systematic scoping review of international academic and grey literature on geriatric oncology in undergraduate and postgraduate training curricula using Arksey and O'Malley's six step approach in combination with guidelines from the Joanna Briggs Institute [7,8].

Conduct a Mixed Methods study in order to gather quantitative and qualitative data on optimum geriatric oncology curriculum design and implementation. The study design will involve a multi-phase

project based on consecutive empirical data collection, combining results by merging separate strands of data in order to generate a composite curriculum model and implementation strategy.

Quantitative data collection will be carried out using survey instruments sent to all UK medical schools and bodies responsible for UK foundation and specialty training.

Qualitative data will be collected using a combination of semi-structured interviews and focus groups with medical school curriculum leads, geriatric oncology experts, medical education experts, medical students and other stakeholders. A document analysis will capture key data on extant curricula to inform future developments.

The final phase will involve the DELPHI Method to develop consensus around proposals for curriculum design and implementation. Proposals would be taken forward to the Medical Schools Council for consideration as part of the consensus building process.

Public and patient involvement (PPI) will be in-built with careful attention paid to principles of inclusive curriculum development. PPI will be incorporated into refinement of study design and the DELPHI process of consensus building amongst other stages to be determined, following guidance from NIHR INVOLVE and the GMC guidance on PPI in undergraduate medical education.[9]

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Clinical Trials Unit

Project 11 - **Evaluating the Value and Impact of Conducting Process Evaluation Alongside Randomised Controlled Trials** chris.partlett@nottingham.ac.uk

Rationale

Process evaluation is an important aspect of applied health research, which aims to better understand the contextual factors and causal mechanisms behind clinical interventions and research processes [1-4]. Process evaluation may also support refining and shaping those interventions that are tested in research, so that they are practice-ready and more easily implemented.

A systematic review of trials published in 2015 identified inconsistent implementation and poor reporting of process evaluation within randomised trials [1]. Subsequently, there has been a notable shift in the research landscape with the MRC issuing guidance for researchers and major funders of trials such as the National Institute of Health and Care Research (NIHR), recognising its importance [2]. This has naturally led to more widespread implementation of process evaluation in randomised trials but without evidence of its effectiveness.

Aims and Methodology

Aim 1: To describe how process evaluation is being used within NIHR funded research

Aim 2: To develop a typology of process evaluation methods

Aim 3: To evaluate the impact and cost effectiveness of process evaluation

Aim 4: To develop guidance for effective implementation of process evaluation within randomised trials

These aims will be addressed across three broad work packages (WPs).

WP1: A scoping review of published NIHR funded randomised trials

[Aims 1—3]

We will review NIHR-funded trial publications over a period of 10 years to assess the evolution of process evaluation research. This will provide a comprehensive picture of when, how and why process evaluation has been used within randomised trials, illustrating:

- The prevalence of process evaluation across different funding streams
- What approaches, theories, and tools are being used
- When process evaluations are typically conducted in the evidence lifecycle
- How process evaluations relate to other elements of the trial

WP1 will identify a typology of process evaluation methods, which describes when they are done, and how they are done (i.e., what theories, tools and methods are used). Provisionally we might expect this typology to distinguish process evaluations undertaken prior to a trial (i.e., in intervention or trial development), those carried out within a trial (i.e., considering research processes or intervention fidelity), and those carried out post-trial to support the implementation of trial findings.

WP2a: Interviews and focus groups with key stakeholders *[Aims 2–3]*

Using the typology from WP1 as our starting point, we will undertake focus groups and/or interviews with principal investigators to understand in greater detail, the purpose and design of the different types of process evaluation. Subsequently, we will construct a series of “programme theories” which will explain (for each *type* in the typology):

- The ideal context for a process evaluation
- The mechanisms of action that a process evaluation is designed to trigger
- The intended outcomes of a process evaluation

We will use our extensive links to existing trial networks (for example, the Trials Methodology Research Partnership, the UK Clinical Research Collaboration Clinical Trials Unit network, the UK Trial Managers Network, as well as personal contacts) to identify principal investigators who have overseen process evaluation research within (or alongside) randomised controlled trials.

This insight will enable us to theorise about where and when process evaluation might be more or less beneficial, and how it should be optimally conducted.

WP2b: Detailed case studies *[Aim 3]*

We will test the "programme theories" developed in WP2a by building detailed case studies of on-going or recently completed process evaluations. In this we will compare the ideal planned process evaluation (i.e., programme theory) with what actually happened in the research environment.

We will identify process evaluations which reflect each of the types identified in WP1. For each case study, we will review study documents (e.g., protocols and minutes) and study outputs (e.g., funder report, publications, and recommendations). A range of stakeholders will also be interviewed to gain their perspective on the design, delivery and utility of the process evaluation. These stakeholders may include study principal investigators, process evaluation leads, research staff, public partners and study participants.

We will frame the case studies using the question "what worked, for whom and in which circumstances?", analysing data and synthesising with the original programme theory to build a more detailed understanding of how process evaluations work in practice.

WP3: Consensus building, guidelines for implementation in trials*[Aim 4]*

A workshop involving the study team and independent experts in process evaluation and trials methodology will be held to review the typology and refine the programme theories by considering the evidence generated in WP2a and 2b. The workshop attendees will review the study findings and provide recommendations for implementation and future research.

The ultimate aim is to provide recommendations for the conduct of process evaluation within randomised trials, identifying the optimal methodology and timing in different circumstances.

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