Overview:

We will use the Acceleration Award to develop a master protocol and HTA application for **PROTECT** (**P**latform **R**andomised evaluation of clinical **O**utcomes using novel **TEC**hnologies to optimise antimicrobial **T**herapy), a phase III, adaptive, multi-arm multi-stage (MAMS) platform trial to assess the effectiveness, implementation, and efficiency of biomarker-guided antimicrobial stewardship interventions, to reduce unnecessary antibiotic usage by excluding severe bacterial infection in acutely unwell patients. To maximise efficiencies when designing the PROTECT trial and related processes, we will use learning from: 1) COVID-19 platform trials integrated directly into clinical care (e.g., REMAP-CAP, PANORAMIC, RECOVERY, PRINCIPLE, AGILE, CONDOR) [1] , in several of which co-applicants have been directly involved; and 2) currently recruiting or recently completed NIHR-funded studies on biomarker-guided antimicrobial stewardship led by co-applicants (PRONTO, BATCH/PRECISE, ADAPT-Sepsis, PEACH, ALABAMA) and our first-hand experience of challenges faced when conducting them during the pandemic.

Background:

Approximately 20% of antibiotics are overprescribed in primary and secondary care in the NHS [2,3], compromising safety and wellbeing of current and future patients due to adverse effects of antibiotics and the ever-growing threat of antibiotic resistances. Safely reducing patients' exposure to unnecessary antimicrobials is therefore a national and global priority. Recent studies, including those led by co-applicants, have focused on single biomarkers to optimise antibiotic decision-making in different patient sub-populations and at different points along the care pathway [4-8]. These studies will answer crucially important clinical questions but are costly and slow to generate clinical impact. We are now seizing the opportunity to extend this work and create a flexible, adaptive platform trial to comprehensively evaluate commercially available biomarker-guided interventions in combination and across the patient pathway, to robustly establish clinical utility.

The proposed PROTECT platform, embedded in routine NHS care, is ideally suited to address the complex problem of antimicrobial optimisation in a clinical syndrome where diagnostics which support immediate clinical decision-making can enhance quality of care and patient safety, and reduce the risk of complications. The platform trial can be conducted much more efficiently than individual trials of single biomarker interventions, and so obtain clinically relevant results and introduce novel technologies into the care pathway sooner [9-12].

The UK 5-year action plan for tackling antimicrobial resistance, updated in May 2022, recommends: a) building the evidence base to support antimicrobial stewardship interventions, b) developing research methods for improving and supporting clinical confidence in diagnostic testing, and c) randomised trials to compare duration of antibiotics and examine impact on clinical and economic outcomes [13].

Platform trial outline:

PROTECT will address this by providing long-term trial infrastructure to evaluate existing and future biomarker-guided interventions. Importantly, the adaptive platform design enables the evaluation of multiple interventions, or combinations of interventions, in multiple sub-populations of patients along the care pathway under a common master protocol. The modular structure of the adaptive platform and associated master protocol (with sub-protocols as appropriate) [14] will allow for:

1) individual experimental arms to be stopped once:
    a. superior effectiveness compared to control can be concluded early, or
    b. futility of continuing an arm due to lack of effectiveness can be concluded early, or
    c. the planned sample size is reached;
2) new experimental arms to be added [15-17];
3) the control arm to be updated to reflect changes in standard of care.

Decisions to stop arms will be based on pre-specified statistical criteria, and the addition of new arms will follow a rigorous process involving an appraisal of preliminary scientific evidence for the new intervention, involving an independent multi-stakeholder advisory group. Similarly, any change to the control arm will require approval from the advisory group [**Figure A**]. These processes will be fully mapped out as part of the Accelerator Award.

People presenting to primary care, pre-hospital, emergency, or hospital care with suspected bacterial infection, in whom antibiotics (oral or intravenous) are being considered, will be eligible to be randomised into PROTECT. The overall aim of the trial will be to evaluate biomarker-guided interventions to optimise clinical decision-making within the first 72 hours of presentation, to improve speed of diagnosis, speed of starting or stopping antimicrobial therapy, and patient and carer experience for people with suspected bacterial infection. This will be achieved by: a) giving appropriate antibiotic therapy promptly, b) reducing inappropriate antibiotic use, c) reducing harm from adverse drug effects, and d) ensuring patients and carers are given the correct diagnosis.

Interventions:

All interventions to be evaluated in PROTECT will already have regulatory approval and existing evidence to show that they can work, with implementation strategies mapped using the Expert Recommendations for Implementing Change (ERIC) framework [18]. In the platform, we will compare them to current standard care to determine if they are clinically and cost-effective at scale in typical NHS or social care settings with typical NHS or social care users.

The biomarker technologies considered for evaluation must be able to guide clinical decisions about at least one of: a) antimicrobial initiation, b) discontinuation, c) de-escalation from broad to narrow spectrum antimicrobials, d) switch from intravenous to oral antimicrobials.

Interventions will fall into one of two domains: 1) technologies which detect and/or quantify host biomarkers with the aim of distinguishing between bacterial and other (e.g., viral) causes of infection; 2) technologies which detect infection pathogens directly using molecular diagnostics. The platform will allow multiple interventions in each domain to be evaluated in parallel, whereby trial participants can be randomised to one intervention arm from one domain (or control), or to a combination of interventions involving one arm from **each** domain (or control) in an innovative factorial manner [**Figure B**], thereby making full use of the platform infrastructure [19,20].

Host biomarkers of infection (Domain 1): Within this domain, multiple tests can be used at different stages in the care pathway, from pre-hospital to hospital ward. Examples of technologies include those for use:

1) **In primary care, an ambulance, or an emergency department (ED):** e.g., FebriDx®, a rapid, point-of-care test device in lateral flow format that can differentiate viral from bacterial infection.
2) **In an ED, ward, or hospital laboratory:** e.g., MeMed Key®, a host response immunoassay that provides rapid (within 15 minutes) results to differentiate between bacterial and viral infection.
3) **In a hospital laboratory:** e.g., DiaSorin LIAISON®, an analyser which measures up to 15 host biomarkers, is already installed in over 60 NHS Trusts (148 instrument placements), and connects to the hospital Laboratory Information Management System (LIMS) in a bi-directional interface. Tests can be added without any adaptation to existing workflows and clinical pathways; or SeptiCyte RAPID®, a rapid diagnostic test for likely invasive bacterial infections, producing a host response mRNA signature from blood in 1 hour.

Pathogen molecular diagnostics (Domain 2): Examples of technologies to be evaluated in this domain are suited for use **in an ED or hospital laboratory**, and include e.g., the T2Bacteria® panel, which detects five clinically relevant bacterial pathogens in 3 to 5 hours, directly from a whole blood sample; or the BioFire BCID2 panel, which tests for pathogens associated with bloodstream infections, and antimicrobial resistance genes, with results available in about 1 hour from positive blood culture.

Standard care arm (Control): Standard of care for adults and children across the care pathway as defined by NICE and the Academy of Medical Royal Colleges, advocates for a structured assessment and risk stratification of serious illness or death [21,22]. Severity of illness is assessed using early warning scores (NEWS2 for adults, PEWS for children) and clinical judgement, taking into context setting, co-morbid disease, and other relevant factors. Initial rapid assessment is followed by monitoring, escalation plan, investigation and treatment, and clinical decision-making aims to provide a balance between patient safety and antimicrobial stewardship, while allowing clinicians to exercise accountable clinical judgement in the care of individual patients [22].

Pipeline of interventions to be evaluated in platform trial:

During the Acceleration Award we will seek to identify evaluation-ready technologies for settings including a) primary and pre-hospital care, b) Emergency Departments (ED), c) wards, and d) Acute Medical/Surgical Units (AMU/ASU). Key partners are NIHR Medtech and In vitro diagnostics Co-operatives (MICs), which work with developers to generate evidence for adoption of *in vitro* diagnostic tests within the NHS. We will work in partnership with MICs (Newcastle and Leeds initially) as our primary pipeline, whilst at the same time remaining open to approaches from groups external to MICs. We will establish a process for determining 'HTA-readiness', by commissioning rapid reviews through the MICs and NICE Diagnostics Assessment Programme. We will further seek collaboration with the NIHR Innovation Observatory and NHS Accelerated Access Collaborative to identify innovation at an early stage of the pipeline and accelerate their introduction.

Workstreams:

The core team and workstream leads will meet at least fortnightly. An advisory group including PPI members will meet with the study team monthly and will also attend two stakeholder roundtable events.

The Acceleration Award will enable us to 1) fully understand the environments in which the PROTECT platform trial will be conducted and biomarker-guided interventions evaluated, 2) systematically identify all currently relevant index tests, 3) finalise details of the study design, 4) begin development of study documentation, and 5) address any other practical implementation obstacles which could delay the start of the platform trial [23-27]. This will involve:

- Consultations to ensure that involvement of all stakeholders, including patients and the public, is woven into the platform [see Workstream 1].

- Mapping of the care pathway at a high level, nationally, to inform protocol design details such as inclusion/exclusion criteria [see Workstream 2].
- Specification of all relevant statistical, health economic, and implementation aspects of the patient-centred, pragmatic, hybrid, adaptive, MAMS platform trial design. [see Workstream 3].

The main outputs with substantial contributions from all three workstreams [**Figure C**] will be:

1) A fully worked-up master protocol for a patient-centred, pragmatic, hybrid, adaptive, MAMS platform trial (with finalised trial design, sample size, and co-produced list of outcome measures) ready for publication;
2) A fully costed stage 1 application submitted to the HTA in November 2023;
3) Advanced drafts of key trial documents (e.g., ethics application, data dictionary, and patient-facing materials);
4) Reports of generalisable learning on platform trial design and implementation in NHS settings ready for publication in peer-reviewed journals.

Additional workstream-specific outputs are listed below.

Workstream 1: Public involvement and stakeholder engagement: communication and building trust and confidence

Core team: Prestwich, Ogden, Jones, Thomas-Jones, Carrol, Pallmann, Williams, Waldron, Euden, Howard

The wider PPI group will include public contributors from Liverpool Young Person's Advisory Group, the Newcastle MIC insight panel for patients public and carers, and Leeds MIC PPI groups.

Objectives: Ensure PPI and stakeholder engagement is interwoven into each of the workstreams. PPI and stakeholder engagement will be a cross-cutting stream, which will be integrated and linked across each workstream to ensure interdependencies of PPI, with clear actions, outcomes, and deliverables.
There is an increased incidence of invasive infections in areas of high socioeconomic deprivation. Therefore, it is vitally important to ensure these groups are represented in the platform trial. To achieve this, the PPI group will help the wider project team build trust and confidence in the randomisation process, and ensure all communities are engaged. This includes underserved communities who might be marginalised by factors such as language, (health) literacy challenges, access to electronic devices, or protected characteristics which could prevent them from participating and engaging in the project.

Plans:
- Assess priorities and alignment with clinical pathways using focus groups and surveys with pre-hospital, ED, and ward clinicians to ensure that proposed interventions align with the patient pathway.
- Hold two stakeholder roundtable events (months 1-2 and 6-7) including industry, laboratory, pre-hospital and hospital clinical staff, service managers, service users, primary care team.
- Conduct an equality impact assessment to ensure that the methods and processes used in the project are fair and do not present barriers to participation or disadvantage any groups affected by protected characteristics or other marginalising factors from participation.
- Define feasibility and acceptability of technology evaluation process to patients, carers and healthcare professionals.
- Use learning from COVID to ensure consent processes are low burden and streamlined, and patient-facing materials are accessible, so patient recruitment is as inclusive as possible.
- Shape communications including lay summary and animation video, so project updates and outcomes are shared with the widest public audience.
- Continue to expand the multidisciplinary trial team as necessary, including experts with clinical, methodological, and lived experience, to ensure national coverage and equity of trial participation.
- Begin to grow a UK-wide network of centres prepared to recruit into the platform.
- Co-produce a list of patient-centred primary and secondary outcome measures capturing effectiveness and safety, based on relevant existing core outcome sets or consensus definitions [28,29].
- Link in with other Acceleration Award projects to share learning.
- Engage with patient groups and the wider public via charities such as UK Sepsis Trust and Antibiotics Action.
- Align with NIHR INCLUDE framework.

Outputs & outcomes: 1) accessible study and patient-facing materials; 2) finalised co-produced list of primary and secondary outcomes; 3) equitable participation in platform trial; 4) extensive public and healthcare professional engagement.

Workstream 2: Mapping decision-making pathways: determination of intervention entry points

Core team: Lendrem, Williams, Carrol, Thomas-Jones, Sandoe, Dark, French, Bell, Vale, Howard

Objectives: Ensure comprehensive scoping and troubleshooting exercise for main trial

Plans:

- Synthesise operational learning from completed and ongoing NIHR-funded infections studies (ADAPT-Sepsis, BATCH/PRECISE, PRONTO, PEACH, CONDOR, ALABAMA) to determine feasible processes and outcomes, including the feasibility of assessing host biomarkers vs pathogen diagnostics within the same trial.
- Conduct a broad care pathway analysis [30] to identify entry points along patient pathways, barriers and facilitators when crossing community/primary/secondary care, and current practice in testing infections across settings, including timepoints along the pathway where antibiotic optimisation decisions are made, and criteria-based progression from pre-hospital to admission to ward. Entry points where interventions can be introduced for maximum clinical and cost-effectiveness and efficiency will be determined. In the platform trial this will be refined to determine how each index test would be best placed within the pathway considering time-sensitive nature of decisions about antimicrobials.
- Identify patient populations to guide inclusion and exclusion criteria.
- Confirm evaluation settings.
- Identify high-level requirements for test adoption.
- Define entry parameters for index tests to the platform trial (e.g., minimal threshold for analytical validity and diagnostic accuracy) and a process for including tests.
- Assemble an independent multi-stakeholder advisory committee who will review new evidence and decide which intervention arms to add, and draft guidance.

Outputs: 1) report including high-level care-pathway mapping, indications of patient populations and settings for protocol; 2) report of appropriate trial processes (testing, communications of results to clinicians, and adherence to clinical decision algorithms) which aligns with clinical pathways; 3) decision committee draft guidance: terms of references, processes, criteria for considering candidate technologies.

Workstream 3: Adaptive platform trial methodology: statistics, health economics, implementation

Core team: Pallmann, Gillespie, Wason(statistics); Shinkins, Vale(economics); Ahuja, Sevdalis(implementation)

Objectives: Finalise patient-centred, pragmatic, hybrid, adaptive, MAMS platform trial design assessing both intervention effectiveness and cost-effectiveness and implementation process [31-33], and methodology for adding and stopping arms that aligns to clinical pathways.

<u>Statistics</u>

Plans:

- Identify the most suitable randomisation procedure, which will involve exploring the utility of dynamic and adaptive procedures and changing allocation ratios [34,35].
- Specify rules for stopping arms for futility or effectiveness, and for updating the control arm if the standard of care changes e.g., if one of the experimental arms becomes the new standard.
- Decide on the most appropriate approach to controlling error rates across interim and final analyses and multiple intervention arms (including arms added into the ongoing trial) [36,37], exploring novel ideas such as 'online error control' [38,39] and fully Bayesian approaches [40].
- Determine whether to use non-concurrent control data in comparisons involving experimental arms added into the ongoing trial or following a change of standard of care and if so, how to adjust for temporal drift [41-44].
- Integrate a fully or partially factorial design approach to test combinations of interventions [19,20,45-47].
- Explore the impact of a MAMS setting on the potential use of a primary non-inferiority endpoint [29,48].
- Define appropriate stratification (e.g., adult vs. paediatric patients; primary care/pre-hospital vs. ED vs. AMU/ASU settings) alongside a strategy for efficiently sharing of information across strata.
- Calculate sample sizes and conduct simulations of statistical operating characteristics of the chosen design under different scenarios, informed by data from our current NIHR-funded studies of biomarker-guided antimicrobial optimisation (BATCH/PRECISE, PRONTO, ADAPT-Sepsis, PEACH).
- Formulate analysis objectives and specify appropriate analysis populations and statistical methods using the estimand framework [49].

Outputs: 1) sample size calculation; 2) randomisation plan; 3) simulation study report; 4) draft analysis plan.

<u>Health economics</u>

Plans:

- Synthesise operational learning from existing and completed NIHR-funded studies (e.g., BATCH/PRECISE, PRONTO, ADAPT-Sepsis, PEACH) to produce draft data collection forms for resource use.
- Pilot and refine data collection forms using a 'think out loud' approach with PPI groups.
- Map out principles for costing measured resource use.
- Consider methods to capture effects beyond those captured by a standard cost-utility analysis framework to give a broader assessment of test value.
- Align statistics and health economics methodology through regular meetings with statistics team.
- Identify and review existing cost-effectiveness analyses for the test technologies identified, focusing on model assumptions, data sources, and drivers of the health economics argument.

Outputs: 1) Draft tools for data collection on resource use; 2) judgement on use of alternative tools to go beyond quality adjusted life year metric in an economic evaluation; 3) list of economic outcomes and dummy tables for the economic evaluation; 4) draft health economic analysis plan in line with the guidance set out by [50].

Implementation

Plans:

- Take a systematic, theory-driven approach to identifying existing technological interventions, actively reaching out to companies and providing contact opportunities.
- Develop novel strategies to aid implementation to guide antibiotic decision-making in different patient sub-populations using the ERIC framework [18].
- Use the Consolidated Framework for Implementation Research (CFIR) [51] as an overarching organising framework to connect these multi-level innovations as it facilitates understanding of processes of introduction and management of change within a complex healthcare system or pathway and allows for examination of behaviours.
- Review the published literature, clinical practice standards, and guidelines for relevant interventions. With the help of PPI will provide further intervention components and implementation strategies. All interventions will be retrospectively assessed using the CFIR framework for opportunities, fit with cultural context, and resource environments.
- Map the steps needed to optimise the implementation process of these interventions, via formative evaluation of their acceptability, feasibility, fidelity, and sustainability using both qualitative [52] and quantitative [53,54] methods of inquiry.

Outputs: 1) Report with list of interventions and their implementation strategies with initial implementation evidence to inform the future hybrid trial procedure; 2) hybrid effectiveness and implementation trial design to broaden the scope to study clinical and cost-effectiveness and understand the implementation process [31].

Learning from COVID-19:

To maximise the efficiency of all our activities and processes, will use learning from COVID, which, due to the NIHR Clinical Research Network (CRN) infrastructure, allowed rapid research, dissemination and implementation of COVID-19 treatment trials [55]. Other learnings from COVID platform trials include leadership engagement, embedment into routine care processes and electronic patient record, remote consent and enrolment, regulatory compliance, and regular communication with study sites about adaptive trial updates [56,57]. We will advocate for the platform trials funded after the Acceleration Awards to be prioritised by the CRN. We will capitalise on the culture change resulting from the integration of research into healthcare delivery during the pandemic and seek to implement cross-institutional interoperability solutions [58]. With support from the CRN, we will mobilise a multi-disciplinary research workforce to deliver the platform trial, including clinical fellows, allied health professionals, clinical research practitioners, and incentivisation using the NIHR Associate Principal Investigator Scheme.

Scalability and translation:

The Acceleration Award will enable us to finalise the design and master protocol of the PROTECT platform trial, including a) building an inclusive research team, with PPI input into design and processes from the outset, b) defining clinical utility, and c) using the CFIR to understand the outer setting (external policy and regulatory environment, peer pressure to implement a test, and to what level patient need is currently being met) and the inner setting (structural and cultural characteristics of a healthcare organisation, its setting [primary care/pre-hospital/ED/hospital], its internal formal and informal communication networks, its capability and readiness for change).

We have included an implementation scientist with experience of implementing findings from platform trials. The implementation workstream will seek to embed synergy between trial research activities and routine clinical care, particularly as the NHS workforce faces exhaustion and unprecedented backlogs. Findings from WS3 will inform sustainable practices which will be incorporated in the trial. We will explore existing barriers to efficient roll-out of

platform trials, such as inadequate digital infrastructure, and integration with LIMS and Electronic Patient Record (EPR). Through the NIHR MICs, we will also engage with MHRA and NICE to ensure that trial results are implemented into routine NHS care through policy and regulation.

Socioeconomic position and inequalities:

Our study will ensure that equity, diversity and inclusion are embedded in everything we do: in our research team, in shaping our study design, and in improving the diversity of research participants in our studies. We will use an Equality Impact Assessment Toolkit [59] to institute mitigations to ensure that people with protected characteristics are able to participate, and to better understand their experiences as participants in our study.

Commitment to sustainability and carbon net zero:

Our proposal aligns with the NHS commitment to become carbon net zero, which includes new ways of delivering care closer to home, meaning fewer patient journeys to hospitals, and reducing waste of consumable products e.g., reducing or avoiding doses of IV antibiotics leads to reduced nursing time and CO_2 equivalent from plastic.

Project timetable:

M1-2: ethical approval, first stakeholder event; M2-9: Workstreams 1/2/3 run concurrently (fortnightly core project team meetings; monthly wider group meetings); M6-7: second stakeholder event; M8-9: prepare and submit stage 1 bid; M10-12: finalise master protocol and outputs; M11-12: prepare and submit stage 2 bid.

Project management:

Expertise in trial methodology is provided by the Centre for Trials Research (CTR), a UK Clinical Research Collaboration (UKCRC) registered Clinical Trials Unit, who have fully coordinated several major NIHR-funded biomarker studies (BATCH/PRECISE, PRONTO, PEACH) and have also been a regional coordinator for PRINCIPLE and PANORAMIC platform trials. The Accelerator Award project will be conducted in accordance with CTR standard operating procedures, Good Clinical Practice, General Data Protection Regulation, and the UK Policy Framework for Health and Social Care Research. The sponsor will be Cardiff University. Partners at NIHR MICs in Newcastle and Leeds, and implementation expertise from KCL, are included in the core team, as well as clinical core team members from currently funded NIHR biomarker trials.

Fortnightly project team meetings will be held with the core team, and monthly management meetings with all the team and wider advisors (where required). A stakeholder group will be convened, made up of our clinical advisors, senior methodologists, and wider PPI engagement. PPI throughout the whole process is crucial, and we have included three core PPI members as part of the team, with appropriate reimbursement for their time included.

Ethics:

We will apply for approval from a Cardiff University Research Ethics Committee. We do not anticipate that HRA approval and NHS ethics will be required for this Accelerator Award. Ethical considerations for the platform master protocol and learnings from other biomarker studies will be synthesised to expedite approvals for the platform.

Research team expertise:

Co-CIs: PP is Senior Research Fellow in Statistics; trial statistician for BATCH, PRECISE, PRONTO, PEACH; co-lead of MRC-NIHR Trial Methodology Research Partnership Adaptive Designs Working Group. EC is Professor of Paediatric Infection; NIHR North West Coast CRN Clinical Director; CI for BATCH and PRECISE, co-CI for PEACH, co-I for PRONTO. **Clinical experts:** PD is Professor of Critical Care Medicine; NIHR CRN National Deputy Medical Director; CI for ADAPT-Sepsis. NF is Professor of Infectious Diseases and Global Health; CI for PRONTO. JS is Associate Professor of Microbiology; CI for PEACH, ALABAMA; SB is Consultant Paramedic; Research Lead for North West Ambulance Service NHS Trust. **Methodologists/trialists:** DG is Principal Research Fellow in Statistics; Director of Infection Trials at CTR. ETJ is Principal Research Fellow in Trial Management; Deputy Director of Infection Trials at CTR; co-CI for PRECISE, co-I for BATCH, PRONTO, PEACH. JE is Research Fellow in Trial Management; managing PRONTO and PEACH. CAW is Research Fellow in Trial Management; managing BATCH and PRECISE. SA is Lecturer in Implementation Science. BS is Associate Professor of Health Economics; Associate Director of NIHR Leeds MIC; health economist for PEACH, ALABAMA. LV is Professor of Health Economics; Management Group member of NIHR Newcastle MIC; Director of Newcastle NIHR Technology Assessment Review Centre; NU lead for the NICE External Assessment Group. CL is Senior Statistical Methodologist; Management Group member of NIHR Newcastle MIC. CW is Clinical Test Evaluation Methodologist. **PPI:** MO and GP are PPI co-Is for PEACH. SJ is PPI co-I for BATCH and PRECISE.

Advisory board (to be expanded): Rebecca Allcock: Consultant Clinical Scientist (Lancashire Teaching Hospitals NHS Foundation Trust). Edd Carlton: Professor for the Royal College of Emergency Medicine (Bristol Uni). Philip Howard OBE: Regional Antimicrobial Stewardship Lead (NHS North East & Yorkshire); Visiting Professor (Leeds Uni); Vice President of the British Society for Antimicrobial Chemotherapy. Daniel Lasserson: Professor of Acute Ambulatory Care (Warwick Uni). Nick Sevdalis: Professor of Implementation Science and Patient Safety (KCL); Director of the Centre for Implementation Science. James Wason: Professor of Biostatistics (Newcastle Uni).