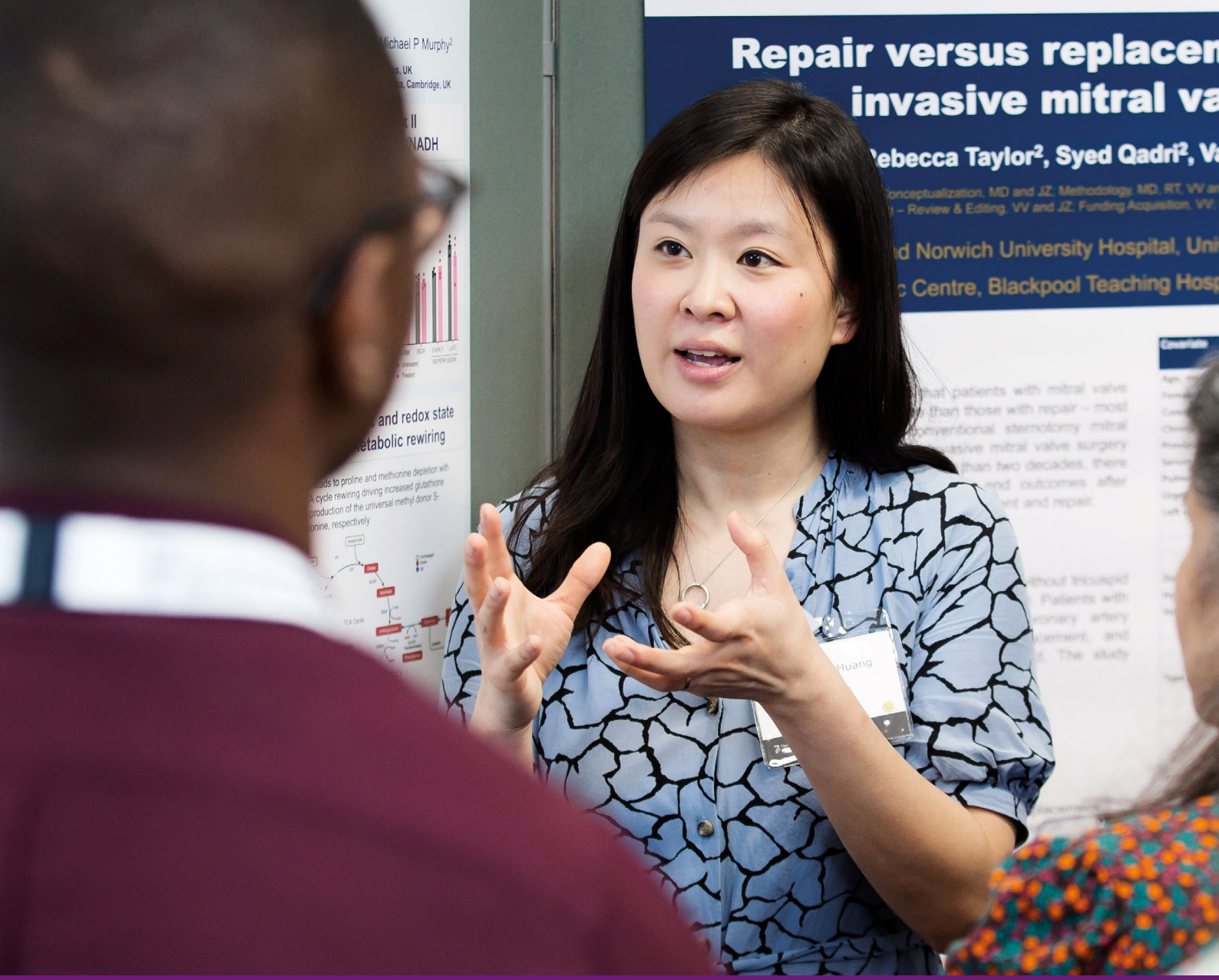

Clinical Academics in Training Annual Conference 2024

Wednesday 17 April 2024

The Academy of Medical Sciences

The Academy of Medical Sciences

The Academy of Medical Sciences is the independent, expert voice of biomedical and health research in the UK. Our Fellowship comprises the most influential scientists in the UK and worldwide, drawn from the NHS, academia, industry, and the public service. Our mission is to improve the health of people everywhere by creating an open and progressive research sector. We do this by working with patients and the public to influence policy and biomedical practice, strengthening UK biomedical and health research, supporting the next generation of researchers through funding and career development opportunities, and working with partners globally.

Opinions expressed in this report do not necessarily represent the views of all participants at the event, the Academy of Medical Sciences, or its Fellows.

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This event is generously supported by Wellcome and The Lord Leonard and Lady Estelle Wolfson Foundation.

Clinical Academics in Training Annual Conference (CATAC) 2024

Contents

Welcome to CATAC 2024

"On behalf of the Academy of Medical Sciences, it gives me great pleasure to welcome researchers in medicine and health across all clinical disciplines to our Clinical Academics in Training Annual Conference (CATAC) 2024, which we are hosting for the first time in Northern Ireland.

This is a critical time in the future of clinical academia. This event, which brings together some of the most talented researchers in the UK, is therefore a vital opportunity to showcase and celebrate your work as well as come together as a community to develop skills relevant to clinical academics of all stages. We hope you find the conference a supportive environment for your interactions with colleagues but also one that challenges and inspires you.

As the independent voice of biomedical and health research, we are committed to growing the clinical academic community by providing innovative career funding and support that builds the capacity of teams and individuals, as well as by ensuring biomedical and health researchers have clear, effective, and attractive career pathways. Through our policy and influencing work, we are working with partners across the UK to reverse some worrying recent trends and deliver a bright future for clinical academia in the UK. Please do ask our staff if you would like to learn more about this or any other aspect of our work.

Please join me in thanking Professor Julie-Anne Little and Professor Danny McAuley FMedSci for co-chairing what is sure to be a fascinating event and Dr Lola Solebo, a former awardee of Starter Grant for Clinical Lecturers and Principal Clinical Research Fellow at University College London, for delivering the keynote speech.

I look forward to meeting you all in person at the conference and urge you to take full advantage of this opportunity by meeting fellow researchers across all career stages, learning about cutting edge research within clinical academia, and sharing your own research with the wider community."

Simon Denegri OBE, Executive Director, The Academy of Medical Sciences

"CATAC is a wonderful opportunity to develop new ideas and partnerships for the future, as well as celebrating your research achievements. This is the first CATAC held in Northern Ireland and it's brilliant to see such a lot of interest and engagement from the local research community in our competitions. I look forward to meeting you all in Belfast and hope you will enjoy this chance to connect with the wider clinical research community and learn about each other's work."

Prof Julie-Anne Little, co-chair for CATAC 2024 and a FLIER participant, Senior Lecturer at Ulster University and registered optometrist

"It's a pleasure to co-Chair this prestigious event, which brings together some of the most inspiring clinical academics from across disciplines to share their impactful work with the community. I'd like to encourage everyone attending to actively participate and make the most of the opportunity to build connections and to learn something new through our interactive skills-based training sessions.'

Prof Danny McAuley FMedSci, co-chair for CATAC 2024, Starter Grant Selection Panel member, and Professor and Consultant in Intensive Care Medicine at the Royal Victoria Hospital and Queen's University Belfast

Keynote speaker

Dr Lola Solebo

Lola is an NIHR Clinician Scientist within the Population, Policy, and Practice department of UCL Great Ormond Street Institute of Child Health (GOS ICH), and a Consultant Paediatric Ophthalmologist at Great Ormond Street Hospital. Her work investigates the determinants of outcome for children with eye disease, and how best to translate these findings into changes in practice and policy. She undertook her PhD at GOS ICH (2008–2011), where she created 'IoLunder2', a nationally representative and internationally unique cohort of children undergoing surgery for cataract (the most important worldwide cause of avoidable childhood blindness). Lola contributes to the development of health policy nationally and internationally (through roles within Office for Health Improvement and Disparities, UNICEF and WHO advisory groups).

Her current projects aim to develop imaging-based disease metrics, patient-reported disease metrics, and pipelines of data extraction from hospital electronic patient records, to stratify a rare, potentially blinding childhood inflammatory eye disease – but also to develop methods and approaches that will support the investigation of other childhood disorders. Lola is passionate about science communication and promoting equity, diversity and inclusion in research (she is Chair of the GOS ICH Race Equity Group). Her work was recently featured in a Nature Spotlight article: https://www.nature.com/articles/d41586-023-03234-9

Her keynote speech will be on "Illuminate, innovate, advocate: mapping a path in clinical academia and childhood eye and vision disorders".

Programme

Riddel Hall, Queen's University Belfast, 185 Stranmillis Rd, Belfast BT9 5EE

09.00 **Registration and poster set-up**

09.25 **Welcome**

Prof Danny McAuley FMedSci, Professor and Consultant, Royal Victoria Hospital and Queen's University Belfast, and Prof Sir Ian Greer FMedSci, President and Vice Chancellor, Queen's University of Belfast

09.35 **Post-doctoral plenary competition**

Each competitor will have 10 minutes to present their research, followed by five minutes of questions from the judges and audience.

High baseline plasma suPAR predicts mortality and treatment response to simvastatin in patients with ARDS: an ancillary analysis of the HARP-2 randomised clinical trial
Dr Andrew Boyle, Queen's University Belfast and Royal Victoria Hospital, Belfast

Early versus delayed weight-bearing following operatively treated ankle fracture (WAX): a randomised controlled trial and health economic evaluation
Mr Chris Bretherton, Queen Mary University of London and Barts NHS Trust

Use of an ex-vivo/in-vitro model of the human airway epithelium to characterise the impact of gestational and developmental age on early-life airway innate immune responses to respiratory syncytial virus (RSV)
Dr Helen Elizabeth Groves, Queen's University Belfast and Royal Belfast Hospital for Sick Children

Mixed-methods evaluation of a face-to-face educational intervention for health and social care professionals to deliver family-centred cancer supportive care when a parent with dependent children is at end-of-life
Dr Jeff Hanna, Ulster University and South Eastern Health and Social Care Trust

PROFILE: a multi-centre, randomised, open-label, biomarker-stratified clinical trial of treatment strategies for patients with newly diagnosed Crohn's disease
Dr Nurulamin Noor, University of Cambridge

10.50 **Refreshments & networking**

11.20 **Pre-doctoral plenary competition**

Each competitor will have five minutes to present their research, followed by five minutes of questions from the judges and audience.

Novel insights into Fuchs endothelial corneal dystrophy through genetic, demographic, and phenotypic correlations
Dr Siyin Liu, University College London

Delirium on presentation with a hip fracture is associated with adverse outcomes: a multicentre observational study of 18,040 patients using prospectively collected national clinical registry data
Dr Rose Penfold, University of Edinburgh and NHS Lothian

Subphenotypes in patients with severe acute respiratory failure requiring extracorporeal membrane oxygenation: a prospective study
Dr Kiran Reddy, Queen's University Belfast and Royal Victoria Hospital, Belfast

Optimum cutoff values for absolute neutrophil count and C-reactive protein in the management of febrile infants at risk of invasive bacterial infection: a prospective multicentre study across the UK
Dr Etimbuk Umana, Queen's University Belfast

12.00 Lunch

12.45 Poster competition

This will be judged by the CATAC attendees. You have been assigned one poster group to judge and this is shown on your attendee badge. Please note: poster competitors cannot act as a judge in this competition.

13.45 Parallel sessions

Please attend one session of your choice

Beyond academia: communicating your research to non-academic audiences
or
Exploring personal and public involvement through the research cycle

15.15 Refreshments & networking

15.45 Prize giving

Prof J Stuart Elborn CBE FMedSci, Interim Provost and Deputy Vice-Chancellor, Queen's University Belfast

16.00 Keynote

Dr Lola Solebo, NIHR Clinician Scientist and Consultant Paediatric Ophthalmologist, UCL and Great Ormond Street Hospital

16.45 Closing remarks

Prof Julie-Anne Little, Senior Lecturer and registered optometrist, Ulster University

16.50 Networking reception

18.00 Event ends

Parallel sessions

Parallel session one:

Beyond academia: communicating your research to non-academic audiences

Communicating your research effectively to non-academic audiences is very important when engaging the public, engaging with TV or radio, or pitching research for funders. A workshop led by Camilla Long from communication experts Bespoke Communications will provide tools and techniques to engage better with your audiences. This includes harnessing the power of storytelling to make your research accessible and relatable, mastering key structures to keep your presentation on track, and techniques to manage performance anxiety.

The workshop does not require participants to come prepared with any pitches or presentations. The facilitator, Camilla Long, will present on communication strategies. You will have the opportunity to discuss and practice them in smaller groups as part of the workshop.

Camilla Long is the award-winning co-founder of Bespoke Communications, a leading UK and Ireland-based training company. Specialising in coaching executives and experts to communicate effectively and authentically, she believes in bringing fulfilment to work by embracing one's true self. Camilla conducts interactive masterclasses grounded in behavioural science, inspiring teams to improve their communication. Camilla is a Professional Member of the Professional Speaking Association, and she received the PSA Emerging Speaker of 2021 Award. Actively involved in various organisations, she serves as a board member of the Causeway Chamber of Commerce, mentors with Women in Business, and volunteers as a Samaritans Listening Volunteer. With degrees in Computer Science and Strategic Management, Camilla brings a diverse skill set to her impactful work.

Parallel session two:

Exploring personal and public involvement PPI through the research cycle

> Nothing about us without us.

At the Academy, we believe that all research should consider the voices of those it affects – in the design, undertaking, evaluation, and dissemination. This is especially relevant in clinical research and is often referred to as personal and public involvement (PPI). In other parts of the UK this can be patient and public involvement.

This interactive session with the Academy's Engagement team will explore what meaningful PPI can look like throughout the research lifecycle, including what to consider when making those first steps to working with patients and the public.

The session has been co-designed with our speakers who have experience of involvement, research, and funding within the Northern Ireland landscape, to ensure that session attendees will find the session relevant and informative.

Please come prepared to discuss involving patients and the public in your own work and to ask any questions – whether you've got experience of PPI or not.

If you'd like to ask anything in advance or think there is something we should discuss, please email engagement@acmedsci.ac.uk

You will hear from:

Debbie Keatley who has experienced cancer as a patient and carer, and lives with long-term sequalae. Debbie has previously worked in the private, voluntary and public sectors, with experience ranging from international finance, IT, training and development, education and community development to policy development. Debbie is involved with many organisations and movements in health research. She's a member of CRUK's Data Advisory Board and Clinical Research Committee.

Most of her work is cancer-specific, but her experience in social policy informs her work in understanding the foundations of good health and the drivers of health inequalities. In non-cancer-specific work, she is working on a research project with the Office of the National Data Guardian and was a former public representative on NIHR's HTA programme and was a PPI member of NIHR's COVID Call College of Experts. She served a term on HDR UK's Public Advisory Board and is now a member of their PPIE Strategy Steering Group.

Locally, she is a member of the Northern Ireland Cancer Research Consumer Forum and the Council of Northern Ireland Cancer Registry. She works with colleagues across the island to further the work of the All-Island Cancer Research Institute (AICRI).

She is also involved in clinical studies from international to local level and advocates for human rights.

Dr Maelíosa McCrudden is the Research Engagement and Impact Officer for the Faculty of Medicine Health and Life Sciences at Queen's University Belfast (QUB) and is the co-ordinator of the QUB PPI Network, which launched in 2020. Having been awarded her PhD in biochemistry from QUB, Maelíosa then spent over 15 years in postdoctoral research and teaching before moving into her current role. She is an advocate of experiential learning and service user-led research, leading to positive societal impact.

Alix Crawford is the Chairperson and Founder of Mae Murray Foundation, a charity set up in 2016 as a result of her lived experience of raising her daughter Talia who has cerebral palsy. She has 24 years' experience of navigating health, social care and education services and is passionate about breaking down the barriers to participation that too many people still face in everyday life. She is also a keen PPI contributor.

Mae Murray Foundation is striving to create inclusive best-practice environments and share our learning with others so that evidenced models can be replicated. They want to see younger generations grow up in communities where diversity is visible, is celebrated, and where people recognise one another to be of equal and inseparable value.

Talia McDowell is 24 years old and studied dance and drama in Cheltenham for two years and then completed an Inclusive Dance training course in Cork. The course was a collaboration between University College Cork and partners and is the first of its kind in Ireland. Looking forward, as a seated powerchair dancer, she is just starting her journey into self-employment as a dance facilitator. In her spare time, she volunteers with Mae Murray Foundation, a charity founded by her mum, which focuses on creating inclusive environments. She is passionate about helping educate others about ability and inclusion and has enjoyed contributing to PPI projects.

Sonia Patton is from Co. Tyrone, Northern Ireland, and retired from a role in procurement following a breast cancer diagnosis in 2014. Prior to this, she worked for many years in retail merchandising and stock control. Living with and beyond cancer, Sonia has experienced many chronic and long-term comorbid conditions and is particularly interested in research that takes a whole-pathway approach to improving the quality of life for people living with and beyond cancer and other long-term conditions. Sonia is a passionate advocate for the patient and public voice, and opportunities are created to ensure parity of participation in research decisions that impact their treatment and care.

Sonia currently works in an advisory capacity with many organisations that rely on health data, who recognise its significance in research to improve outcomes for both patients and the public. This includes HDRUK, as a member of their Public Advisory Board, being a patient representative on the Clinical Research Committee at Cancer Research UK, and a member of the Research Transparency Panel at Flatiron Health UK.

Living in Strabane, a rural town in the north-west of Northern Ireland, Sonia is also a member of the Northern Ireland Cancer Research Consumer Forum (NICRCF) and Patient Involvement Enhancing Research (PIER). She is also a sessional trainer with AWARE N. Ireland, delivering mental health and wellbeing programmes into communities, schools, colleges, universities, and workplaces.

Post-doctoral plenary competition

High baseline plasma suPAR predicts mortality and treatment response to simvastatin in patients with ARDS: an ancillary analysis of the HARP-2 randomised clinical trial

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Background
Soluble urokinase plasminogen activating receptor (suPAR) is a biomarker of nuclear factor kappa B (NF-kB) activation and inflammation. Baseline plasma suPAR may function as a prognostic biomarker in patients with the Acute Respiratory Distress Syndrome (ARDS). Simvastatin can down-regulate NF-kB activity. Therefore, it is plausible that in patients with ARDS, baseline plasma suPAR might identify patients who could benefit from simvastatin therapy. The aims of this analysis were to investigate if, in patients with ARDS, high plasma suPAR is associated with increased mortality, and whether treatment with simvastatin is associated with benefit in patients with high baseline suPAR.

Methods
This was an ancillary analysis of the HARP-2 randomised controlled trial, which evaluated simvastatin 80 mg daily as a therapy for patients with ARDS. Consent for sample storage and future analysis was obtained. Baseline plasma suPAR was measured using the ELLA automated ELISA system. We compared 28-day mortality and response to simvastatin therapy according to baseline plasma suPAR using Cox proportional hazards analysis. High suPAR was defined as ≥6 ng/ml based on previous data. The optimal cut-off for baseline plasma suPAR to predict mortality in these data was also determined using receiver-operator curve analysis with calculation of the Youden index.

Findings
High baseline plasma suPAR (n=217) was associated with increased 28-day mortality (high suPAR 32.3% vs. low suPAR 18.2%), which persisted after adjustment for age, vasopressor use, sepsis, baseline PaO2/FiO2 ratio, and baseline APACHE-II score (adjusted HR 1.56 [95% CI 1.04 – 2.33], p=0.03). In keeping with previous data, the most effective threshold for baseline plasma suPAR to predict 28-day mortality (Youden's J point) was 6.22 ng/ml. Finally, in patients with high baseline plasma suPAR, allocation to simvastatin was associated with a lower probability of 28-day mortality compared with placebo (26.7% vs 37.1, adjusted HR 0.47 [0.27 – 0.80], p<0.01). In contrast, in patients with low baseline suPAR there was no association between simvastatin and 28-day mortality (adjusted HR 0.79 [0.43 – 1.45], p=0.45).

Interpretation
Furthermore, in patients with high, but not low, baseline plasma suPAR, treatment with simvastatin is associated with reduced 28-day mortality. This suggests that baseline plasma suPAR may act as a biomarker to identify patients who have an activated pro-inflammatory NF-kB pathway that simvastatin can down-regulate. This offers exciting future therapeutic potential as a personalised medicine approach for patients with ARDS.

Implications
The identification in a population of patients with ARDS, which is commonly caused by sepsis, that simvastatin may be an effective therapeutic for patients with elevated plasma suPAR offers the possibility that simvastatin may be a future therapeutic in a similar population of patients with sepsis. Furthermore, in patients with COVID-19, high baseline plasma suPAR has been used to guide treatment with an IL-1 receptor antagonist to improve clinical outcomes. Therefore, this is a potential future approach which could be evaluated in patients with ARDS and/or sepsis. Prospective evaluation of plasma suPAR as a biomarker offering prognostic and predictive enrichment in both ARDS and sepsis is now required. With point-of-care assays available, future studies using a personalised medicine approach based on plasma suPAR for patients with ARDS and sepsis may unlock novel therapies.

Early versus delayed weight-bearing following operatively treated ankle fracture (WAX): a randomised controlled trial and health economic evaluation

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Background
After surgery for a broken ankle, patients are usually instructed to avoid walking for six weeks (delayed weight-bearing). Walking two weeks after surgery (early weight bearing) may be a safe and preferable rehabilitation strategy. This study aimed to determine the clinical and cost-effectiveness of an early weight-bearing strategy compared to a delayed weight-bearing strategy.

Methods
A pragmatic, multicenter, randomised non-inferiority trial including 561 participants (aged ≥18 years) who received acute surgery for an unstable ankle fracture in 23 UK National Health Service (NHS) hospitals assigned to either a delayed weight-bearing (n=280) or an early weight-bearing rehabilitation strategy (n=281). Neither participants nor clinicians were blinded to the treatment. The primary outcome was ankle function measured using the Olerud and Molander Ankle Score (OMAS) at four months post-randomisation. The pre-specified non-inferiority OMAS margin (ΔT) was –6 points. Secondary outcomes included health-related quality of life, complications, and cost-effectiveness evaluated from a UK NHS and personal social services (PSS) perspective.

Findings
Primary outcome data was collected from 86% (n=480) of participants. At four months post-randomisation, the mean OMAS score was 65·9 in the early weight-bearing and 61·2 in the delayed weight-bearing group; adjusted mean difference 4·47 95% confidence interval (CI) 0·58 to 8·37; p=0·024 (superiority testing adjusted difference = 4.42; 95% CI 0.53 to 8.32, p=0.026) in favour of early weight bearing. 16·4% (n=46) of participants in the early weight-bearing group and 13·9% (n=39) in the delayed weight-bearing group experienced one or more complications (adjusted odds ratio 1·18, 95% CI 0·80 to 1·75, p=0·40). The mean costs from the NHS and PSS perspective in the early and delayed weight-bearing groups were £725 and £785, respectively (mean difference –£60 [95% CI –£342 to £232]). The probability that early weight-bearing is cost-effective exceeded 80%.

Interpretation
The study found an early weight-bearing strategy was not inferior in terms of ankle function to a delayed weight-bearing strategy as measured by the OMAS. The study also demonstrated comparable complication rates between the two approaches. A health economic evaluation indicated that an early weight-bearing strategy is highly likely to be cost-effective.

Implications
The effective completion of the WAX trial underscores the efficacy of the associate principal investigator scheme in recruiting patients for clinical trials within the NHS. Utilising REDCap for all facets of trial administration, such as randomisation, text message reminders, and outcome assessment, strengthens the use case for future trial delivery. The necessity of evaluating adherence to trial interventions, specifically weight-bearing instructions in this instance, is highlighted to facilitate a comprehensive interpretation of study findings. Ultimately, the WAX trial showcases the feasibility of conducting trials in other surgical specialities where existing treatments carry strong surgeon/practitioner biases.

Use of an ex-vivo/in-vitro model of the human airway epithelium to characterise the impact of gestational and developmental age on early-life airway innate immune responses to respiratory syncytial virus (RSV)

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Background
Respiratory syncytial virus (RSV) is the commonest cause of severe lower respiratory tract infection in infants. Premature birth or being very young at the time of first RSV infection are risk factors for severe RSV-related illness. Airway epithelium innate immune responses represent a vital first line of defence against viral infections in young infants. Emerging work suggests age-related progression in innate immune airway responses. However, the impact of very early-life ageing on human airway epithelium innate immune responses to respiratory viruses remains poorly understood. We sought to characterise the development of early-life innate immune responses in airway epithelium to RSV.

Methods
We exploited an ex-vivo/in-vitro model of the human airway epithelium to generate well-differentiated primary paediatric nasal epithelial cell cultures (WD-PNECs) from nasal brushings. Following ethical approval and parental consent, WD-PNECs were successfully established using nasal cells derived from the same preterm (n=13) and term (n=15) infants at birth and repeated at one year old. Established WD-PNECs were subjected to RSV or mock infection to determine gestation- and age-related impacts on RSV growth and cytopathology, chemokine/cytokine secretion and type-three interferon responses. Next-generation sequencing of extracted RNA was conducted to characterise global transcriptomic responses and identify novel gestation- and age-related genomic signatures.

Findings
Cytopathology and viral growth kinetics in WD-PNECs following RSV infection were similar irrespective of gestation or age. Secretion of interferon lambda-1 (IFN-λ1) and chemokines CXCL10, CCL5 and CXCL8 were comparable between preterm- and term-newborn cultures. Importantly, following RSV infection, secretion of RSV-induced IFN-λ1 ($p<0.005$), CXCL10 ($p<0.05$) and CCL5 ($p<0.05$) and expression of IFN-stimulated genes, IFI6 and ISG15 ($p<0.05$) were significantly higher in one-year- compared to newborn-derived cultures. Furthermore, gene expression analysis demonstrated 156 differentially expressed genes with chronological age, including higher expression of the little-known interferon, IFNε, with increasing age. Transcriptomic analysis revealed gestation-dependent differences at birth, which persisted at one year old. Interestingly, we identified differential expression of endogenous pleiotrophin (PTN), which interacts with nucleolin, a cofactor for RSV cellular entry. PTN expression/secretion following RSV infection was significantly increased with higher gestation ($p=0.01$) and age ($p<0.001$) and we further identified a novel anti-RSV role for PTN.

Interpretation
This study's major strength is the generation and use of a novel ex-vivo/in-vitro model to determine the development of RSV-induced airway epithelium responses in the same individuals over the first year of life. We present the first description of both gestational- and age-related differences in human airway epithelium innate immune responses to RSV infection in early life. We demonstrate lower RSV-induced expression of pro-inflammatory chemokines and antiviral interferons at birth, and developmental differences in expression of the novel anti-RSV protein PTN. These findings may, in part, explain increased susceptibility of preterm and very young infants to severe RSV disease.

Implications
We present the first report of both gestation- and age-related development of innate immune responses of the airway epithelium to RSV infection in the first year of life. Most notably, our findings demonstrate that

in early life, RSV-induced innate immune responses became more robust with increasing age in the same individuals. Our results point to an intrinsic development of RSV-induced innate immune responses in the airway epithelium with increasing gestation and age. These results are vital to furthering our understanding of the increased risk of severe RSV disease in preterm and very young age groups. Furthermore, these results may also provide clues towards the impact of gestation and age on airway innate immune responses to other significant respiratory viral infections, such as SARS-CoV-2 and influenza. This is especially important in light of new evidence highlighting the significant impact of early childhood lower respiratory infections on lifelong respiratory function.

Mixed-methods evaluation of a face-to-face educational intervention for health and social care professionals to deliver family-centred cancer supportive care when a parent with dependent children is at end-of-life

Dr Jeff Hanna

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Background
Families are often uncertain how best to prepare and support children (<18 years) for the end-of-life experience of a parent with a poor cancer prognosis. Parents want and need advice and guidance from their healthcare team on how to include and involve children in the end-of-life experience. Health and social care professionals (professionals) consistently highlight a lack of knowledge, skills and confidence toward supporting parents at end-of-life regarding their children. This project aimed to equip professionals on how best to support this population.

Methods
An evidence-based and theory-driven two-hour face-to-face educational intervention was developed, informed by empirical research studies conducted during a PhD project (2017–2020), and included a bereaved parent's lived experience. The intervention was delivered interdisciplinarily at oncology settings (n=13) for 347 professionals, between September 2021 and September 2023. The intervention was evaluated using a mixed-methods approach. Quantitative surveys were completed immediately before and after the intervention by 216 professionals using a modified validated self-efficacy scale and single-item questions evaluating perceived usefulness and relevance. At ≥3 months post-intervention, qualitative interviews explored if and how the intervention impacted professionals' practice, analysed using reflexive thematic analysis.

Findings
Quantitative findings highlighted a statistically significant improvement in self-efficacy post-educational intervention ($p<0.001$). Qualitative data highlighted professionals were more confident in taking an active role in initiating conversations with parents about their children. This included ensuring parents were provided with clear and honest information surrounding a poor prognosis, and reassuring parents of the importance of telling the children about the poor prognosis, with advice and guidance on how best to do this. Key components from the educational intervention that positively shaped clinical practice included the bereaved parent's lived experience, the communication framework and videos emulating good practice. To consolidate learning in practice, professionals felt they would require opportunities to practise conversations through advanced communication skills training, alongside regular 'booster' training sessions. Findings are discussed under two themes: (1) impact of the intervention in practice, and (2) how to progress family-centred cancer conversations and support in routine care.

Interpretation
Evidence- and theory-driven education can positively impact professionals' provision of family-centred cancer care in practice. To promote sustainability, using the 'Person-based Approach', this face-to-face educational intervention has recently been adapted and optimised to a digital health intervention, which is freely available for professionals on a national and international level. An evaluation of the eLearning educational intervention is required to explore its acceptability and usability in practice. Through the lens of parents (pre- and post-bereavement), there is a need to explore if and how the provision of this educational intervention to professionals has impacted on the familial end-of-life experience.

Implications
Children less prepared for parental death when it is expected are at increased risk of adverse outcomes in bereavement and later life. The benefits of open and honest communication at end-of-life are clear in

maintaining and sustaining trusting relationships, and mediating for adverse outcomes such as a decline in education, risk-taking behaviours and involvement with mental health services. Professionals, of all disciplines, are ideally placed to support parents as they prepare children for the death of a parent. Equipping professionals to support parents at end-of-life has the potential to reduce the burden on overstretched health services, resulting in better mental and physical outcomes for the whole family, pre- and post-bereavement.
Also, promoting the well-being and resilience for professionals, who consistently highlight emotionally struggling with this important aspect of supportive cancer care at end-of-life. Policy is required to integrate family-centred cancer care as part of routine care at end-of-life.

PROFILE: a multi-centre, randomised, open-label, biomarker-stratified clinical trial of treatment strategies for patients with newly diagnosed Crohn's disease

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Background
Clinical outcomes differ substantially between patients with Crohn's disease and there is variability in how newly diagnosed patients are managed. Recent interest has focused on developing biomarkers to predict outcomes and guide therapy. However, no biomarker has been formally assessed for utility in the field of inflammatory bowel disease. PROFILE was designed to evaluate the clinical utility of a blood-based prognostic biomarker in patients randomised to "top-down" or "accelerated step-up" treatment strategies for newly diagnosed Crohn's disease.

Methods
PROFILE (PRedicting Outcomes For Crohn's dIsease using a moLecular biomarker, ISRCTN 11808228) was a multi-centre, open-label, biomarker-stratified, randomised controlled trial. It enrolled adults with newly diagnosed active Crohn's disease (Harvey Bradshaw Index >7, either elevated C-reactive protein or faecal calprotectin or both, and endoscopic evidence of active inflammation). Following biomarker testing, patients were randomised to "top-down" (infliximab and immunomodulator) or "accelerated step-up" (conventional) treatment stratified by: biomarker subgroup (termed IBDhi/IBDlo), endoscopic inflammation (mild/mod/severe) and extent (colonic/other). The primary endpoint was sustained steroid and surgery-free remission to week 48. The full analysis population (equivalent to 'intention-to-treat') was analysed. This trial has completed.

Findings
Between 29 December 2017 and 5 January 2022, 386 patients were randomised. Median time from diagnosis to trial enrolment was 12 days (range 0–191). Primary outcome data were available for 379 participants. Sustained steroid and surgery-free remission was significantly more frequent in "top-down" compared to "accelerated step-up" (149/189 [79%] vs 29/190 [15%], absolute difference 64%, 95% CI=57% to 72%, p<0.0001). There was no biomarker-treatment interaction effect (absolute difference 1%, 95% CI=–15% to +15%, p=0.944).Endoscopic remission at week 48 was significantly greater in "top-down" compared to "accelerated step-up" (67% vs 44%, absolute difference 23%, 95% CI=11% to 36%, p-value <0.0001), with no biomarker-treatment interaction effect. Incidence of adverse events (including disease flares) and serious adverse events was lower in "top-down" vs "accelerated step-up" (168 vs 315; 15 vs 42, respectively), with fewer complications requiring abdominal surgery (1 vs 10, odds ratio=0.095, 95% CI=0.001 to 0.505) and no increase in infections.

Interpretation
"Top-down" treatment with combination infliximab and immunomodulator achieved substantially better outcomes at one year compared to "accelerated step-up" therapy in patients with newly diagnosed Crohn's disease. The magnitude of difference in the primary endpoint between "top-down'' and "accelerated step-up'', combined with the benefit of "top-down'' across all secondary endpoints, underpins confidence in the result. The biomarker assessed in the PROFILE trial did not show clinical utility. "Top-down" therapy should now be considered standard-of-care for patients with newly-diagnosed active Crohn's disease.

Implications
PROFILE is the first biomarker-stratified trial in Gastroenterology and one of the first across immune-mediated inflammatory diseases (IMIDs). Inflammatory bowel disease, like other IMIDs, has a profound health and socio-economic impact on patients, affecting education, relationships, and employment. It impacts most when the disease is poorly controlled, leading to repeated symptomatic flares and complications. PROFILE provides evidence for an effective treatment strategy for patients through early intervention and treatment, and has major potential implications for all other IMIDs. Where previous studies have considered "early Crohn's disease" to be within 2 years of diagnosis, the median time from diagnosis to enrolment and treatment in PROFILE was 12 days, making this substantially the earliest Crohn's disease intervention trial ever conducted. If similar findings were demonstrated for early treatment across other IMIDs, then it is possible that large improvements in clinical outcome could be delivered across a range of specialities and disease areas.

Pre-doctoral plenary competition

Novel insights into Fuchs endothelial corneal dystrophy through genetic, demographic, and phenotypic correlations

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Background
Fuchs endothelial corneal dystrophy (FECD) is a degenerative corneal disease commonly associated with an intronic CTG repeat expansion (termed CTG18.1) in TCF4. In a minority of FECD cases, rare disease-associated variants in other genes have also been reported. Here we present findings from a large multi-centre extensively genotyped and sequenced FECD cohort to explore correlations between genotype, ethnicity, sex, and age of first corneal transplantation surgery (a surrogate metric for disease severity).

Methods
This study received approvals from Moorfields Eye Hospital (MEH; 13/LO/1084) and the General University Hospital (GUH) in the Czech Republic (2/19GACR). Genomic DNA was collected from participants recruited at MEH (n=569) and GUH (n=353). FECD diagnosis was ascertained by cornea fellowship-trained ophthalmologists. We determined the ethnicity from genome-wide SNP array data using FRAPOSA. CTG18.1 repeat length was determined by capillary electrophoresis of CTG18.1 PCR. Cases with one or more expanded alleles (≥50 CTG repeats) were classified as expanded (Exp+). Biallelic unexpanded (Exp–) cases underwent exome/genome sequencing to explore the alternative FECD-associated genes COL8A2, SLC4A11, ZEB1, AGBL1, LOXHD1.

Findings
A CTG18.1 expansion was detected in 80.6% of European cases (n=856) compared to 37.5% in non-European cases (P<0.0001), conferring a >91-fold increased risk for FECD (OR = 91.09, 95% CI: 58.50–141.85, P<0.0001) when compared to an age and ethnicity-matched control group (n=550). In the Exp+ group, the CTG18.1 repeat length was inversely correlated with age of first keratoplasty (r=–0.0859, P=0.011), independent of sex and ethnicity. Females were enriched in the total cohort (58.25%), with a more striking skew seen in the Exp– group (76.1%) than the Exp+ group (52.6%). There was enrichment of Exp+ alleles in the homozygous state versus the heterozygous state in European FECD patients compared to the controls (chi-squared=218.62, P<0.00001). Furthermore, biallelic Exp+ cases had corneal transplantation at a younger mean age than monoallelic Exp+ cases (66 vs 69 years, P=0.02). Potentially pathogenic variants (MAF<0.01; CADD >10) in FECD-associated genes were identified in <17% of Exp– cases (33/202).

Interpretation
We demonstrated that CTG18.1 repeat length is a modifier of FECD severity. The female preponderance in FECD is mainly driven by CTG18.1 independent factors. The notable enrichment of homozygous vs heterozygous Exp+ allele status in the FECD cohort, coupled with the younger age of needing corneal transplantation surgery in the biallelic Exp+ cases, indicates that CTG18.1 allelic dosage elevates both disease penetrance and severity. Interrogation of FECD-associated genes in the Exp– group suggests additional important genetic causes and modifiers remain to be discovered.

Delirium on presentation with a hip fracture is associated with adverse outcomes: a multicentre observational study of 18,040 patients using prospectively collected national clinical registry data

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Background
Delirium, a severe neuropsychiatric syndrome, is common in hip fracture patients and is associated with multiple adverse outcomes. However, large-scale routine data studies examining prevalence and associations of delirium on initial presentation are rare.

This study aimed to describe the prevalence and outcomes of delirium on first presentation with a hip fracture in a large national population sample. Our hypothesis was that delirium detected as part of routine care is independently associated with mortality and return home within 30 days of admission. We also explored whether patients with no delirium assessment recorded have higher risks than patients without delirium.

Methods
Retrospective analysis of prospectively collected routine national clinical registry data for all people in Scotland aged ≥50 years presenting with hip fracture between July 2019 and December 2021. Delirium was assessed by clinical staff using the 4 'A's Test (4AT; www.the4AT.com), an extensively-validated two-minute assessment tool. Associations of 4AT score with mortality as an inpatient within 30 days and within one year and with return home within 30 days were analysed using logistic regression models adjusted for confounders.

Approval was obtained from NHS National Services Scotland. Data release ID: DP22230478. The study complied with UK Caldicott principles.

Findings
Of 18,040 patients (mean age 80 years; 70% women) presenting with a hip fracture during the study period, 16,476 (91%) had a 4AT assessment on presentation and 3,386 (21%) had delirium (4AT≥ 4). Patients with delirium were older, more likely to reside in care homes and had higher American Society of Anesthesiologists (ASA) grades (all p<0.001). Patients with no recorded 4AT score were more likely to be male, from higher care settings, and had higher ASA grades (all p<0.001).

Delirium was independently associated with a two-fold increased mortality risk as an inpatient (adjusted odds ratio [aOR] 2.17, 95% confidence interval [CI] 1.73-2.72) and at one year (aOR 2.02, 95%CI 1.81–2.25) and lower likelihood of returning home within 30 days (aOR 0.28, 95%CI 0.25–0.31).

Interpretation
Around 20% of patients presenting with a hip fracture have delirium detected on initial presentation using routine 4AT assessment. Delirium is associated with higher mortality as an inpatient and in the year following admission and lower likelihood of returning home. Integrating delirium assessment into the initial clinical assessment of patients presenting with a hip fracture is feasible and should be standard care. Future studies should focus on identifying modifiable pre-admission and inpatient care factors to ameliorate both delirium and its harmful outcomes in this high-risk, high-volume emergency surgical population.

Subphenotypes in patients with severe acute respiratory failure requiring extracorporeal membrane oxygenation: a prospective study

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Background

Hyperinflammatory and hypoinflammatory subphenotypes have been identified in patients with the acute respiratory distress syndrome (ARDS), which consistently have different clinical characteristics, biomarker profiles and outcomes. These subphenotypes may not be specific to ARDS. Patients on veno-venous extracorporeal membrane oxygenation (VV ECMO) represent a distinct population in which subphenotypes have not been previously identified. The aim of this research was to identify if subphenotypes are present in a mixed cohort of patients with severe acute respiratory failure requiring VV ECMO.

Methods

Adult patients requiring VV ECMO from a single centre in Regensburg, Germany were included. Clinical and ventilation data were recorded. The inflammatory cytokines IL-6, IL-8, and TNF-α were measured by ELISA from plasma taken immediately prior to initiation of ECMO. Latent class analysis (LCA) was used to identify subphenotypes and included both clinical and biomarker variables. Subphenotype association with hospital mortality was assessed.

Findings

437 patients initiated on VV ECMO were included. The most common indications for ECMO were bacterial infection (41%), viral infection (15%), and post-operative (16%). Using LCA, a two-class model was the best fit ($p < 0.001$). There were 322 (74%) patients in Class 1 and 115 patients in Class 2 (26%). Class 2 was characterised by higher cytokine concentrations, more metabolic acidosis, and more organ failure, consistent with the ARDS hyperinflammatory subphenotype. Patients with the hyperinflammatory subphenotype (Class 2) had worse hospital mortality (49% vs. 31%, $p = 0.001$) than those with the hypoinflammatory subphenotype (Class 1).

Interpretation

Two subphenotypes were identified in patients with severe acute respiratory failure requiring ECMO, with characteristics similar to those previously identified in data from non-ECMO ARDS patients, including worse outcomes in the hyperinflammatory subphenotype. These subphenotypes could be targeted with precision medicine treatments in future trials of patients on VV ECMO.

Optimum cutoff values for absolute neutrophil count and C-reactive protein in the management of febrile infants at risk of invasive bacterial infection: a prospective multicentre study across the UK

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Background
Febrile infants are at risk of invasive bacterial infection (IBI) necessitating prompt treatment. This can lead to an overly cautious approach for the management of these infants. In recent years, sequential assessment has been implemented in North America and Europe, incorporating biomarkers, such as absolute neutrophil count (ANC) and C-reactive protein (CRP). Multiple cutoffs for both biomarkers have been proposed in the literature with no current evidence from a UK population. This study aimed to evaluate the proposed cutoffs for ANC and CRP in the sequential assessment of febrile infants at risk of IBI.

Methods
The febrile infant diagnostic assessment and outcome (FIDO) study is a multicentre prospective observational study of febrile infants (0–90 days) presenting to the emergency department. Patients were recruited from centres across the UK from July 2022 to August 2023. The patients underwent routine care at each centre. IBI was defined as a single growth of bacterial organism in the blood or cerebrospinal fluid. ANC cutoffs assessed were 4.0, 5.2 and 10 × 109/l. CRP cutoffs were 13.1, 15, 16.2 and 20 mg/l. The diagnostic performance was reported for each cutoff and the rate of IBI in a low-risk cohort.

Findings
The first 1000 patients from 25 centres were used for this interim analysis. The median age was 44 days (IQR: 27–62 days), with a male predominance of 60%. Of the 1000 infants, 4.5% (n=45) had IBI. Blood tests were done in 91% of infants with 879 infants having results for ANC (41 with IBI) and 913 for CRP (45 with IBI). The sensitivity and specificity of ANC 4.0, 5.2, and 10 × 109/l were 0.68/0.52, 0.51/0.67, and 0.22/0.91, respectively. For CRP cutoffs 13.1, 15, 16.2 and 20 mg/l, the sensitivity/specificity were 0.76/0.58, 0.76/0.60, 0.76/0.63 and 0.71/0.68, respectively. The cutoff with the lowest rate of IBI in a low-risk population for ANC was 4.0 × 109/l (2.9%; 13/449), while for CRP it was 16.2 mg/l (1.9%; 11/556). The AUC for ANC and CRP were 0.65 (CI: 056–0.74) and 0.77 (CI: 0.70–0.84), respectively.

Interpretation
The optimum cutoff values for ANC and CRP were 4.0 × 109/l and 16.2 mg/l respectively, within a large UK cohort. Lower thresholds could be applied in the sequential evaluation of febrile infants to improve their care and effectively identify a low-risk group that can be managed without invasive tests or the need for hospitalisation. Future studies will need to validate clinical decision aids incorporating these cutoffs, particularly in the context of a UK population.

Poster competition

Cervical lymph node aspirations: cellular and proteomic phenotyping reveal a distinct immune environment enriched for brain-relevant biomarkers

A1

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Background
Overlaps in neuro- and immuno-biology provide fruitful perspectives to translational neuroscience. A key example is the role of the glymphatic-meningeal lymphatic-cervical lymph node (CLN) system in brain waste clearance. Consequently, CLN sampling is a promising candidate to provide biological material relevant to not only brain biochemistry but also its immunology, together with their interactions.

Building on our previous application of ultrasound-guided fine needle aspiration (FNA) of CLNs in encephalitis, here we aimed to characterise CLN FNA samples at greater depth, optimise processing, and collate participant feedback towards future application in health and disease.

Methods
We did a laboratory study of CLN material from ultrasound-guided FNA matched with venous and capillary blood samples in four healthy volunteers (three male, one female; 24 to 38 years of age) who provided informed written consent (REC: 16/YH/0013). We assayed the fluid phase with broad proteomic and specific neurodegeneration panels (O-link proximity-extension and Quanterix single molecule array (SIMOA) assays, respectively. We characterised the cellular fraction with spectral flow cytometry and single-cell RNA-sequencing (scRNA-seq). Current and previous participants completed a survey regarding discomfort/pain, tolerability, and overall acceptability of the procedure in a research context.

Findings
Spatial flow cytometry and scRNA-seq confirmed previous findings of enrichment for B and T lymphocytes including T follicular helper cell subsets, but also identified innate immune cells including classical and plasmacytoid dendritic cells. By direct comparison with blood we found relative CLN abundance.

In the fluid phase, we found 152 of 722 (21%) measured proteins were specific to the CLN fluid versus either capillary or venous blood. Protein Ontology identified neural processes in four of the top five Gene Ontology (GO) annotations with targets of known neurologic significance including TREM2 and ADAM22. Furthermore, we detected phospho-Tau181, a biomarker of Alzheimer's disease, in CLN samples at a ratio of 330 versus plasma (mean CLN 6047 vs plasma 18.3 pg/mL, P=0.03 paired t-test) whereas plasma was equivalent to capillary blood (ratio 1.2).

There were no adverse events. Current and past participants found the overall research experience highly acceptable (n=18 higher, vs n=2 lower).

Interpretation
We provide evidence that CLN FNA provides material with cellular and molecular profiles distinct from blood with minimal contamination. We find a distinctive proteome with enrichment for neural markers including abundant phospho-Tau181 compared to blood. This could be consistent with constitutive drainage of the extracellular cerebral compartment in health, drainage from other head and neck structures, local production, or a combination. Expansion to include cerebrospinal fluid and more anatomically distant lymph nodes is needed to be more certain. Translationally, we provide further qualitative evidence that the procedure is well tolerated and acceptable in a clinical research context.

Implications
These findings are of broad utility for understanding lymph node physiology both in health and disease. There is immediate relevance for studying autoimmunity and infection including detailed dissection of vaccination - in which axillary lymph node FNA is already being deployed productively by several groups.

For brain research, these findings fit with predictions from animal models. Changes in drainage across age and brain health could be quantified through diverse larger sample sizes. Through broad sample types with deep analyses in smaller participant numbers, detailed maps of brain-derived antigen transport and immune handling could be re-constructed. Overall, this could give insights into both normal function over the lifespan and impairment such as dementia and brain injury.

In the longer term, this could be deployed in late translational research including proxy markers in trials and in diagnostic protocols, potentially yielding relevant information beyond blood and CSF samples alone.

Developing a porcine ex-vivo living limb system to investigate the bidirectional control of advanced prostheses

A2

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Background
Limbs play a vital role in how humans interact with the world. Myoelectric prostheses (gold standard not widely available) operate using muscle signals. They fall short of replicating the intricate function of a human hand, especially when muscle targets are weak or absent. An ideal approach is to capture signals directly travelling down (movement) and up (feeling) peripheral nerves, fulfilling their native function.

Our understanding of how these biological signals appear remains unknown. This impedes our ability to programme sensors on a prosthetic limb, such that the ability to feel cold, heat, light touch and painful stimuli is an under-investigated research opportunity.

Methods
This study perfused porcine forelimbs (Landrace species, 80 kg) for 24 hours via Ex-vivo Normothermic Perfusion (EVNP). This platform restores tissue metabolism outside of the body using a bespoke oxygenated, autologous blood-based medium, supported by critical substrates for health and recirculated at normothermia. This offers an affordable, high-throughput, ethical approach for electrophysiological studies that avoids the perception of unwanted stimuli in live animals and humans with the inadvertent risks of acute nerve injury. Physiological parameters were recorded in real time.

Findings
A pilot study was carried out preserving pig limbs physiologically for 24 hours using a protocol optimised by our lab. Bilateral paired forelimbs were randomised to EVNP (n=5) or cold static storage (CSS; n=5) with each group subjected to continuous serial electrical stimulation of the proximal median nerve (frequency 100 Hz, Amplitude 1.000 Vpp). Electromyography (EMG) was recorded using surface electrodes (Shimmer sensingTM) from the flexor mass. Tissue perfusion was macroscopically observed throughout EVNP and confirmed using thermal imaging.

Haemodynamics and blood biochemistry remained within stable physiological parameters. Preliminary data shows that stimulation of the severed proximal median nerve generates detectable surface EMG signals with macroscopic contraction of the flexor mass observed after 30 minutes of perfusion, reaching a peak at nine hours with decay until the end of perfusion. No contraction or electrical activity was observed in control limbs.

Interpretation
The main innovation from this proposal is the development of a 3Rs animal model, given the authors have a duty and have values aligned with the ethical practices in the use of animals. We have performed several 24-hour limb ex-vivo limb perfusions and completed pilot experiments demonstrating that neuromuscular activity up until 19 hours is observed compared with control cold stored limbs. This demonstrates there is electrical activity arising from the neuromuscular unit. This is confirmed both macroscopically with strong contractions at the elbow and detectable via transdermal EMG recordings.

Implications
Modern prostheses are critiqued for their degradation in signal quality secondary to muscle fatigue and electrical interference. Practical models for electrophysiological research for nerve stimulation are lacking that reliably differentiate diverse tactile stimuli and test configuration, application, and properties of engineered electrodes such as bioavailability and selectivity. Direct neural stimulation in humans has been criticised for its unwanted perceptions, evoking paraesthesia-like sensations.

EVNP presents a unique avenue for exploring these attributes, previously unthinkable in live subjects. A systematic review could not identify a single ex-vivo limb perfusion study using this model for the development of bionic prostheses (PROSPERO CRD42022363528). Leveraging biomimetic sensory encoding strategies, akin to natural tactile codes, holds the potential for better quality sensory perception that is likely to improve device acceptance.

Identifying new immunotherapy targets using machine learning and ex vivo validation

A3

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Background
Immunotherapy has revolutionised cancer treatment. However, existing immune checkpoint inhibitors (CPIs) yield low response rates in most cancers, highlighting the need for new therapeutic options. Traditional immune-oncology (IO) target discovery relies on preclinical models, which struggle to recapitulate human tumour complexity, limiting translation potential. Attention is thus directed at harnessing multimodal patient molecular data with modern machine learning (ML) techniques to identify new IO targets that may have higher clinical viability.

Methods
We trained ML systems on IO targets that progressed to stage I or higher clinical trials. We constructed a knowledge graph for model development. Graph nodes (n=11,919) comprised genes; edges represented n=99,275 protein–protein interactions (PPIs). Genes were annotated with n=6,387 disease associations alongside exome and transcriptome features from n=1,317 CPI-treated patients. We considered immune cell biology by incorporating cell type-specific PPIs from single-cell transcriptomic atlases (n=350). To capture how antigen processing affects immunotherapy response, we examined the immunopeptidome of n=60 patients. Causal data on immune responses to genetic perturbation stemmed from CRISPR tumour-T cell co-cultures and n=15,442 SNP-phenotype links.

Findings
Firstly, we developed an ensemble ML approach, which achieved test ROC-AUC>0.75. Next, we used a graph-based ML framework, which yielded superior performance (test ROC-AUC>0.90). Orthogonal validation confirmed these models can discriminate known targets by trial phase ($p<0.001$), predict patient response in new CPI trials ($p<0.05$), and identify genes that rank highly in unseen genome-wide CRISPR screens. Targets from both methods have entered experimental validation in patient-derived explants and organoid-immune co-cultures. Already, we have identified two novel targets predicted to relate to macrophage activity. Early data suggest that perturbing them leads to macrophage repolarization. Further validation experiments are ongoing.

Interpretation
Our method is effective at uncovering new IO targets as evidenced by its impressive performance on external and orthogonal validation tasks. It can identify critical nodes in biological networks that might be attractive hits. In addition, deciphering data types that drive model predictions provides a broader immunobiological understanding of anti-tumour immune responses. Thus, our results endorse using ML and multimodal data for novel IO target discovery.

Development of a patient-derived explant model using a tissue culture system to investigate the immunology of cutaneous squamous cell carcinoma

A4

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Background
Cutaneous squamous cell carcinoma (cSCC) is the commonest cancer worldwide, with substantial capacity to metastasise, and its incidence is rapidly increasing. Conventional treatments for advanced disease are ineffective and immunotherapy provides complete response in fewer than 15% of patients, so there is an urgent need for more effective treatments. Animal models can correlate poorly with human immunotherapy clinical trial results, so effective human pre-clinical models are required to develop and test novel treatments. We report the development of a tissue slice culture (TSC) model in cSCC, enabling immunological investigation of human tumours, while maintaining their microenvironment and normal cell-to-cell interactions.

Methods
Fresh tumour samples were obtained from patients attending for standard surgical excision of their cSCC. 300-micron thick slices were taken from tumours, using a Leica VT1200 vibratome, and cultured on PTFE culture-well inserts (Millipore) in 35 mm well plates. Media containing therapeutic molecules was added and the slices were incubated for between 48 and 120 hours. Cell viability was assessed by flow cytometry and confocal microscopy. Immune cell activation was detected through measurement of Ki67, granzyme B (GzB), CD69, and CD25 by flow cytometry, and detection of cytokines in the culture supernatant by ELISA.

Findings
Samples from 38 cSCCs (diameter 10 to 52mm) have yielded a mean of 7.9 (SD 2.9) full tumour-diameter slices per tumour. Live/dead staining with confocal microscopy and flow cytometry showed a high degree of tissue viability following 72 hours of TSC, with 92.3% of T cells and 99.5% of B cells viable. Graded stimulation with anti-CD3 (up to 1000 ng/ml) increased markers of T proliferation and activation compared to unstimulated cultures, including expression of Ki67 (5.2% to 20.6%, respectively, $p < 0.0001$), GzB (46.2% to 70.5%, respectively, $p < 0.0001$), and CD69 (21.0% to 31.9%, respectively, $p < 0.05$) in a dose-response manner ($n = 10$). Interferon-gamma concentrations increased from <12.6 ng/ml to 369.2 ng/ml ($p < 0.05$, $n = 6$). Anti-CD3-induced immune activation could be suppressed with ciclosporin (10ug/ml), shown by T cell Ki67 (48.2% reduction), GzB (12.4% reduction), and CD25 expression (58.9% reduction) ($n = 12$, $p < 0.01$).

Interpretation
This is the first reported use of a TSC system for the study of cSCC immunology. The results show that immune responses can be reliably recorded and manipulated (both stimulated and suppressed) using both antibody and small-molecule therapeutic agents. This is a promising platform that will allow the investigation of the effect of new anti-cancer treatments on human tumour-infiltrating immune cells in parallel in cSCC to gain insight into both their efficacy and mechanisms of action.

The role of the immune checkpoint TIGIT in CD4+ T cell dysfunction in patients with decompensated cirrhosis: a translational research study

A5

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Background
Liver cirrhosis is responsible for over 10,000 deaths each year in the UK, with many patients ultimately succumbing to overwhelming bacterial infections. It has been observed that CD4+ T cells, which normally play a key role in supporting and directing anti-bacterial immune responses, are impaired in cirrhosis, but the mechanisms underlying this are not fully understood.

TIGIT is an immune checkpoint expressed on T cells that transmits an inhibitory signal when bound to its ligand CD155. The aim of this study was to determine if TIGIT blockade could improve the function of CD4+ T cells from patients with cirrhosis.

Methods
Patients with stable decompensated cirrhosis (SD, n=9), acute decompensated cirrhosis (AD, n=17) and acute-on-chronic liver failure (ACLF, n=11) were recruited within 48 hours of admission to hospital, along with healthy controls (HC, n=8). Mononuclear cells were isolated from peripheral blood and the expression of membrane-bound TIGIT and CD155 on immune cell subsets was assessed by flow cytometry.

An anti-TIGIT monoclonal antibody was used to block TIGIT ex vivo. The impact of this on CD4+ T cell function, following CD3 stimulation, was determined by their expression of exhaustion markers (PD-1, LAG-3, TIM-3), proliferation, and cytokine production (IFNγ, IL-2, TNFα).

Findings
CD4+ T cells from patients with AD and ACLF expressed more TIGIT compared to those from HC (HC 15.9%, AD 26.1%, and ACLF 27.3% positive for TIGIT; $p = 0.005$). This up-regulation of TIGIT was particular to the CD4+ T cell compartment: no significant difference in TIGIT expression on CD8+ T cells or NK cells between the groups was observed, nor any difference in CD155 expression on CD14+ monocytes.

Patients who died within 90 days had higher TIGIT expression on their CD4+ cells at baseline than those who survived (31.7% versus 21.2% positive; $p = 0.002$). Those with subsequent bacterial infection within 90 days had a trend towards higher TIGIT at baseline than those who remained infection free.

TIGIT blockade reduced expression of the exhaustion markers LAG-3 and PD-1, and increased IFNγ production by CD4+ T cells from AD and ACLF, but had no impact on CD4+ T cell proliferation.

Interpretation
This study identifies a possible mechanism for CD4+ T cell dysfunction in cirrhosis. Expression of the inhibitory immune checkpoint TIGIT is increased on CD4+ T cells in decompensated cirrhosis and blockade of TIGIT ex vivo partially reversed CD4+ T cell exhaustion and improved proinflammatory cytokine production. A limitation of this study, and the focus of future work, is elucidating the impact TIGIT blockade has on innate immune cell function by disrupting cross-talk with T cells. Nevertheless, TIGIT could serve as a novel immunomodulatory target in decompensated cirrhosis, reducing reliance of antimicrobials in the era of emerging multidrug-resistant organisms.

Multicentre prospective cohort study of diaphragmatic defect phenotype and repair in neonates with congenital diaphragmatic hernia: "The Defect Study"

A6

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Background
Neonates with congenital diaphragmatic hernia (CDH) survive (~70%) to undergo diaphragmatic defect closure usually within the first week of life. Defect size and closure technique (primary vs. patch) has long-term consequences in survivors. Although subjective operative reporting of defect size has been standardised by the CDH working group (Type A–D classification), objective evaluation is lacking.

We aimed to objectively describe diaphragmatic defect size and repair methods, at the time of neonatal CDH repair.

Methods
Multicentre prospective study of neonates undergoing CDH repair in paediatric surgical centres across the UK, Ireland and New Zealand. We included neonates over a 24-month period surviving to diaphragmatic repair (REDCap database).

Diaphragmatic measurements and closure technique were recorded intra-operatively alongside standardised defect reporting (Type A–D). 1-year outcomes were captured. Defect size (cm2) was calculated and represented as a percentage hemi-diaphragmatic loss (%). Demographics and peri-operative data (n=(%) were checked for normality and reported as median (IQR), mean (±SD) or categorical variables. $p<0.05$ was considered significant.

Findings
21 centres reported on 140 patients; n=87 male (62%), gestational age (GA) 37 weeks (30 to 41 weeks), body weight (BW) 3.02±0.7 kg, age of operation 5 (3–9) days.

The majority of defects were left-sided (n=108; 77%) and posterolateral (n=97; 69%). Repair (primary n=73 [53%]) was laparotomy (n=105; 75%) and thoracoscopic (n=30; 21%), with conversion to laparotomy in n=9 (30%).

Defect was measured in n=117 (84%). Defect classification (n=61) correlated to measured % hemidiaphragm loss Type A (n=6): 17.3%±11%, type B (n=35): 26.5%±13%, Type C (n=14): 61.8%±21%, Type D (n=6): 80.8%±15% $p<0.0005$. Non-absorbable (n=128; 91%), interrupted (n=127; 91%) sutures were used in the majority.

Patch repairs were with either non-absorbable (n=40; 65%) or biological (n=20; 32%) patches. Patch was domed in n=26 (19%). At 1-year follow-up, there were n=10 (7%) recurrence, n=4 (3%) small bowel obstruction (SBO), and n=5 (4%) chylothorax. In patch repairs, 75% of recurrences were in biological patches.

Interpretation
The CDH working group classification (A–D) correlates to percentage diaphragmatic loss measurements at the time of diaphragmatic repair. The majority of repairs are undertaken by laparotomy with a high conversion rate for thoracoscopy. There is variation in surgical technique for defect closure that may have an impact on outcomes including recurrence.

Implications
This was a collaborative network study from the UK Paediatric Surgical Trainee Network (PSTRN). It shows the feasibility of multicentre data collection in rare diseases in a tertiary hospital setting. Furthermore, it establishes international collaborative trainee studies in paediatric surgery. It also is the first to prospectively look at defect closure in CDH.

‘The downhill race for a Rainbow jersey.’ The epidemiology of injuries in downhill mountain biking at the 2023 UCI Cycling World Championships using the International Olympic Committee Consensus: a prospective cohort study

A7

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Background
Downhill Mountain Biking (DHMTB), one of the more extreme sub-disciplines of mountain bike (MTB) cycling, is where riders navigate high-speed, steep, technical descents on rugged, downhill trails, aiming for the fastest time. The 2023 UCI Cycling World Championships in Fort William, Scotland witnessed elite downhill mountain bikers converging to test their skills on a technically demanding course. Cycling lacks high-quality and comparable prospective injury and illness studies across all disciplines. The primary aim of our study was to prospectively document the injury rate, severity, aetiology, location, and type during official training and competition by DHMTB throughout the championships.

Methods
The participants of this prospective study were junior and elite male and female cyclists competing at the UCI DHMTB World Championships located at the Nevis range in Fort William, Scotland between 1 and 5 August 2023. This study followed the injury-reporting guidelines established by the International Olympic Committee (IOC), including STROBE-SIIS and the cycling-specific extension. All the cyclists were notified of the study and advised that if they objected to their anonymised medical information being shared they were free to do this. Ethical approval for this study was gained by the Medical Faculty, Queen’s University Belfast.

Findings
Throughout the championships, 10.4% of riders sustained one injury, with 4.3% of riders injuring more than one location per injury event. The overall injury incidence was 3.3 injuries per 100 rides. The incidence rates were higher in the training group (6.4/100 rides) than in the race group (2.3/100 rides). There was a greater incidence of injury in females in the training 5.7/100 rides and racing 4.4/100 rides groups than in male riders who had 3.6 injuries/100 rides in training and 0.93/100 rides in racing. The mode of injury was typically from landing on the ground. Compared with male athletes, female athletes experienced more severe injuries, with double the estimated time to injury. Additionally, female athletes were found to have a significantly greater risk of head injuries and concussion than males did, with risk ratios (RRs) of 9.5 and 6.34, respectively.

Interpretation
This is the first study to prospectively examine injuries during the UCI DHMTB World Championships and report these injuries in line with the cycling extension of the IOC consensus statement. Overall, injuries are more prevalent in training than in competition. Compared with male DHMTB athletes, female DHMTB athletes are more at risk of injury and show a greater incidence of injury within official training and competition as well as more severe injuries. Targeted injury prevention initiatives may help reduce the incidence and severity of injury in female athletes.

Circulating tumour DNA for detection of minimal residual disease: hunting for microscopic cancer remnants in the blood – a pilot observational trial

A8

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Background
Circulating tumour DNA (ctDNA) are cancer-derived DNA fragments shed into the blood, offering the ability to provide molecular information on a tumour through non-invasive testing – 'liquid biopsy'. ctDNA is a promising biomarker in Oncology with potential utility for numerous clinical applications.

Minimal residual disease (MRD) describes microscopic cancer lesions remaining after definitive treatment, not detectable radiologically. These occult lesions have the propensity to cause disease relapse in the future. ctDNA detection after surgery is associated with worse prognosis. The ability to detect MRD after surgery would be a valuable guide to recommending adjuvant chemotherapy/radiotherapy and determine post-operative monitoring.

Methods
We conducted a pan-tumour pilot trial to test the ability of ctDNA to detect MRD after surgery. Eligibility criteria were patients with solid tumours due to undergo surgical resection, with a high risk of post-surgical relapse.

Patients underwent FoundationOne® Liquid testing prior to surgery in addition to plasma sequencing in Leicester Molecular Diagnostics at the University of Leicester. To remove 'non-shedders', only patients who were ctDNA-positive pre-surgery were continued on trial. Plasma was sequenced at 12 weeks post-surgery and ctDNA-positive was defined as detection of variants in cell-free DNA. Patient records were followed to determine progression.

Findings
30 patients were recruited (ovarian:13, colorectal:10, gastro-oesophageal:3, pancreatic:1, head and neck:1). 23 patients were continued on the trial based on detectable ctDNA pre-surgery. Median turnaround time for commercial testing was 13 days (range: 9–37). At baseline, 79.3% of patients were ctDNA-positive on commercial testing (324 gene panel) compared to 89.7% on in-house sequencing (52 panel).

14 patients underwent surgery, of which seven achieved an R0 resection. Variants were detectable in all patients post-surgery. Using a more stringent definition of variant allele frequency (VAF)>1%, five patients were ctDNA-positive post-surgery. In three patients these represented variants also detected pre-surgery, whereas two patients had emergence of new variants.

We demonstrate proof-of-concept of the ability of ctDNA to detect MRD, with a trend to poorer progression-free survival (PFS) in the ctDNA-positive group (ctDNA-positive 325, ctDNA-negative 381 days, HR 1.344, CI 0.3–6). However, in this pilot study this was not significant (p=0.699) and underpowered with significant heterogeneity between groups.

Interpretation
Detection of ctDNA post-operatively is associated with poorer prognosis, through detection of MRD. This pan-tumour pilot study has both helped inform the design of further trials and highlights remaining factors of controversy before clinical implementation.

The main outstanding issue is the timing for liquid biopsy sampling. It should be performed soon enough to usefully determine clinical management; however, early sampling could result in false-negative readings from raised post-operative cell-free DNA. Genomic assay characteristics, gene panels and definition of 'ctDNA-positive' also require consensus. In trial design, completeness of surgical resection and concurrent neoadjuvant/adjuvant therapy needed to be considered.

Observational study of the association between myocardial injury and right ventricular dysfunction following lung resection

A9

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Background
Our research group have previously demonstrated a reduction in right ventricular (RV) ejection fraction (EF) in patients undergoing lung resection without any change in left ventricular (LV) EF. Following major non-cardiac surgery, large numbers of patients have biochemical evidence of perioperative myocardial injury (PMI). Recent work suggests inflammation is a major driver of PMI and advances in cardiac magnetic resonance (CMR) imaging allows non-invasive assessment of myocardial inflammation and myocardial scarring, measured by increases in native T1 time and extra-cellular volume (ECV). It is hypothesised that a peri-operative inflammatory injury to the RV is implicated in post-operative RV dysfunction.

Methods
With informed consent and ethical approval, 15 patients undergoing lobectomy underwent T1-weighted CMR scans pre and post contrast; pre-operatively, on post-operative day two (POD2) and at two months. Imaging correlates of myocardial inflammation (native T1 time) and myocardial scarring (ECV) were measured on CMR in the LV and RV (at the ventricular insertion points) using Circle cvi42 (Calgary, Canada) post-processing software. Within-subject analysis of covariance with the patient as factor was performed to investigate the association between changes (from pre-op) in T1 and ECV with RV function.

Findings
As previously reported, RVEF was lower post-operatively from 60.0% (5.5) pre-op to 51.6% (6.7) on POD2 and 51.1% (7.8) at two months ($p<0.001$) whilst LVEF was unchanged over the timepoints ($p=0.814$). RV native T1 time was increased from pre-op (936 ms [923–958]) on POD2 (1041 ms [991–1066]) and at two months (954 ms [949–970]) ($p<0.001$). RV ECV was also increased from pre-op (28.0% [27.0–29.0]) on POD2 (35.5% [34.3–38.0]) and at 2 months (31.0 [29.3–32.0]) ($p=0.004$). There was no change in either measure in the LV ($p>0.614$). There was strong within-subject association between the change in RVEF and T1 from pre-op to POD2 ($r=-0.911$, $p<0.001$) and the change in RVEF and ECV from pre-op to two months ($r=-0.818$, $p=0.004$).

Interpretation
This is the first study to demonstrate post-operative imaging correlates of myocardial inflammation (T1 on POD2) and residual scarring (ECV at two months) in patients undergoing major non-cardiac surgery. The strong associations between the change in RVEF and measures of myocardial inflammation on POD2 and scarring at two months supports the hypothesis than inflammatory injury drives the RV dysfunction observed following lung resection. Further work is required to confirm the relationship between the CMR correlates of inflammation and biomarker evidence of myocardial inflammation in this setting.

Implications
This research has implications both for patients undergoing lung resection and broader peri-operative practice.

Our group has demonstrated that, following lung resection, post-operative RV dysfunction may be secondary to a peri-operative inflammatory injury. We hypothesise that RV dysfunction contributes to the poor functional capacity and quality of life that patients have after lung resection. Ultimately, limiting this peri-operative inflammatory response may help limit the significant morbidity associated with lung resection.

In broader peri-operative practice, the evidence of myocardial inflammation in this study may not be specific to lung resection. We hypothesise that the injury is caused by intra-operative ventilation of one lung and therefore may occur in any surgery that uses this technique (for example oesophagectomy); however, RV inflammatory injury may occur more broadly in major surgery.

We are actively investigating all of these hypotheses.

Developing a core outcome set for dysphagia intervention trials in intensive care

A10

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Background

Approximately 67% of critically ill patients who are mechanically ventilated for longer than two days develop swallowing difficulties (dysphagia). Our systematic review of dysphagia interventions reported a small but rising trend of trials in critical care patients.[1] Reported outcomes had wide variability in outcome choice, measures and time points, thus emphasising the need to develop a core outcome set. This study aimed to develop an international core outcome set for dysphagia intervention trials for adult patients in intensive care, using standardised guidance for core set development.[2]

Methods

A consensus methodology approach was used, which included a two-round online Delphi study and three virtual meetings. Participants represented three groups: clinicians; researchers; and former ICU patients. Outcomes were gathered from various information sources: published trials; observational studies; patient focus group; and national clinician survey findings. Each outcome was ranked on a 9-point Likert scale from 1 (least important) to 9 (most important) and were included if ≥70% of responses had scored an outcome as 7 or higher. Three consensus meetings followed with the aim of agreeing measures and time points for each outcome identified in the Delphi study.

Findings

The study was conducted from November 2020 to June 2021 with 181 participants from 22 countries across six continents. Participants included 18 former ICU patients who had all experienced dysphagia during their intensive care stay, 36 critical care researchers and 127 critical care clinicians from five professional groups (intensivists, nursing, physiotherapy, speech and language therapy and clinical nutrition).

In the online Delphi study, 181 participants rated 28 outcomes in round one. Participant feedback added two outcomes to round two.

160 participants rated 30 outcomes in round two. Six outcomes met consensus criteria: aspiration; severity of aspiration; swallow function; efficiency of cough; pneumonia; and mortality. Twenty-seven participants (clinicians, researchers and former ICU patients) engaged in consensus meetings. Definitions for all core outcomes and minimum measures and time points for five of the six outcomes (except pneumonia) were agreed.

Interpretation

Six core outcomes are recommended for trialists to provide consistency in outcomes in all future dysphagia intervention trials in intensive care. Adoption of this core outcome set would enhance comparability in outcomes across trials and ultimately strengthen conclusions about the effectiveness of dysphagia treatments in intensive care.

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Implications
This core outcome set will be adopted as part of a single-centre phase II clinical effectiveness trial, testing a dysphagia intervention in general medical surgical intensive care patients within Belfast Health and Social Care Trust. I received funding to complete this post-doctoral research starting in September 2024 for three years.

This is the first core outcome set (COS) to be developed in the field of critical care dysphagia. It will be disseminated through publication in a high-impact medical journal and via conference presentations at UK, European and international levels to dysphagia researchers and clinical trials teams in this field. If this COS is adopted by trialists, it means that future systematic reviews will be able to synthesise outcome findings across all included trials and thereby draw stronger conclusions about whether or not a dysphagia intervention in this setting is effective.

Frailty in trials of glucose-lowering therapy for type 2 diabetes

B1

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Background
Frailty is an age-related state of reduced physiological reserve associated with increased risk of adverse clinical outcomes. Frailty is common among people with type 2 diabetes. However, representation of frailty within diabetes trials is unclear as trials do not routinely measure or report frailty in trial participants. As a result, the applicability of trial findings to people living with frailty is uncertain. This study aims to use individual participant data (IPD) from randomised controlled trials (RCTs) of glucose-lowering therapies for type 2 diabetes to quantify frailty and assess the association between frailty and adverse events, hypoglycaemia and trial attrition.

Methods
We analysed IPD from 28 RCTs of SGLT2 inhibitors, GLP1 receptor agonists and DDP4 inhibitors. Frailty was quantified using a frailty index based on Rockwood's cumulative deficit model of frailty: a count of health deficits identified from medical history, laboratory data, and patient-reported measures from baseline questionnaires. For each trial, we quantified the distribution of the frailty index. We then assessed the association between frailty and trial attrition using logistic regression, and between frailty and total adverse events, total serious adverse events, and number of hypoglycaemic episodes using negative binomial regression. All models were adjusted for age and sex.

Findings
Across the 28 RCTs, the total number of trial participants analysed was 24,744. Mean age ranged from 53.8 to 74.2. Mean frailty index ranged from 0.04 to 0.26. Using a conservative cut-point of 0.2 (mild frailty), median frailty prevalence was 5% (interquartile range 1.5% to 8.2%). Four trials had frailty prevalence ≥25%, and focused either on older people or those with renal impairment. In all but one trial, <5% of participants had a frailty index >0.3. Across all trials, frailty was associated with increased odds of trial attrition (pooled odds ratio 1.41 per 0.1-point increase in the frailty index, 95% confidence interval 1.26 to 1.58), and with an increased incidence of adverse events (incident rate ratio [IRR] 1.44, 95% confidence interval 1.34 to 1.55), serious adverse events (IRR 2.08, 95% confidence interval 1.79 to 2.41) and of hypoglycaemic events (IRR 1.24, 95% confidence interval 1.03 to 1.50).

Interpretation
Frailty was rare in most trials, but was more common in trials focused on higher-risk populations such as older people or those with renal impairment. However, even in trials assessing higher-risk populations, severe frailty was uncommon. Frailty was associated with clinically important adverse events and trial attrition. Clinicians should be cautious when applying trial findings to people living with severe frailty, who are largely excluded from many trials. However, it is also clear that trials focusing on higher-risk groups can and do successfully recruit people living with frailty. Future analysis will assess whether treatment efficacy varies by frailty.

Implications
It is currently unclear how frailty should influence the management of individual long-term conditions. RCT data is currently an under-utilised resource for analysis of frailty, its clinical implications, and its impact on treatment efficacy. This study demonstrates that frailty can be quantified in multiple trials simultaneously, given access to IPD. Furthermore, findings related to frailty can be synthesised using IPD meta-analysis. Future development of this work will also investigate how frailty influences treatment efficacy. These insights may inform (i) the clinical management of type 2 diabetes in people living with frailty; (ii) the quantification of frailty in future trials both in type 2 diabetes and in other disease areas, in which these methods can also be applied; and (iii) assessment of the representation of frailty within trial populations across multiple disease areas.

The oral health of older adults living in nursing homes in Northern Ireland: an epidemiological study

B2

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Background

To utilise oral health screening data, collected by the Community Dental Service (CDS) in Northern Ireland, to establish an epidemiological picture of the oral health of nursing home residents.

Methods

In Northern Ireland the CDS provides periodic extraoral and intraoral examination of older adults living in nursing homes as part of an oral health needs assessment. This allows the dental staff to identify oral health problems in order to plan patients' ongoing care. This screening data is stored by each of the Health and Social Care Trusts and is the basis for our data collection.

Findings

Oral health data was available for 1476 residents, from 43 nursing homes in the Belfast Trust area and 12 nursing homes in the South Eastern Trust Area. The majority of residents were female (67%) and dentate (n=997; 67.5%) with 52 residents experiencing dental pain at the time of screening (3.5%). The total number of teeth present ranged from 0 to 31 (mean=9.75). There was no significant difference in the number of remaining teeth when comparing male and female residents (p=0.325). A large proportion of residents had retained roots in situ (n=516; 35.0%). A total of 286 residents had caries charted on coronal or root surfaces (19.4%). 598 care home residents wore dentures (40.5%), with the majority constructed from acrylic resin (75.6%). Within the South Eastern Trust sample (n= 360), there was no significant difference in mean number of teeth when comparing groups with impaired cognitive status and number of remaining teeth (p=0.857).

Interpretation

Although these are preliminary results it should be noted that over two-thirds of care home residents in this sample were dentate. A large proportion of residents had active caries (19.4%) and large numbers of retained roots (35.0%). These results should be interpreted with caution as the challenges encountered in data collection within the nursing home setting may mean that clinical examinations have reduced accuracy.

A physiotherapy-led prehabilitation programme for patients awaiting liver transplantation – a service evaluation

B3

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Background
Liver disease is the third leading cause of death in the UK, the only cure being liver transplantation (LT). Patients awaiting LT can experience emotional, physical, and nutritional impairments, which may be attributed to sarcopenia and frailty. In turn, this can contribute to poorer post-operative outcomes or mortality awaiting LT. Usual care whilst awaiting LT in the Royal Victoria Hospital (RVH), Belfast included regular medical and dietetic management. With the absence of established physiotherapy support interventions in the UK for patients awaiting LT, a new physiotherapy-led prehabilitation intervention was implemented alongside existing dietetic usual care in the RVH.

Methods
Aim: To evaluate the RVH physiotherapy-led prehabilitation service.

Design: Retrospective review of clinical notes between 1 June 2022 to 31 May 2023.

Participants: All new patients referred to physiotherapy and dietetic services for LT assessment.

Intervention: Individualised online exercise classes, twice weekly for 12 weeks, with dietetic advice and meal plans.

Outcomes: Number of patients who received initial physiotherapy and dietetic assessments, offered, and attended the online exercise classes. Pre and post assessments; six min walk test (6MWT), liver frailty index (LFI), mid-arm circumference (MUAC) and grip strength.

Analysis: Descriptive analysis, percentages, mean (SD) or median (interquartile range).

Findings
Participants: 48 patients, 35 (73%) male, mean age 55 (11.1), range 17–69 years.

Findings: 48/48 patients received initial physiotherapy and dietetic assessments, identifying sarcopenia (decreased muscle mass and strength) and frailty (poor physical function). 10/48 (21%) had reduced physical capacity, 33/48 (69%) were pre-frail, 8/48 (17%) frail, 24/48 (50%) had MUAC below 5th centile and 36/48 (75%) below normal grip strengths.

23/48 (48%) were offered the online exercise classes. 4/23 (17%) attended, with 3/4 attending only 10% of classes. Of the 4/23 who attended: 6MWT was recorded in 2/4, 1/4 improved by 320 (240–630) m and 1/4 remained unchanged. LFI was recorded in 4/4, 2/4 improved (frail to pre-frail), 1/4 remained unchanged (frail), and 1/4 decreased (pre-frail to frail). MUAC was recorded in 3 patients: 1/3 improved by 2 (26 to 28) cm and 2/3 decreased by 1 (30 to 29 and 38 to 37) cm. Grip strength was recorded in 3/4: 1/3 improved by 3 (20 to 23) kg, and 2/3 declined by 4 (21 to 17) kg and 1 (19 to 18) kg.

Interpretation
While all patients received an initial physiotherapy assessment, uptake of the online exercise classes and subsequent attendance was poor. Limitations to the service evaluation include poor availability of consistently documented clinical data and poor patient uptake of the classes. There is a clear need for improved delivery of prehabilitation within the clinical services. Improvements should include ensuring standard care incorporates (with clear documentation) discussing and offering classes to patients and documenting reasons for non-attendance. Patient and MDT feedback on the content of classes is important to establish reasons for poor documentation and attendance and implementation of improvement strategies.

Functionally enriched human genetic association studies and bespoke mouse models demonstrate that damaging mutations in LXRalpha uncouple lipogenesis from hepatotoxicity and implicate hepatic cholesterol sensing in human liver health

B4

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Background
Liver X Receptor-alpha (LXRalpha) is a cholesterol-sensing nuclear receptor, which is highly expressed in liver. It has well-described lipogenic actions - increasing the expression of lipogenic genes such as SREBP1 and FASN. Hepatic lipogenesis plays a key role in the development of metabolic dysfunction-associated fatty liver disease (MAFLD), an increasingly common complication of obesity, and inhibition of LXRalpha has been proposed as a therapeutic approach for this disorder. However, LXRalpha regulates other key cellular processes and the net effect of its inhibition on human health is unclear.

Methods
To clarify the role of LXRalpha in human cardiometabolic health, we conducted a functionally enriched genetic association study. We queried the exome-sequencing data from 454,787 participants in UK Biobank for rare mutations in LXRalpha. We characterised selected mutations in vitro using two assays of receptor function to generate a high-quality list of loss-of-function LXRalpha variants and performed gene burden testing to determine their effects on 16 pre-defined cardiometabolic traits. To provide orthogonal evidence of the cardiometabolic effects of LXRalpha we generated a knock-in mouse carrying one of the most severely damaging mutations present, p.W441R, and undertook cardiometabolic phenotyping.

Findings
We characterised 64 rare variants in the ligand-binding domain of LXRalpha in 454,787 participants in UK Biobank. On functional characterisation, 42 of these were found to be severely impaired. Consistent with loss of the lipogenic actions of LXRalpha, carriers of damaging mutations in LXRalpha had reduced serum triglycerides (ß=−0.13±0.03,P=4.86×10−5) and a nominal reduction in liver fat. Surprisingly, carriers of deleterious LXRalpha variants exhibited elevated liver enzymes (e.g. ALT: ß=0.17±0.03,P=8.4x10−9) with a 35% increased risk of clinically significant elevations in ALT (OR=1.35,95%CI:1.17–1.55,P=3.82x10−5), suggestive of hepatotoxicity. Mice homozygous for a damaging mutation in LXRalpha rapidly developed severe hepatitis and fibrotic liver injury following exposure to the Western diet despite markedly reduced steatosis, liver triglycerides and lipogenic gene expression. The phenotype of these mice was substantially rescued by viral over-expression of wildtype LXRalpha specifically in hepatocytes, indicating a cell autonomous effect of the mutant on hepatocyte health.

Interpretation
In summary, our results show that loss-of-function mutations in LXRalpha occur in >~1/450 people and are associated with evidence of liver dysfunction, implicating LXRalpha in the maintenance of human liver health. We provide orthogonal supportive evidence of these findings using a mouse model and by happenstance identify a new murine model of diet-dependent rapidly progressive fibrotic liver disease. Our findings caution against LXR antagonism as a therapeutic strategy for MAFLD. The significance of the marked suppression of lipogenesis to the mouse and human phenotype is unclear and is being tested in ongoing work.

Longitudinal assessment of glucocorticoid toxicity in patients with severe asthma treated with biologic therapies

B5

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Background
Toxicities associated with oral corticosteroids (OCS) are well described. Targeted biologics for severe asthma (SA) substantially reduce OCS exposure with the potential to reduce cumulative OCS toxicities.

We have previously published data showing that all individuals in a cohort of patients with SA who met UK prescribing criteria for biologics had evidence of OCS-related toxicity.[1] Of these, 62% (62/101) had significant toxicity improvement at 1-year.[2] However, improvement in some toxicity domains at 1-year was marginal, mean prednisolone exposure remained substantial (6 mg/day) and the relatively short timeframe may have been insufficient to offer insight on the trajectory of toxicity reduction.

Methods
This was a prospective, real-world, observational assessment of OCS toxicity in SA patients sequentially commenced on biologics in a regional SA clinic in the UK. The aim was to assess the trajectory of OCS-related toxicity over 3 years of biologic therapy and assess for predictors of toxicity improvement. 89 of the 101 SA cohort had clinical and Glucocorticoid Toxicity Index (GTI) assessment at baseline and after 1 and 3 years of biologics.

The GTI systematically assesses OCS-related toxicity; the GTI Aggregate Improvement Score (AIS) is a bidirectional measure of toxicity change over time with a minimal clinically important difference(MCID) of AIS≤–10.

Findings
At 3 years, daily prednisolone use continued to decrease (6.9 mg/day [4.0,9.4] year 1 v 0.8 mg/day [0.0,3.7] year 3, p<0.001), OCS-related toxicity continued to decline (AIS at 3 years –36 [–94, 19]), and 61% met the toxicity change MCID.

There was a significant positive correlation between toxicity outcomes at year 1 and year 3 (rho 0.65, p<0.001). Nearly half (49%) met the AIS MCID at year 1 and year 3; 29% did not meet the AIS MCID at either timepoint. Toxicity change at year 1 was predictive of toxicity change at year 3 for 78%. Those who met the AIS MCID had a better patient-reported quality of life than those without toxicity reduction (EuroQol utility score 0.81 [0.65,0.95] versus 0.69 [0.51,0.81], p=0.01).

Toxicity reduction was not proportional to OCS reduction, those who met the AIS MCID and those who did not had similar total (mg) and proportional (%) OCS reduction. There were no pre-biologics characteristics that predicted toxicity reduction with biologic therapy.

Interpretation
Two-thirds of patients had toxicity reduction with biologics and prednisolone wean. There were no pre-biologic patient factors that predicted toxicity improvement, but early individual toxicity outcomes (at 1 year) correlated with longitudinal toxicity outcomes. This suggests that individual susceptibility to OCS toxicities is a key issue as the burden of harm for the same OCS exposure will vary from individual to individual, and that additional interventions alongside OCS reduction may be needed to decrease morbidity in some patients.

Implications
The main aim of targeted biologic therapy is to have efficacious treatments without the adverse toxicity profile of OCS. Research has shown that OCS toxicities accumulate at relative low-dose exposure, with the adverse effects of OCS being more apparent in younger adults when compared to age-matched individuals who have not been exposed to OCS.

In the UK/Europe, the threshold for access to biologics requires significant OCS exposure. This work is important in showing that not all patients will 'lose' their accumulated OCS toxicity when OCS are stopped, challenging the current threshold for access to biologics and suggesting that further measures, alongside OCS reduction, will be required to reduce morbidity in some patients.

This work also has implications for other disease processes where significant OCS use is still central in their treatment algorithms, e.g. sarcoidosis, chronic rhinosinusitis with nasal polyposis, temporal arteritis, to name a few.

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Correlation of NT-proBNP to exercise capacity in children with single ventricle physiology

B6

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Background
Children with single ventricle (SV) physiology may have reduced exercise capacity despite preserved systolic function. We hypothesised that SV patients with reduced exercise tolerance would demonstrate an elevated NT-proBNP on blood analysis.

Methods
19 children with SV physiology underwent supervised exercise stress testing (EST) to exhaustion using the Bruce protocol on a treadmill. Echocardiograms were performed on a Phillips machine with standardised protocol and ejection fraction (EF) calculated using Simpson's biplane. Bloods were obtained prior to exercise testing and analysed for NT-proBNP using Roche's assay.

Findings
Participants were aged 7–16 years (mean=10.7 years). There were 13 females and six males.

All participants were in Class I (no heart failure) using the Modified Ross Score and 11 (58%) participants reported at least mild limitations in daily exercise capacity.

Length of EST ranged from six to 15 minutes (mean=9 minutes). EST time was compared to healthy children of the same age and sex. Seven participants' time were <10th percentile for healthy children, two participants were in the 10th–25th percentile, two participants in 25th–50th percentile, two participants in 50th–75th percentile and six participants >90th percentile.

Participants' mean EF=55.84% (33%–69%). Mean NT-proBNP levels=88.8 ng/L (42–189 ng/L).

Using paired t-testing there was no statistically significant correlation between total EST time and EF (R=0.074, p=0.762) or NT-proBNP values (R=–0.133, p=0.586). There was no statistically significant correlation between age and total EST time (R=0.45, p=0.855).

All participants were asymptomatic during EST.

Interpretation
Participants' perceived levels of exercise capacity were reflected by their age/sex-adjusted EST time. Six participants performed better than the 90th percentile for healthy children of the same age and sex. Marginally higher NT-proBNP levels demonstrated in participants with poorer exercise capacity, but this was not statistically significant. This small study suggests there may be little benefit in using NT-proBNP to determine exercise capacity in children with SV physiology and well-preserved ventricular systolic function.

Are we nudging in the right directions? A scoping review of electronic nudge tool technology in the ICU and peri-anaesthetic setting

B7

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Background
Electronic nudge (e-nudge) clinical decision-support technology uses patient data to modify clinician behaviour by guiding towards a decision beneficial to the patient, while allowing clinicians to maintain freedom of choice. ICUs and anaesthetic settings have benefited from significant investment in digitisation with potential to utilise e-nudge technology. These e-nudge clinical decision-support technologies have not yet undergone effective evaluation.

This scoping review aimed to identify literature specifically addressing the development, implementation, and evaluation of e-nudge clinical decision-support technology in the ICU and anaesthetic setting.

Methods
A scoping review was conducted in compliance with Arksey and O'Malley [1], Joanna Briggs Institute [2] and the PRISMA-ScR checklist.[3] Databases included MEDLINE, Embase, Web of Science, CINAHL, CENTRAL, Cochrane and Sage. Searches were limited to literature in the English language and published within the last 15 years. Citation screening and data extraction was performed by two independent reviewers. Data extracted included context, e-nudge tool type and design features, development, implementation strategies and associated impact on end users where available.

Findings
35 of the 4200 returned studies were included in the final review. The included manuscripts were grouped into 12 clinical categories. Significant heterogeneity of reporting outcomes related to patients and/or staff led to challenges comparing development, implementation, and evaluation tactics when the reviewers attempted to synthesise the outcomes of the included studies. 90.7% of included manuscripts reported detail of development processes. More commonly, included manuscripts lacked adequate detail or failed to report implementation (60.4%) and evaluation (61.8%) strategies. No single publication discussed adequate detail of all features sought by the reviewers.

Interpretation
The rapid pace of progress in this burgeoning field has allowed little time to effectively evaluate the strategies and/or frameworks employed in the development processes, implementation approaches utilised or reflection upon intended end-user experience. This field would benefit from the development of an agreed group of reporting standards for the development, implementation, and evaluation of future e-nudge clinical decision-support technology.

Is there an antihypertensive class-specific effect on arterial stiffness? A systematic review/meta-analysis of randomised controlled trials and comparison with an acute modulation of transmural pressure

B8

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Background
Arterial stiffness estimated non-invasively as carotid-femoral pulse wave velocity (PWV) is a predictor of hypertension and adverse cardiovascular events. Increased arterial stiffness and PWV of the aorta and large arteries imposes adverse haemodynamic effects on the heart and other organs. Antihypertensive treatment reduces PWV and the only intervention that has been consistently shown to do this is a reduction in blood pressure (BP). However, it is unknown whether this results from an unloading of stiffer elements in the arterial wall or is due to an alternate functional or structural change that might differ according to class of antihypertensive drug.

Methods
We performed a systematic review and meta-analysis of randomised controlled trials investigating the effects of antihypertensive drugs on PWV to explore if there was a between-class difference, with and without adjustment for change in mean arterial blood pressure (MAP) (study one). We also studied patients from the hypertension outpatient service at St Thomas' Hospital, London to investigate changes in PWV after an acute change in transmural pressure (TMP) across the intrathoracic wall simulating a change in BP. Subjects exhaled and inhaled through a mouthpiece against a resistance. TMP was calculated as the difference between MAP and mouth pressure (study two).

Findings
Study one: 83 studies involving 6,200 subjects were included. Meta-regression for all drug classes revealed that reductions in PWV and MAP were significantly associated. Reduction in PWV was 0.65 [95% CI 0.46–0.83] m/s per 10 mmHg reduction in MAP, P<0.001. All antihypertensive drug classes resulted in a significant decrease in PWV, with the largest decrease observed for angiotensin-converting enzyme (ACE) inhibitors/angiotensin-receptor blockers (–1.23 [95% CI –1.4 to –1.0] m/s, P<0.001) and smallest for diuretics (–0.62 [95% CI –0.97 to –0.27] m/s, P<0.001). When adjusted for change in MAP, reduction in PWV after treatment with beta blockers or diuretics was less than that after treatment with ACE inhibitors/angiotensin-receptor antagonists or calcium-channel antagonists (P<0.05).

Study two: 99 subjects were recruited and changes in PWV were strongly related to those of TMP with a change in PWV of 0.58 m/s per 10 mmHg change in TMP (95% CI 0.45–0.7 m/s per 10 mmHg), P<0.001.

Interpretation
The change in PWV related to the change in MAP in our meta-analysis was similar to that observed when a change in MAP was simulated by an acute reduction in TMP acting to distend the arterial wall in our recruited participants. Reduction in PWV after antihypertensive treatment is largely explained by the reduction in BP but there are BP-independent differences, and this also differs according to the class of antihypertensive used. Irrespective of the mechanism of de-stiffening, reduction of PWV is likely to have beneficial effects beyond that of concomitant reduction in MAP.

Implications
Given the prognostic importance of PWV for cardiovascular events, it is important to determine whether antihypertensive treatments might have a specific effect to reduce PWV or whether such effects are mediated simply through a reduction in the BP. Our research suggests that whilst the majority of the effect is mediated through reduction of BP, there are some class-specific effects that are likely to relate to a structural and/or functional change in the arterial wall that is independent of the change in BP. ACE inhibitors/angiotensin-receptor blockers and calcium-channel blockers appear to be more effective than beta blockers and diuretics after adjustment for change in MAP. This class-specific effect on PWV could contribute to the better outcomes associated with the use of these classes of drugs. Even when effects are due to a reduction in BP alone, they are likely to provide haemodynamic benefit and reduce hypertension-mediated organ damage.

Exploring Virtual Reality as a clinical tool for autistic children: Speech and Language Therapists' knowledge and attitudes

B9

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Background

Persistent difficulties with social skills form part of the diagnostic criteria for autism and can require Speech and Language Therapy (SLT) management. However, many speech and language therapists (SaLTs) are frustrated by the lack of real-world practice opportunities available, and limited generalisation of social skills. Research demonstrates that Virtual Reality (VR) interventions overcome these challenges and promote skill generalisation. VR has been explored as an SLT intervention; however, not in an autism context. Therefore, this research examines SaLTs' knowledge and attitudes towards VR as an intervention for autistic children to understand why it has not been adopted into clinical practice.

Methods

A online mixed methods questionnaire was created using Microsoft Forms, with included informed consent. The questionnaire was disseminated via Clinical Excellence Networks to recruit SaLTs working in the autism field. A total of 22 questions were asked regarding knowledge of VR, attitudes towards VR and the support SaLTs required to adopt VR into clinical practice. This included Likert scales, open-ended responses, and single and multiple-choice questions. Quantitative data was analysed descriptively and presented through percentages, counts and visually. Free text questions were analysed thematically, and direct quotes from text were used to contextualise results.

Findings

A total of 60 responses were included for analysis. 92% of SaLTs were aware of VR but had not used it, and 3.8% had used VR with autistic children. Three common themes emerged: (1) mixed general knowledge of VR, which was poor in relation to applications for autism; (2) attitudes were generally positive towards VR; however, SaLTs were unsure about autism specific considerations for VR. Several barriers to adoption were noted; (3) SaLTs require an improved neuro-affirming evidence base, guidelines, and training to adopt VR into clinical practice. Future research should seek to explore neuro-affirming alternatives to the social skills approach.

Interpretation

This provides the first exploration of VR as a clinical tool for autism in the SLT field. VR is perceived as a promising and motivational tool amongst SaLTs, despite poor autism specific VR knowledge. Solutions to the barriers presented are required before VR can integrate into the SLT clinical toolkit. Clinicians need support from employers, alongside funding, a strengthened evidence base and education and training to adopt VR. Clinical guidelines are also required. Future VR research should be co-designed with autistic end users and facilitate neuro-affirming practice, and recommendations for SLT VR education and training programme are also suggested.

A cohort study evaluating longitudinal trajectories of plasma polyunsaturated fatty acids and associations with psychosis-spectrum outcomes in early adulthood

B10

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Background
There is evidence for associations between levels of polyunsaturated fatty acids (PUFAs) such as docosahexaenoic acid (DHA) and psychosis. This includes findings from Mendelian randomisation analyses consistent with a protective effect of long-chain PUFAs on schizophrenia risk. However, the existing literature has focused on PUFA measurements at single timepoints, which may overlook dynamic patterns of variability over time. We aimed to perform the first characterisation of longitudinal trajectories of plasma PUFA measures across multiple timepoints in a large general population cohort, and to evaluate associations between PUFA trajectories and psychosis-spectrum outcomes in early adulthood.

Methods
We performed a cohort study within the Avon Longitudinal Study of Parents and Children, a UK-based birth cohort. Longitudinal trajectories of plasma omega-6:omega-3 ratio and DHA (% total fatty acids), measured by nuclear magnetic spectroscopy at seven, 15, 17 and 24 years, were derived using growth mixture modelling. Outcomes at 24 years included three binary (definite psychotic experiences [PEs], at-risk mental state, psychotic disorder) and two continuous measures (number of PEs and negative symptoms score). Ethical approval was obtained from ALSPAC Ethics and Law Committee. Consent for biological samples and clinical data was obtained following Committee recommendations at the time.

Findings
Outcomes were available for n=3635 (2247 [61.8%] female). A three-trajectory solution was optimal for both omega-6:omega-3 ratio and DHA. Logistic, negative binomial or linear regression was used as appropriate for each outcome to evaluate associations between trajectory membership and psychosis-spectrum outcomes. Relative to stable average trajectories, persistently high omega-6:omega-3 ratio and persistently low DHA trajectories were associated with increased odds of definite PEs and psychotic disorder in unadjusted analyses, with these associations explained by included covariates. The persistently high omega-6:omega-3 ratio trajectory was associated with number of PEs (adjusted β 0.41, 95% confidence interval [CI] 0.05–0.78) and negative symptoms score (adjusted β 0.43, 95% CI 0.14–0.72), as was the persistently low DHA trajectory (number of PEs: adjusted β 0.45, 95% CI 0.14–0.76; negative symptoms: adjusted β 0.35, 95% CI 0.12–0.58).

Interpretation
Persistently high plasma omega-6:omega-3 ratio and persistently low plasma DHA were associated with psychosis-spectrum outcomes in early adulthood, and in the case of number of PEs and negative symptoms, not explained by included covariates. Optimisation of PUFA status during development warrants further investigation in relation to psychosis-spectrum outcomes in early adulthood. Limitations include that causality cannot be inferred and residual confounding is possible. Attrition occurred along a socioeconomic gradient, although we used multiple imputation to avoid complete-case biases. Strengths include the use of a well-characterised cohort, and the use of objective measurement of plasma PUFAs (rather than dietary data alone).

Implications
Our findings suggest substantial proportions of the UK population evidence trajectories characterised by persistently high plasma omega-6:omega-3 ratio (approximately 8%) and persistently low DHA levels (approximately 18%) compared to the population average. Average omega-3 PUFA intake in the UK is already suboptimal compared to World Health Organisation recommendations. Given multiple reported health benefits associated with omega-3 PUFAs, the results have implications beyond psychosis risk alone. Notably, several adverse sociodemographic factors were associated with trajectories characterised by persistently high omega-6:omega-3 ratio and low DHA levels. These patterns likely reflect effects of social determinants on diet as well as physical and mental health. The observed trajectories did not overlap following the first measurement at age seven years, underscoring the importance of addressing social determinants in early life.

Post-radiotherapy dental disease in patients with head and neck cancer – a prospective cohort study

C1

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Background

Post-radiotherapy head and neck cancer (HANC) patients are at increased risk of dental caries and periodontitis due to the direct and indirect effects of radiation on the dental and surrounding oral tissues. This observational study aimed to explore potential variation in the incidence of dental caries and periodontitis among post-radiotherapy HANC patients. The primary objective was to explore the effect of dental and salivary gland radiation dose on the occurrence of post-radiotherapy dental disease.

Methods

The study commenced in December 2018 in the Centre for Dentistry, Belfast. Eligible patients with HANC were assessed and rendered dentally fit prior to radiotherapy (baseline assessment), including provision of high fluoride (5,000 ppm) toothpaste. Patients were followed-up at 6 months and 12 months post-radiotherapy. Oral health data were collected at each visit via clinical dental assessments and validated patient-administered questionnaires. The radiation dose exposures of the teeth and salivary glands were determined by a blinded assessor. Data from 151 patients that attended for follow-up is presented (n=151). Due to the COVID-19 pandemic, data from 6- and 12-month post-radiotherapy dental assessments were pooled.

Findings

Approximately half (49.0%) of patients presented with new carious lesions 6–12 months post-radiotherapy. The mean number of carious teeth was 3.7 (SD 4.1). Approximately one-third (31.8%) of patients were diagnosed with periodontitis 6–12 months post-radiotherapy. Multivariate statistical tests including logistic regression revealed that patients with: (i) continued intake of high-sugar dietary supplements ($p \leq 0.020$); (ii) daily dietary consumption of tea/coffee with added sugar ($p \leq 0.023$); and (iii) the presence of pre-radiotherapy dental caries ($p \leq 0.012$), had an increased odds of post-radiotherapy dental caries. At the dental sextant level (n=644), a 10-unit increase in both mean ($p \leq 0.027$) and maximum ($p \leq 0.006$) dental radiation dose (Gray) were associated with a 26%–32% increase in the odds of post-radiotherapy dental caries after adjusting for other variables. Contrastingly, the radiation dose exposures of the teeth and parotid glands were found to have no effect on the incidence of post-radiotherapy periodontitis ($p > 0.05$).

Interpretation

Post-radiotherapy HANC patients experience high levels of dental disease. Increased dental radiation dose, previous caries experience, and the continued intake of prescribed high-sugar dietary supplements after radiotherapy may increase patients' risk of post-radiotherapy dental caries. Oral health instruction and stringent oral prevention strategies are essential to reduce the burden of post-radiotherapy dental disease among HANC patients.

Paediatric delirium in European critical care units: current practice and point prevalence survey

C2

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Background

A systematic review of critical care studies reporting international prevalence rates of paediatric delirium (PD) in 2021 estimated the pooled prevalence rate at 34%. Studies were mainly from the US and no UK or Ireland studies were included. Review authors concluded that poor screening practices might have resulted in under- or overestimation of the true prevalence rates. European and US guidelines strongly recommend daily screening using validated tools to detect delirium. This study assessed the current service delivery, delirium screening, management practices, and prevalence rates in European paediatric critical care units.

Methods

European paediatric critical care units participated in a one-day point prevalence survey on World Delirium Awareness Day 2023. Using an online Survey Monkey tool, clinical staff collected recorded delirium prevalence at 8am and 8pm and entered data about their unit's current delirium practices. Data were analysed using descriptive statistics. Delirium prevalence rates were determined using the number of patients assessed with a validated screening tool as the denominator. Ethical or clinical governance approval was obtained as required.

Findings

Fifty paediatric units participated; seventeen (34%) were from the UK and Ireland. Protocols for pain management (92%), sedation (82%) and delirium (74%) were reported as being used. Delirium awareness interventions used most often were educational sessions (68%) and posters (24%). Validated delirium screening tools included the Cornell Assessment for Pediatric Delirium (46%), Sophia Observation Scale-Paediatric Delirium (14%) and the pediatric Confusion Assessment Method (6%). Nine units (18%) used personal judgement only. Screening was conducted twice daily (36%) or only following sudden changes in consciousness (44%). Delirium prevalence rates reported by 35 units using validated tools were 15.7% (22/140 patients) at 8am and 18.1% (28/154 patients) at 8pm. The UK and Ireland prevalence reported by 15 units was 19.4% at 8am and 20.4% at 8pm, and 87% reported undertaking twice-daily screening.

Interpretation

The European paediatric critical care units showed lower delirium prevalence rates than the international average. Two reasons might explain this: first, effective management shown by the relatively high reported use of pain, sedation and delirium protocols; second, potential under-detection indicated by low rates of recommended twice-daily delirium screening. UK and Ireland prevalence rates were slightly higher than the overall average, possibly due to better adherence to screening guidelines. The recent implementation of a national screening strategy by the Paediatric Delirium Group UK and Ireland may have influenced these findings.

The effect of size of tracheostomy tube on work of breathing in adults in ICU: a benchtop study

C3

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Background
Tracheostomy tubes (TTs) are artificial airways inserted into the front of the neck. In ICU they are commonly used for patients requiring prolonged mechanical ventilation (MV). Size of TT impacts work of breathing (WOB) through a TT with an inflated cuff or around a TT with a deflated cuff and one-way valve (OWV). OWVs can help restore voice and aid the transition to unsupported breathing. A poorly sized TT can cause respiratory and psychological distress related to tissue trauma, increased WOB and/or being voiceless whilst critically ill. The effect of TT size on WOB with/without an OWV is poorly understood.

Methods
Breathing with a TT was modelled using a lung simulator, small, medium and large 3D-printed tracheas, a model larynx and different size TTs. All possible combinations of trachea and TT were trialled with both an inflated cuff and a deflated cuff and OWV at low, moderate, and high respiratory rates and breath (tidal) volumes of 200, 500 and 700 mL. Baseline data was collected from plain, non-cannulated tracheas. Pressure and flow data were used to calculate WOB in Joules/min. WOB was plotted against tidal volume stratified by respiratory rate and TT size to compare WOB across sizes and against baseline.

Findings
The effect of TT size on WOB with an inflated cuff was similar across all trachea sizes: WOB increased with descending size of TT. With an OWV, size of trachea strongly influenced the effect of TT size on WOB. In the medium and large tracheas the smallest TT generated the lowest WOB and the largest generated the highest. The reverse was seen in the small trachea, where WOB was up to eight times baseline values. In the large trachea, WOB with an OWV was below baseline values for all TTs. OWV trials with a cuffless tube generated substantially lower WOB than the cuffed equivalent. Increases in respiratory rate and tidal volume led to progressively larger increases in WOB. Not all TTs fitted all tracheas: the size 8 TT only just fitted in the small trachea; the size 6's cuff did not reach the larger trachea's walls.

Interpretation
Having a large trachea is advantageous for TT size selection; WOB with a large TT approximates or falls below baseline WOB with an inflated cuff or deflated cuff and OWV. In a medium trachea, WOB for a given TT size might remain low with either an inflated cuff or a deflated cuff and OWV, but not both. Fewer sizes of TT fit patients with small tracheas and all cause high WOB at higher airflows with a deflated cuff and OWV. However, patients with lower tidal volumes and/or respiratory rate would experience lower WOB. Better TT design could reduce WOB.

Women with recurrent miscarriage have reduced uterine natural killer cell activation: an observational study

C4

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Background
Abnormal implantation is a leading cause of maternal and fetal morbidity and mortality worldwide. Uterine natural killer (uNK) cells comprising up to 70% of leukocytes in the pre-implantation endometrium and decidua are crucial regulators of implantation. uNK cell activation is necessary in optimising trophoblast invasion and placental blood flow, for instance the activating Killer Immunoglobulin-like Receptor (KIR)-2DS1 on uNK is protective against pre-eclampsia. Recurrent miscarriage (RM), whereby a women experiences ≥3 miscarriages, forms a part of the great obstetric syndrome characterised by inadequate placentation. This study investigates the uNK cell receptor profile in women with RM and controls.

Methods
Women of reproductive age with a history of RM or no history of pregnancy disorders (controls) were recruited into this study. Paired endometrium and peripheral blood (pb) were taken timed according to the menstrual cycle. Lymphocytes from the endometrial biopsies were isolated using collagenase digestion and Lymphoprep. Multiparameter flow cytometry was used to determine NK cell differentiation, activating (KIR2DS1/S2/S4, NKG2C) and inhibitory (KIR2DL1/2/3, NKG2A, LILRB1) receptors on uNK and pbNK in women with RM and controls. The ratio of activating to inhibitory receptors was determined in uNK and pbNK in women with RM and controls.

Findings
66 women have been recruited into this study (19 control, 47 RM). Multiparameter flow cytometry has identified uNK1, uNK2 and uNK3, and distinct KIR2DS1+, KIR2DL1+ and KIR2DS1/L1+ populations. Preliminary analysis (n=14) has shown a higher percentage of NK cells in endometrium compared to peripheral blood mononuclear cells (PBMCs) (p=0.004): median 22.4% NK cells in endometrium and 7.8% NK cells in PBMC. Women with RM had an increased %NK cells in the endometrial lymphocyte population (median of RM group 25.3%, median of control group 15.3%, p=0.0207). Within pbNK, there was no significant difference in the activating:inhibitory NK receptor profiles between RM and controls. Within uNK, there was a significantly reduced KIR2DS1:KIR2DL1 ratio in RM compared to controls (p=0.045). There was no significant difference in the KIR2DS2:KIR2DL2/L3 ratio (p=0.201) or the NKG2C:NKG2A ratio (p=0.060) between RM and controls.

Interpretation
Reduced activating KIR2DS1 in the RM cohort compared to controls suggests the importance of uNK activation in successful pregnancy. Activation of KIR2DS1 on uNK may be necessary to promote important cellular interactions and production of cytokines to assist trophoblast invasion and healthy placental development. Future work will determine in detail the uNK phenotype and function comparing women with reproductive failure versus controls. This study also highlights the need to identify KIR2DS1–peptide ligand interactions at the maternal–fetal interface to improve our understanding of uNK function and its effect in determining pregnancy outcome.

The diagnostic test accuracy of procalcitonin and C-reactive protein for predicting invasive bacterial infections in young febrile infants: a systematic review and meta-analysis

C5

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Background
The evaluation of febrile infants, under 90 days of age, for invasive or serious bacterial infections (IBI/SBI) is challenging. International practice is evolving from a "treat all" approach towards safely identifying a lower-risk population and reducing unnecessary invasive tests, antibiotics, or admissions. Biomarkers, namely procalcitonin (PCT) and C-reactive protein (CRP), are used within recommended sequential assessments of this population. Evidence suggests PCT may outperform CRP; however, it is unclear and PCT is not universally available. This uncertainty acts as a barrier to the adoption of guidelines using sequential assessment in settings where PCT is unavailable and updated meta-analysis is warranted.

Methods
A search strategy to identify all diagnostic test accuracy studies compliant with STARD criteria was performed through MEDLINE, Embase, Web of Science and The Cochrane Library. Studies were selected by independent authors against eligibility criteria followed by data extraction. Two analysis models were used for each biomarker (PCT/CRP) in detection of IBI/SBI. A bi-variate model was used to pool diagnostic accuracy data, calculate partial AUC at internationally used cutoff values and compare accuracy between biomarkers. A multiple cutoff model was used to calculate the optimum cutoff values per biomarker. Bias assessments using modified QUADAS-2 tools and heterogeneity assessments were performed.

Findings
14 studies, involving 7755 febrile infants, were included in the meta-analysis. The pooled sensitivity/specificity of PCT (>0·5 ng/ml) for the detection of IBI was 0·78/0·85, respectively. This was 0·65/0·80, respectively, for CRP (>20 mg/L).

The pAUCs to detect IBI using PCT and CRP were 0·72 (0·51–0·79) and 0·23 (0·21–0·83), respectively. The observed difference in AUC of the biomarkers was not statistically significant for IBI, nor SBI analysis (p=0·5). The review demonstrated that PCT and CRP have similar test accuracy characteristics.

The multiple cutoff model identified optimal PCT cutoffs of 0·49 ng/ml and 0·17 ng/ml for the detection of IBI and SBI, respectively. Optimal CRP cutoffs were 13·12 mg/L and 16·18 mg/L for the detection of IBI and SBI, respectively. The optimum cutoff for PCT is approximately 0·5 ng/ml, similar to international standard, and the optimum cutoff for CRP is approximately 15 mg/l, lower than international standard.

Interpretation
This study represents the only systematic review to directly compare the diagnostic test accuracy of PCT and CRP in this unique and challenging population. Results were limited by a lack of extractable data causing selection bias and heterogeneous definitions of reference standards.

Demonstrating that the biomarkers have similar test accuracy characteristics suggests that in settings without access to PCT, CRP could represent an alternate biomarker. However, substituting CRP at a cutoff of 15 mg/L (rather than 20 mg/L) for a PCT of 0·5 ng/ml has the potential to allow a greater number of clinicians to apply the principles of sequential assessment.

Investigating the impact of *Fusobacterium nucleatum* on apoptosis and sensitivity to the Inhibitor of Apoptosis Protein antagonist, tolinapant, in colorectal cancer models

C6

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Background
Fusobacterium nucleatum, a Gram-negative anaerobic bacterium originating from the oral cavity, can enrich colorectal tumours, exerting a range of pathogenic effects and promoting chemotherapy resistance, culminating in poorer patient outcomes. Using in vitro models of colorectal cancer (CRC), including three-dimensional tumour spheroids, we investigated the impact of *F. nucleatum* on apoptosis and potential sensitisation to the clinically relevant Inhibitor of Apoptosis Protein (IAP) antagonist, tolinapant.

Methods
Human CRC cell lines, HCT116 and HT29, were cultured using standard techniques. Spheroids were generated by seeding cells into ultra-low adherence 96-well plates. Infections were performed with live *F. nucleatum* (subspecies *animalis, nucleatum, polymorphum* or *vincenti*) or bacterial lipopolysaccharide (LPS). Infected models were treated with combinations of tolinapant, tumour necrosis factor alpha (TNFa) and 5-fluorouracil (5FU). Imaging with light microscopy was analysed using ImageJ software. Apoptosis was measured by quantitative polymerase chain reaction, western blotting, cell viability (3D-CellTiterGlo) and caspase 3/7 and eight activity assays, as well as annexin V/propidium iodide flow cytometry.

Findings
Treatment with *F. nucleatum* increased the proliferation of cancer cell lines and reduced the efficacy of 5FU. *F. nucleatum* significantly increased the expression of the anti-apoptotic protein, cellular IAP 2 (cIAP2). This effect could be attenuated with a small molecule Toll-like receptor 4 inhibitor. Increased cIAP2 is known to be correlated with a worse response to chemotherapy in CRC. Although the IAP antagonist, tolinapant, could prevent the *F. nucleatum*-induced increase in cIAP2, it did not confer increased chemotherapy sensitivity compared to non-infected controls.

Interpretation
F. nucleatum infection elevated the expression of the poor prognostic, anti-apoptotic protein, cIAP2, in experimental CRC models, likely via TLR4 signalling. Tolinapant successfully degraded cIAP2 but this did not translate into greater cell death in *F. nucleatum*-infected cells. An exploratory objective of the upcoming ASTFOX phase 1 clinical trial (tolinapant combined with chemotherapy in metastatic CRC) is to explore the association between tumour response and intra-tumoural *F. nucleatum*.

Development of an integrated diabetic retinopathy screening programme using digital retinal imaging in a lower-middle-income country (LMIC): data to policy

C7

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Background
Diabetes mellitus (DM) is one of the most prevalent non-communicable diseases. Diabetic retinopathy (DR) is a common microvascular complication of DM, which can lead to sight loss, and it is avoidable by early screening and treatment. A situational analysis conducted in the Western province of Sri Lanka showed a major gap in DR screening service delivery and there is no systematic DR screening programme. This study aimed to assess the feasibility of integrating DR screening (DRS) services into free public sector health care in Sri Lanka to improve equitable access to DR care.

Methods
The study was conducted using mixed methods, from 2015 to 2019. The barriers to accessing DRS by service users, and service providers' views were assessed using qualitative studies. A systematic literature review was conducted to assess the diagnostic test accuracy of DRS using digital retinal imaging to understand effective screening strategies. Based on the results of the formative stages, a local context-specific DRS modality was defined and validated. Imaging strategy was 2-field using a non-mydriatic handheld retinal camera (Zeiss-Visuscout 100®). Finally, a locally applicable health educational intervention (HEI) was adapted and acceptability was assessed using participatory approach.

Findings
The focus group discussions with people with DM revealed a lack of knowledge and awareness on DR and the importance of screening as main barriers. Service providers expressed that a lack of skilled human resources and DRS imaging infrastructure were the main barriers to provide screening services and proposed that physicians who treat for DM as best cadre to train in DRS. In the meta-analysis, highest sensitivity was observed in mydriatic more than 2-field strategy (92%, 95% CI 90%–94%). Physicians at a tertiary level medical clinic underwent training in DR grading. In the DRS model validation study, sensitivity of the defined referable DR was 88.7% for grader 1 and 92.5% for grader 2, using mydriatic imaging. The specificity was 94.9% for grader 1 and 96.4% for grader 2. The overall acceptability of the HEI material was satisfactory and service users preferred to have a leaflet and a video as the HEI.

Interpretation
Knowing the barriers to access DRS is a pre-requisite. Non-mydriatic 2-field handheld imaging with mydriatic imaging for those who have ungradable images is a more pragmatic approach in implementing DRS programs in resource-poor non-ophthalmic settings. The process of adapting an HEI was not simply translation into the local language, instead a tailored approach for the local context. The evidence generated in this feasibility study was used to inform development of a policy brief on DRS for the first time in the country. Currently a pilot DR screening program is being conducted in Sri Lanka using this screening model.

Implications
I observed that sight loss due to diabetic retinopathy is not yet a priority for Sri Lanka, as in most of the LMICs due to high prevalence of cataract blindness. However, DR affects economically active young populations, which has a significant socio-economic impact. I generated substantial level of evidence through the feasibility study to convince national-level decision-makers to highlight the gaps in DR service delivery and the importance of implementing a DR screening program. Therefore, generating high-quality evidence in the local context may be a pragmatic approach in policy advocacy, which is applicable for other areas of research in health care as well. In addition, engagement with service providers at the formative stages helped to understand the local requirements at an early stage of program planning. The integrated care models may provide successful strategies to deliver "Patient Centred Care" compared to having a vertical program.

Midlife exposures to civilian conflict associated with accelerated biological ageing but better cognitive performance in older age – secondary data analysis of the impact of the Northern Ireland Troubles within the Northern Ireland cohort for the longitudinal study of ageing (NICOLA) study

C8

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Background
Psychological stress is associated with cognitive decline and increased risk of memory disorders such as Alzheimer's disease. Methyl tags at specific sites on our DNA, called DNA methylation, is proposed as a mechanism by which environmental exposures like stress become biologically embedded. Algorithms allow biological age to be estimated to quantify the potential impact of these exposures.

For thirty years, Northern Ireland (NI) experienced conflict commonly known as the Troubles. It has had lasting effects on the physical and mental wellbeing of the population. This presents a unique case investigating how stress and exposure to conflict affects cognitive ageing.

Methods
NICOLA is a nationally representative, longitudinal study of 8,283 community-dwelling adults, aged 50 or older. In Wave 1, between December 2013 and August 2018, participants completed a computer-assisted personal interview (CAPI), a self-completed questionnaire (SCQ) and were invited to complete a detailed health assessment comprising a battery of measurements across various domains capturing ageing outcomes, including blood sampling. DNA methylation was derived from DNA extracted from buffy coats for the first 2,000 participants in WAVE 1 of NICOLA with high-quality DNA using the Infinium Methylation EPIC BeadChip.

Findings
8,283 participants completed the CAPI, 4,911 (59.3%) the SCQ and 3,656 (44.1%) the health assessment. Mean age was 64.7 years (SD 8.97) with 45.3% (3,751) being male and 25.0% (2,103) receiving primary-level education or less. 45.9% (2,183) participants reported the NI Troubles had a moderate to an extreme impact on their lives and 11.6% (961) reported >15 Troubles-related events, including knowing someone who was murdered, witnessing bombs, or themselves experiencing violence. Mean Mini Mental State Examination (MMSE) score was 28.44 (SD 1.84) and Montreal Cognitive Assessment (MOCA) score was 25.33 (SD 3.27).

Those reporting experiencing a traumatic event had better cognitive performance with on average a 0.49 (p value 1.49 × 10–13) higher score on MMSE, 0.91 (p value 3.43 × 10–14) MOCA score and recalled on average 1.82 more animals (p value 2 × 10–16). Those with greater Troubles exposure had accelerated biological ageing but mediation analysis identified depression, smoking and loneliness as major contributors.

Interpretation
This study is the first to examine the impact of NI Troubles on cognitive and biological ageing. The findings that those who experienced traumatic events had accelerated biological ageing identifies and supports potential causative pathways including cardiovascular risk factors and psychological morbidity. Individual resilience and social connectedness were high amongst those who experienced Troubles-related events but had normal cognitive performance, indicating psychosocial factors could mediate future dementia risk. A consequence of study design, NICOLA participants' are relatively cognitively well, which is a limitation of this work, but the longitudinal follow up planned will allow repeated measures to be assessed.

A longitudinal observational cohort study of recovery following Multisystem Inflammatory Syndrome in Children

C9

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Background
Multisystem Inflammatory Syndrome in Children(MIS-C) is a rare, severe, hyperinflammatory disease, which occurs two to six weeks following a COVID-19 infection. Given the severity of the disease, the difficulties in accurate diagnosis and the lack of knowledge on the causal mechanisms, we profiled the longer-term outcomes of children hospitalised with MIS-C following discharge. We aimed to identify any persistent inflammatory processes following discharge. We further aimed to investigate organ system involvement following discharge. Finally, we aimed to investigate the longitudinal humoral response to SARS-CoV-2 antigens of MIS-C cases.

Methods
Children hospitalised with MIS-C at the Royal Belfast Hospital for Sick Children were recruited prospectively. Data was extracted from clinical notes at admission. Follow-up clinical data was then collected at review appointments following discharge of these patients at timepoints between two and twelve weeks. Plasma samples were collected from children on admission and at follow up, and titres of antibodies to the SARS-CoV-2 spike protein were quantified using commercial ELISA. Continuous data was compared using nonparametric tests, while categorical data was compared using the chi-squared test. London – Chelsea Research Ethics Committee (REC Reference - 20/HRA/1731) provided ethical approval.

Findings
11 MIS-C cases were followed up a median of 33 days following discharge. While all cases had evidence of systemic inflammation on admission, at follow up none had systemic inflammation. On admission, five (45.5%) cases had a left ventricular ejection fraction (LVEF) below 55%, while at follow up all cases had an LVEF above 55% ($p<0.03$). Median CRP levels on admission were 129 mg/L, decreasing significantly to 1 mg/L at follow up ($p=0.03$). Median lymphocyte counts increased significantly from admission to follow up, as did platelet count ($p=0.016$ and $p=0.014$, respectively).

On admission, all cases had detectable antibodies to SARS-CoV-2 spike protein. Titres of circulating IgG and IgM antibodies to spike protein did not significantly change from admission to follow up ($p=0.51$, $p=0.15$). There was a significant decrease in titres of circulating IgA antibodies to spike protein at follow up ($p=0.024$).

Interpretation
This cohort study shows that the laboratory variables of MIS-C cases after discharge trend towards normalisation. Although cases had marked hyperinflammation on admission there was no evidence of persistent inflammation at follow up. Further, organ system dysfunction decreases following discharge. Importantly, the maintenance of antibodies to SARS-CoV-2 viral antigen following discharge indicates that following MIS-C children maintain a humoral response to SARS-CoV-2, which may contribute to preventing a further occurrence of MIS-C. Although a small cohort due to the rarity of MIS-C, this is one of the first cohorts of MIS-C cases that reports on outcomes following discharge.

Integrated plasma proteomics identifies tuberculosis-specific diagnostic biomarkers

C10

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Background
Mycobacterium tuberculosis (Mtb) kills 1.5 million individuals each year and an estimated four million cases of active tuberculosis (TB) remain undiagnosed annually. Biomarkers that identify individuals with active pulmonary disease transmitting Mtb and fuelling this pandemic are urgently needed. We hypothesised that proteins released into the plasma will be clinically useful biomarkers of active pulmonary TB. Such protein biomarkers could be used to develop novel diagnostic tests, which are a central priority of the WHO TB control strategy.

Methods
A highly sensitive non-depletion tandem mass spectrometry discovery approach was utilised to investigate plasma protein expression in pulmonary TB cases compared to healthy controls from South African and Peruvian cohorts. Significantly differentially expressed proteins were identified by three complementary bioinformatic analysis pipelines. Selected candidate biomarkers were then validated in two separate larger validation cohorts using antibody-based proximity extension assays. Diagnostic performance of individual and combinations of candidate biomarkers was then explored using receiver operator characteristics.
All study participants gave written informed consent. Institutional ethics approval was provided in source countries for all cohorts and in the UK.

Findings
Discovery proteomics was performed for 11 pulmonary TB and 10 healthy control (HC) individuals. We profiled the most comprehensive plasma proteome in TB to date and identified 118 significantly differentially expressed proteins using combined linear modelling and correlation network analysis. Candidate biomarkers were analysed in a UK-collected validation cohort (n=88) of mixed ethnicity comprising HC (n=20), pulmonary TB (n=32) and other respiratory infections (ORI, n=26). Four proteins, FCGR3B, FETUB, GGH and SERPIND1, significantly differentiated TB from both HC and ORI, with high TB specificity. Combinatorial analysis identified a six-protein panel (FCGR3B, FETUB, ADA2, CD14, LRG1 and SELL), which differentiated TB from HC (AUC 0.972) and ORI (AUC 0.930) with high sensitivity (90.6% and 90.6%, respectively) and specificity (90.0% and 80.0%, respectively). Validation of this panel in a South African cohort (n=78) confirmed high diagnostic performance with an AUC of 0.882 vs HC and 0.876 vs ORI.

Interpretation
We describe the most detailed plasma proteome of pulmonary TB to date. Our unique integrated proteomic and bioinformatics approach has demonstrated a high validation rate of biomarkers, and identified host plasma proteins with a high TB specificity. Initial validation of the best-performing combination biomarker panel confirms a diagnostic performance that meets the WHO Target Product Profile for a triage test for TB. Subsequent validation in a second cohort demonstrates similar diagnostic performance; however, it was limited by smaller numbers within each clinical group. The new biomarkers have potential for further development as near-patient TB screening assays, with significant potential impact.

Implications
The protein biomarkers identified through this work are plasma correlates of active pulmonary TB and open new lines of hypothesis-driven study into the pathology of TB disease, and their involvement in other destructive lung pathologies such as chronic obstructive pulmonary disease and fibrotic lung disease. Longitudinal plasma expressions of these proteins also have potential as markers of TB treatment response and predictors of post-TB lung disease. Importantly, these biomarkers could underpin a new blood-based test to screen high-risk populations for transmissible TB disease, which could rapidly reduce both transmission and disease. Such a test would require multiplex detection at high sensitivity over a wide dynamic range, in addition to being low cost and simple to use. We are continuing cross-disciplinary research to explore such translation for patient benefit. This has huge potential impact to reduce the TB pandemic whilst concurrently developing a test platform with broad applicability.

Description of a new scoring system and development of lesion feature profiles to evaluate mucosal surface pathology in equine glandular gastric disease

D1

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Background
Equine glandular gastric disease (EGGD) is highly prevalent in horses, and associated with adverse performance and welfare. Knowledge is lacking regarding the pathophysiology and optimal treatment. Ordinal scale and descriptive systems are reported for assessment of EGGD; however, each has limitations and no single system has demonstrated superiority across multiple characteristics such as validity, reliability, objectivity, and usefulness in research. This project describes the development of a new point scoring system (NPSS), which aims to quantify specific features of glandular mucosal pathology and facilitate the assessment of progressive pathophysiology and healing in horses with EGGD.

Methods
Sequential gastroscopy videos were reviewed from Thoroughbreds (n=26) in a longitudinal cohort study diagnosed and treated for EGGD by specialists in equine medicine. Lesions were first (T0) categorised qualitatively as 'mild', 'moderate', or 'severe'. Change in appearance of glandular lesions with treatment was assessed. NPSS was developed by assigning numerical values to lesion features of erythema, fibrin, and haemorrhage. Total NPSS was scaled according to lesion surface area. The proportion contribution ($\hat{p}$) of each feature score to NPSS was calculated and feature profiles were generated according to disease severity, progression, and healing. University of Glasgow Research Ethics Approval: EA43/21.

Findings
At T0, disease was categorised as mild in 7 horses, moderate in 16 horses, and severe in 3 horses. Features with the highest mean proportion in NPSS for mild, moderate, and severe EGGD at T0 were erythema ($\hat{p}$=0.45), fibrin ($\hat{p}$=0.4) and haemorrhage ($\hat{p}$=0.53), respectively. Modal category change for horses with worsening EGGD was mild to moderate. Within this group, increasing lesion fibrin was the greatest feature change (increase $\hat{p}$ =0.18) and a feature profile similar to moderate EGGD at T0 was observed. Modal category change for horses with improving EGGD was moderate to mild and decreased lesion haemorrhage was the greatest feature change (decrease $\hat{p}$=0.2); a feature profile different to mild EGGD at T0 was observed. There were no adverse events associated with treatment for EGGD.

Interpretation
NPSS quantitatively scores surface features of EGGD and highlights qualitative variability in mucosal surface pathology for differing disease severity at initial diagnosis and after treatment. Surface feature profiles change over time, suggestive of the separate processes associated with progressive pathophysiology and healing. Compared to currently utilised scoring systems, newly described NPSS may better represent a clinician's assessment of lesion complexity, help determine the significance of specific lesion types, and indicate the dynamic stages of deterioration and healing. Future work to explore the usefulness of NPSS in other clinical and research settings is required.

Exploring cell therapies for infectious diseases: human mesenchymal stromal cells inhibit *Mycobacterium avium* in clinically relevant models of lung infection

D2

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Background
Mycobacterium avium complex (MAC) is an emerging, multidrug-resistant pathogen driving a global rise in pulmonary infections. MAC persist inside lung macrophages and generate a chronic inflammatory response that damages lung tissue. Prolonged courses of poorly tolerated antimicrobial combinations are needed to achieve cure. Novel therapeutic strategies are urgently needed.

Human mesenchymal stromal cells (MSCs) are mature, multipotent cells with broad-spectrum antimicrobial and immunomodulatory properties. We hypothesised that MSCs could inhibit MAC growth and reduce inflammation in two clinically relevant models of MAC pulmonary disease: in vitro primary human macrophages and in vivo chronic MAC pulmonary disease in BALB/c mice.

Methods
Human monocytes were isolated from healthy volunteers and differentiated into monocyte-derived macrophages (MDMs). MDMs were infected with *M. avium* Chester strain and treated with human bone marrow-derived MSCs or pulmonary fibroblasts (cellular control). Intracellular and extracellular colony-forming units (CFUs) were counted at 72 hours.

Six-week-old female BALB/c mice were infected by nebulisation of *M. avium* Chester strain. Mice were treated with 1×10^6 intravenous human MSCs or saline control at 21 and 28 days post-infection. Lungs, liver and spleen were harvested 42 days post-infection for bacterial counts. Cytokines were quantified by ELISA. All experiments were performed in accordance with ARRIVE guidelines.

Findings
MSCs reduced intracellular bacteria in MDMs over 72 hours by median 35% ($p=0.027$, $n=5$) compared to untreated MDMs. MSC treatment also reduced levels of the pro-inflammatory cytokine TNF-α by median 28% ($p=0.025$). These effects were not dependent on cell–cell contact, suggesting a paracrine mechanism.

We screened for soluble factors important for macrophage response to mycobacteria and found prostaglandin E2 (PGE2) to be specifically elevated by MSCs, but not fibroblasts. Inhibition of MSC PGE2 production using celecoxib abrogated their antimicrobial and anti-inflammatory effect on infected MDMs, but this was restored by adding exogenous PGE2.

In vivo, BALB/c mice developed a proliferative lung infection over 42 days after exposure to nebulised MAC. MSC-treated mice had lower pulmonary CFUs (median 18% reduction, $p=0.012$), but no difference in spleen or liver CFUs compared to controls ($n=11$/group). There was no difference in lung concentrations of inflammatory mediators (IL-6, CXCL-1, TNF-α and PGE2) between treatment groups.

Interpretation
MSCs modulate inflammation and reduce intracellular MAC growth in human macrophages. MSCs can also inhibit pulmonary bacterial replication in a murine model of chronic MAC pulmonary disease. Cellular mechanistic studies revealed MSCs mediate this effect in part via PGE2 signalling.

The clinical relevance of the MAC infection models was a major strength of this study, though generalisability of the in vitro findings was limited by the small sample size of human macrophage donors (typically 4–6 in each experimental series). Nevertheless, these data support further study into MSCs and preparation for human trials as an adjunctive cell therapy for MAC pulmonary disease.

Implications
To date, over 1000 clinical trials have been registered to study human MSCs for inflammatory and infectious conditions. Meta-analyses of completed trials report MSCs to be safe and well tolerated, with signals of efficacy against some infectious diseases. Our findings add important preclinical knowledge about MSC potential to enhance immunity against MAC infections.

We now plan to better characterise MSCs in preparation for human trials of MAC pulmonary disease. This will involve comparative studies of MSCs from different donors and tissue sources, as well as dose-finding and preconditioning work to optimise their efficacy. Our preclinical models can also be repurposed for screening other candidate therapies for MAC infection.

Beyond MAC, these studies will inform research into novel therapeutic strategies against other mycobacteria that drive immune-mediated inflammation, such as *Mycobacterium tuberculosis* and *Mycobacterium abscessus*. They may also help identify potential applications for MSC therapies in managing drug-resistant and difficult-to-treat infections.

Lower female genital tract bacterial diversity in racially matched pregnant women living with HIV from the UK and South Africa, a sub study of the DolPHIN-2 RCT

D3

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Background
Pregnant women-living-with-HIV-infection (WLWH) have two- to five-fold higher preterm birth (PTB) rates compared to the general population. Maternal antiretroviral therapy (ART), essential for preventing vertical HIV transmission, may enhance this. In UK WLWH, PTB occurs in association with a vaginal niche inhabited by diverse anaerobes including *Gardnerella vaginalis* (Community State Type [CST]-IV) or dominance of *Lactobacillus iners* (CST-III). These CSTs are pro-inflammatory and upregulate proteins important in the labour cascade. The additional impact of geography and race on this phenomenon is unknown; here we compare vaginal microbiota in black pregnant WLWH from the UK with pregnant WLWH from South Africa (SA).

Methods
Menstrual cup cervical vaginal fluid (CVF) samples were obtained from SA pregnant WLWH enrolled in the DolPHIN-2 RCT comparing two ART regimens (dolutegravir-based v efavirenz-based) initiated late (from 28 weeks) in pregnancy. For comparison with UK pregnant WLWH, high vaginal swabs (HVSs) from the observational HIV-PTB Network study were identified from racially and gestationally matched WLWH. Clinical data were collated. Bacterial DNA was extracted, and composition was determined using metataxonomic sequencing with Illumina MiSeq and assignment with R, using SILVA and Blast. SPSS, ClustVis and Microanalyst were used to generate diversity matrices, data visualisation and compare microbiota and PTB by country.

Findings
Third-trimester CVF was available from 55 SA-WLWH and 31 black UK-WLWH. SA-WLWH were ART-naïve and younger (median 28 v 35 years, p<0.001) than UK-WLWH, the majority of whom conceived on ART (22/31). SA-WLWH had a lower CD4 cell count (median 412 v 672 cells/μL, p=0.002) and higher HIV plasma viral loads (median 19000 v <40 copies/mL, p<0.001). PTB rates were similarly high (SA 13% v UK 16%, p=0.734). SA-WLWH had a higher prevalence of diverse CST-IV (58% v 39%, p=0.025), with several unique subtypes compared to UK-WLWH. SA-WLWH had a lower relative abundance of *Lactobacillus* genera, p=0.007. Similar to UK-WLWH, the majority of PTB (6/7) occurred in SA-WLWH with CST-IV.

Interpretation
Vaginal microbiota of pregnant SA-WLWH off ART were different from virologically suppressed black pregnant UK-WLWH stable on ART, with less *Lactobacillus crispatus/Lactobacillus iners* and greater vaginal dysbiosis. PTB in SA-WLWH, like seen in UK women, co-occurs with these highly prevalent adverse vaginal microbiota groups. Modern ART may partially reduce the bacterial diversity common in WLWH that is associated with PTB; however, even in the UK, where most women conceive on ART, rates of dysbiosis and PTB remain high. In understanding the safety of ART in utero exposure, we should also consider the potential impact on maternal vaginal microbiota and PTB.

Implications
Understanding the mechanism underlying inflammation-driven PTB in WLWH is key to developing translational interventions and relevant to women with and without HIV. The majority of pregnant WLWH live in low- and middle-income countries where healthcare and neonatal support access is highly heterogeneous, and preterm birth complications are the leading cause of death in under-fives. Recently developed live biotherapeutics containing a *Lactobacillus . crispatus* strain have huge potential benefit in the reversal of adverse bacterial communities and establishing immune protective colonisation for the reduction of PTB and treatment of bacterial vaginosis. The interaction between ART, microbiota and mucosal immune function needs to be explored further in assessing drug safety in pregnancy and is also highly relevant to the HIV prevention field, where adverse vaginal pathobionts both increase risk of sexual HIV transmission and can reduce the potency of pre-exposure ART through local drug metabolism.

Characterising mechanisms of ischaemia to stratify therapy in patients with angina and non-obstructive coronary arteries

D4

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Background
Angina with non-obstructive coronary arteries (ANOCA) is a prevalent condition comprising several distinct endotypes; these include coronary microvascular disease (CMD) and myocardial bridge (MB). Our understanding of the underlying mechanisms remains limited, which subsequently has led to a paucity of treatment options. I sought to determine the relationship between invasive coronary physiological metrics and their (a) clinical phenotype and (b) response to physiology-stratified therapy. Three parallel clinical studies were performed in patients with ANOCA, with the aim of improving diagnostics (study 1), refining therapeutics (study 2) and exploring mechanisms (study 3). All enrolled patients underwent comprehensive blinded coronary physiology assessment.

Methods
Study one: patients underwent a blinded exercise treadmill test (ETT) and were classified into ischaemic or non-ischaemic groups. I hypothesised that ischaemic ECG changes, on ETT, will have a high specificity for underlying CMD.

Study two: a phenotype-blinded randomised crossover trial where patients undertook four ETTs four weeks apart (baseline, drug one, drug two and without drugs). I hypothesised that patients with CMD will have a greater improvement in exercise time with anti-ischaemic therapy compared to those without CMD.

Study three: patients with MB undertook in-lab supine bicycle exercise with simultaneous coronary pressure and flow measurements to assess mechanisms of ischaemia.

Findings
Study one: 102 patients were enrolled; 32 had ischaemia on ETT and 70 did not (groups were phenotypically similar). Ischaemia during ETT was 100% specific for CMD (defined as abnormal endothelium-independent or endothelium-dependent microvascular dysfunction).

Study two: 87 patients underwent randomisation (57 retrospectively classified as the CMD group and 30 as reference group; groups were phenotypically similar). Patients with CMD had a significantly greater increment in exercise time, in response to anti-ischaemic therapy, compared to those without CMD. Coronary flow reserve (CFR; invasive coronary physiological metric) was the only predictor of response on multivariate regression.

Study three: 30 patients with MB and 62 without MB (33 with CMD and 29 without CMD) were enrolled. Patients with MB had three distinct mechanisms of ischaemia; namely, impaired coronary perfusion efficiency during exercise (secondary to the bridged segment), endothelium-dependent and -independent microvascular dysfunction.

Interpretation
In patients with ANOCA, (i) ischaemic ECG changes on ETT had a high specificity for diagnosing underlying CMD, (ii) an impaired CFR predicts a beneficial effect of anti-ischaemic therapy and (iii) those with MBs have multiple different substrates for ischaemia, each representing a distinct therapeutic target.

Strengths of the study include the novel phenotype-blinding in study two and the use of novel in-lab bicycle exercise whilst simultaneously measuring intracoronary pressure and flow in study three. Limitations include the single-centre nature and the patient selection meaning that these results may not necessarily be extrapolated to patients with atypical chest pain.

Implications

ETTs are perceived to have a high false-positive rate and are now seldom used. However, when assessed against the reference standard of comprehensive coronary physiology assessment, ETTs were highly specific for underlying CMD in patients with ANOCA. ETTs may be re-introduced in the diagnostic pathway of patients with angina to non-invasively diagnose CMD.

Whilst measuring CFR provides diagnostic and prognostic utility, it was unknown if it adds value to patients' management. We have demonstrated that, in a phenotypically identical patient group with ANOCA, it was only those with an impaired CFR that derived benefit from anti-ischaemic therapy. This provides further weight for including CFR assessment as part of routine clinical work-up in patients presenting to the catheter laboratory with angina.

Selected patients with MBs have three distinct mechanisms of ischaemia. This may lead to the development of novel therapeutic agents to improve quality of life in these patients.

SARS-CoV and SARS-CoV-2 packaging signals and subgenomic RNA formation: characterisation via a novel in silico pipeline for predicting conserved features in RNA viruses

D5

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Background
All viruses must solve the problem of ensuring their genetic material is recognised and packaged by a viral capsid. Coronaviruses must additionally solve the problem of ensuring correct transcription of the subgenomic RNAs used to produce the proteins encoded towards the 3' end of their genomes. Using the abundance of primary structural data available for SARS-CoV-2, we aimed to make experimentally testable predictions of regions in the viral RNA whose sequence has to be maintained for the virus to function. We aimed to corroborate those predictions using sequence data from the related virus SARS-CoV.

Methods
We developed a novel method for finding conserved regions in low-signal, low-noise datasets. The method is based on one we previously developed but with substantial advances that take into account the variable amount of information given by genomic loci, and the sometimes marked differences from parametric distribution limits seen in these datasets. We applied our novel method to SARS-CoV-2 sequences from human hosts in the GISAID database, and to SARS-CoV sequences from human hosts in GenBank. We used the results from our analyses to prime a secondary structure prediction algorithm and compared our findings with explanations in the literature.

Findings
We analysed 5,121,523 SARS-CoV-2 and 119 SARS-CoV sequences. In our main analyses, we found 21 conserved regions in SARS-CoV-2 genes and 15 conserved sub-regions within SARS-CoV-2 1ab, and seven conserved regions in SARS-CoV genes plus 10 conserved sub-regions within SARS-CoV 1ab. In both viruses we identified regions associated with packaging, and we predicted secondary structures comparable with a packaging-associated region from another coronavirus, Murine Hepatitis Virus. We further identified regions correctly placed to function as the transcription-regulatory sequences necessary for formation of coronavirus subgenomic RNA, and predicted their structures. We predicted conservation in several other regions whose functional importance is not yet known. In general, it was easier to delineate clearly boundaries of conserved regions using the SARS-CoV-2 data than using the SARS-CoV data.

Interpretation
Our predictions move us from knowing that important RNA elements are present within a general region of the SARS-CoV(-2) genome, to precise predictions of those elements' locations and structures. It consequently becomes possible to postulate mechanisms by which the known functions occur. We predict sufficiently specific structures to plan mutational analyses to verify the predictions. The predicted conserved regions without known function can be investigated for novel biology. By comparing the granularity of predictions between SARS-CoV and SARS-CoV-2 datasets, we can understand how differing amounts of underlying sequence data affect the precision of our results.

Implications
Our research focusses on finding new viral mechanisms without mammalian analogues. These mechanisms are candidate targets for antivirals with a low risk of off-target cross-reactivity in the host, and therefore our research opens a pathway to drug discovery.

Applying our work to delineate packaging signals in segmented viruses, such as influenza A, gives insight into which segments can compatibly package and hence have reassortment potential. Our work can therefore improve understanding of the pandemic potential of different influenza A viruses, and hence where surveillance and mitigation effort should be focussed to avoid/delay a pandemic.

The novel mathematics underlying our sequence analyses can be applied to find outlier regions in any sequence of numbers. It has the potential to improve granularity of predictions in any sequence analysis that currently relies upon e.g. sliding window techniques to find significant regions. Such analyses of genetic data are common.

Examining ways to improve sleep quality and support healthy ageing in older adults with sleep disturbances through targeting the gut microbiome with saffron supplementation

D6

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Background
Age-related neurodegenerative diseases are a growing societal problem with numerous repercussions. Lifestyle and environmental factors play a key role in their development, with sleep quality being one of the major contributors to age-related cognitive decline and dementia. Insomnia symptoms tend to increase with age, with prevalence rates approaching 50% in adults aged 65 and over, hence strategies to improve sleep quality in older people are essential. The gut–brain axis plays an important role in health and disease, with recently reported impacts on healthy ageing.

Methods
To address this knowledge gap, we designed a double-blind randomised placebo controlled (RCT) study (n=52, 70% female) in older adults (65 years old) with sleep disturbance. Participants received either a placebo or a saffron extract (30 mg) for four weeks. Sleep quality was assessed both subjectively through validated questionnaires (Pittsburgh Sleep Quality Index [PSQI], Karolinska Sleepiness Scale [KSS], and Insomnia Severity Index [ISI]), and objectively using a portable EEG device (Dreem 3). Faecal samples were collected before and after the intervention to monitor changes in microbiota composition.

Findings
Four weeks' supplementation with saffron significantly improved subjective sleep quality measures, ESS ($p<0.05$) and PSQI ($p<0.01$) scores, with better sleep efficiency observed in females ($p=0.01$). Organic sleep measurements were positively impacted with an increase in REM sleep in the saffron group in females ($p<0.05$).

Changes in sleep quality were paralleled with an increase in the genus *Faecalibacterium* and *Lachnoclostridium* ($p<0.05$), as well as a significant enrichment of the genera Prevotella and Prevotellaceae (positive LDA scores), which are bacteria that have previously been reported to improve circadian disturbances. In addition, Turicibacter was decreased in the saffron group ($p<0.05$).

Interpretation
Both sleep quality and microbiome composition are altered with ageing, paving the way for potential strategies to target sleep via the modulation of the gut.

Saffron and its related food bioactive compounds safranal, crocin and crocetin have been reported to independently improve sleep and to affect the gut microbiota. However, the effect of saffron on sleep quality through the modulation of the microbiome is currently lacking.

These results are promising since polypharmacy is a significant problem in elderly patients.

This study provides further evidence for the effectiveness of bioactive compounds improving sleep quality through gut health in older adults.

A prospective translational study examining intra-alveolar neutrophil-derived microvesicles released after one-lung ventilation and their association with postoperative pulmonary complications

D7

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Background
Patients undergoing one-lung ventilation (OLV) during surgery are at risk of postoperative pulmonary complications (PPCs), including pneumonia and ventilator-induced lung injury (VILI), in part due to unphysiological lung stretch. This process instigates alveolar inflammation, which may predispose the lungs to PPCs. Given the limited preventative strategies and significant mortality/morbidity associated with PPCs, there's an urgent need for further mechanistic work to identify novel preventative or therapeutic targets. Microvesicles (MVs) may be a hidden compartment of inflammation as they carry a plethora of pro-inflammatory cargo. We investigated the role of intra-alveolar MVs in mediating alveolar inflammation in patients undergoing OLV.

Methods
Patients who have an oesophagectomy undergo a prolonged period of OLV. We obtained serial blood and bronchoalveolar lavage fluid (BALF) samples from both the overstretched ventilated lung and the deflated atelectatic lung of such patients. Gastrectomy patients undergoing prolonged two-lung ventilation (TLV) acted as controls. BALF cells (alveolar macrophages, monocytes, neutrophils) and plasma and BALF MV subtype populations, including neutrophil-derived (CD11b+CD66b+), macrophage-derived (HLA-DR+/CD206+), alveolar epithelial-derived (T1α+/CD326+), endothelial-derived (CD62E+/CD144+/146+/324+) and platelet-derived (CD61+/CD41+) were phenotyped using our established flow cytometry protocols and correlated with intraoperative and postoperative clinical data. BALF total protein, a marker of lung injury, was also measured.

Findings
Forty-two oesophagectomy and seven gastrectomy patients were recruited.

Following OLV, there was a significant increase in BALF neutrophil-derived MVs (NMVs) (pre-OLV: 206 MV/µl vs post-OLV: 1062 MV/µl, $p<0.001$, n=42), neutrophils (48 vs 107 cells/µl, $p=0.003$, n=29), macrophages (236 vs 354 cells/µl, $p=0.040$, n=29) and protein (0.28 vs 0.44 µg/µl, $p=0.002$, n=23) in the ventilated lung. Post-OLV NMVs were higher in patients who developed PPCs compared to those who didn't (PPC: 3478 MV/µl vs no PPC: 441 MV/µl, $p=0.008$, n=42).

There was no significant increase in BALF NMVs, neutrophils, macrophages, or protein after OLV in the non-ventilated lung. No other BALF MV population increased significantly following OLV in either lung, and there was no significant increase in any BALF MVs, cells or protein following TLV in the same patients, or control patients.

Plasma NMVs increased significantly throughout the operation although no other MV subtype did; plasma NMVs didn't correlate with PPCs.

Interpretation
We have demonstrated that lung stretch associated with overventilation during OLV causes significant intra-alveolar NMV release, immune cell recruitment and BALF protein. Interestingly, only NMVs, but not their parental cells, correlated with an increased incidence of PPCs, suggesting neutrophil 'activation' is a crucial factor for the development of PPCs. These results suggest that these MVs may be a potential, clinically relevant biomarker for PPCs after surgery with OLV, and provide evidence in humans that NMVs may play an important role in initiating stretch-induced lung inflammation, contributing to VILI.

Create or integrate? Designing interventions to support critical illness recovery after hospital discharge: systematic review and qualitative evidence synthesis

D8

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Background
Survivors of intensive care unit (ICU) admission experience significant deficits in health-related quality of life due to long-term physical, psychological, and cognitive sequelae of critical illness, which may persist for many years after hospital discharge. There has been a recent proliferation of post-hospital interventions that aim to support ICU-survivors; however, there is currently limited evidence to inform optimal approach. We therefore aimed to synthesise factors that impacted the implementation of these interventions from the perspective of healthcare providers, patients, and their carers, and to compare different intervention designs.

Methods
We conducted a systematic review and synthesis of qualitative evidence using four databases (MEDLINE, Embase, CINAHL and Web of Science), which were searched from inception to September 2022. Studies were included if they contained qualitative data from adult ICU survivors, or their carers, relatives, or healthcare providers, on factors that impacted the implementation of post-ICU interventions. Data extraction and synthesis was informed by the Consolidated Framework for Implementation Research (CFIR) and the template for intervention description and replication (TIDieR) checklist.

Findings
Searches generated 11741 unique citations, of which 28 met the inclusion criteria. Included studies reported on a range of interventions including follow-up clinics and rehabilitation programmes. We identified some overarching principles and specific intervention component and design factors that may support in the design of future strategies to improve outcomes for ICU survivors. For each intervention characteristic, various patient, staff, and setting factors were found to impact implementation. Considering how the intervention will rely on and integrate with existing outpatient and community resources is likely to be important.

Interpretation
This review provides a framework for future research examining the optimal approach to support patient recovery after critical illness following hospital discharge. Implementation factors were identified relating to which components to include, who will deliver the intervention and how it will be delivered, and the impact of patient, staff and setting factors. A key unanswered question is how any novel intervention interacts with and relies upon existing resources and care delivery, including the optimal approach to integrate with the patients' primary care providers.

NF1 copy number loss is associated with poorer survival in the homologous recombination-deficient subpopulation of whole-genome sequenced high-grade serous ovarian carcinoma

D9

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Background

NF1 protein loss results in hyperactivity of the mitogen-activated protein kinase (MAPK) pathway in cancer. *NF1* copy number loss (*NF1-CNL*) has been identified as a frequent event in high-grade serous ovarian carcinoma (HGSC), alongside other common molecular aberrations (*TP53, BRCA1,* and *BRCA2* mutation; *CCNE1* copy number gain and *EMSY* overexpression; RB1 and PTEN protein loss). The molecular context and prognostic consequence of *NF1*-CNL in HGSC requires investigation.

Methods

NF1-CNL cases were identified from uniformly analysed in-house (N = 81) and publicly available (N = 124) whole-genome sequencing data of HGSCs. Homologous recombination deficiency (HRD) status was designated by HRDetect Score. *NF1* mRNA expression and MAPK Pathway Activity Score (MPAS) were quantified using RNA sequencing data (N = 149). Progression-free and overall survival were defined as the interval between diagnosis and first radiologically identified recurrence or death, respectively. R version 4.2.2. was used to conduct Mann–Whitney *U* tests, calculate odds ratios, and fit Cox proportional hazards models.

Findings

NF1-CNL was identified in 46/205 cases (22.4%). *NF1*-CNL tumours demonstrated lower *NF1* mRNA expression levels and higher MPAS than non-*NF1*-CNL tumours (P = 0.008 and 0.013, respectively). *NF1*-CNL events were highly enriched in the BRCA1/2-mutated (OR = 4.25, 95% CI [2.09, 8.72]) and HRD subpopulations (OR = 9.7, 95% CI [3.68, 34.2]). Within the HRD subpopulation, *NF1*-CNL cases experienced shorter overall survival than non-*NF1*-CNL cases (multivariable HR = 1.86, P = 0.029).

Interpretation

NF1-CNL occurs at an appreciable frequency in HGSC and is associated with reduced *NF1* mRNA expression and increased MAPK pathway activity. Increased MAPK pathway activity in this subpopulation represents a novel therapeutic opportunity requiring further investigation. *NF1*-CNL events are highly enriched in *BRCA1/2*-mutated and HRD cases. Patients with HRD tumours and *NF1*-CNL events experience shorter overall survival.

Awake, alert and voiceless – communication in critical care tracheostomy patients: a scoping review

D10

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Background
Approximately 14,000 adults in the UK undergo a tracheostomy annually. It is often undertaken for patients requiring an artificial airway for an extended period. However, the presence of an inflated tracheostomy cuff means that no airflow is directed past the vocal cords and larynx, and vocalisation is impossible.

This review sought to synthesise the evidence regarding communication in adult critical care patients dependent on cuffed tracheostomy tubes. It aimed to identify: the psychological impact on patients awake and alert with tracheostomies but unable to speak; strategies utilised to enable communication; and facilitators and barriers for the success of these strategies.

Methods
A scoping review, following the Joanna Briggs Institute framework, gathered evidence from CINAHL, Embase, MEDLINE, and Web of Science, alongside manual reference searches. A protocol was developed a priori and published on Open Science Framework. Eligibility criteria included English-language papers reporting qualitative and quantitative research (2000–2022). Studies addressing the psychological impact of voicelessness; structure, process and outcomes of communication strategies; and factors influencing effectiveness were considered. The population included critical care adults with cuffed tracheostomy tubes, families and healthcare professionals. Screening and data extraction were conducted independently by two reviewers. Data analysis employed descriptive statistics and content analysis.

Findings
Of 1006 publications identified, 23 were included in final analysis. 11 (48%) used qualitative, nine (39%) quantitative, and three (13%) mixed methods. Quantitative studies predominantly used a prospective observational design, with case studies the most common design employed for qualitative research.

Voicelessness evoked negative emotions, notably frustration. Moreover, the inability to communicate extended beyond the absence of speech; it profoundly affected an individual's well-being and identity.

Communication interventions identified included: electronic systems (n=5), talking tracheostomy tubes (n=4), Above Cuff Vocalisation (ACV) (n=2), and the electrolarynx (n=1). Electronic devices served to overcome functional limitations but could require significant patient learning. Talking tubes and ACV facilitated phonation, but speech was often akin to a whisper.

Seventeen (74%) papers investigated factors that either facilitated or hindered communication. Of 11 papers identifying multidisciplinary collaboration as a facilitator, 73% reported speech therapy input. Patient-related challenges including fluctuating cognitive status were the most frequently cited barriers.

Interpretation
Facilitating communication for tracheostomised patients unable to tolerate cuff deflation is integral from a psychological perspective. Whilst communication strategies are feasible, they are not without limitations, implying the absence of a universally applicable solution. This reinforces the need for ongoing assessment, potentially strengthened by a comprehensive multidisciplinary team approach. This review consolidates knowledge pertaining to communication in cuff-dependent tracheostomy patients. A particular strength lies in stakeholder engagement to define review objectives, thereby enhancing its relevance and practical applicability. Nevertheless, several limitations are inherent in this review, most notably constraints regarding language restrictions.

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