1. Full title of project

Rheumatoid Arthritis Prevention: catalysing PlatfORm Trial delivery (RAPPORT).

2. Summary of Research

Our ambition is to deliver a pan-European precision medicine platform for preventative interventions in people at risk of rheumatoid arthritis (RA) – a disease of immune dysregulation in which destructive joint inflammation impairs quality of life. Current management aimed at long-term suppression of inflammation incurs unwanted effects and sustained financial cost. However, ever-advancing understanding of RA pathogenesis, during which symptoms may accompany latent autoimmunity in people *at risk of* the condition – together with emergent biomarkers of relevance for *quantifying* that risk and an array of targeted *therapies* – all suggest disease *prevention* is now within reach. Isolated trials of time-limited interventions have addressed this possibility and shown promise, but progress is hampered by recruitment challenges and inconsistent enrolment criteria. A coordinated, multicentre strategy to deliver interventional trials efficiently and responsively in suitably characterised populations of at-risk volunteers therefore remains a major unmet need. Leveraging a recently-established Europe-wide registry of people at risk of RA (*European Risk RA Registry*) together the UK NIHR Musculoskeletal Translational Research Collaboration (TRC), and building on an *existing* international network of clinician scientists in the field (*RT-Cure* and *NORMALISE Consortia*), our aim is to bring about a step-change in progress towards RA prevention by launching a platform trial whose sequential readouts accelerate new knowledge and directly inform precision medicine guidelines for the clinic. During a 12-month Accelerator Project we will first convene an international *At Risk RA Precision Platform Trial Management Group (TMG)* with representation from expert UK/EU units, individuals with experience of living at risk of RA and the *Risk RA Registry* to plan coordinated participant identification, enrolment and follow-up that builds on existing infrastructure. Having refined and achieved consensus on optimal clinical and immunological biomarkers (including cut-offs and implementation strategies) for participant stratification in a precision medicine platform, we will next design and establish a Master Protocol compatible with the range of healthcare infrastructures of countries in which it is to be deployed. Recognising challenges to delivery, this will be informed by systematic literature review and expert sponsorship, information governance and contracting teams at Newcastle Hospitals NHS Foundation Trust (NuTH). In parallel we will engage existing industry/academic partners to finalise initiator interventional arms and feasibility, supported by robust power calculations based on real-life data. Further supported by local and international PPI/E groups, our collaboration with NuTH and Newcastle Clinical Trials Unit (NCTU) paves the way for a UK-led funding application to launch our international precision medicine platform study in April 2024. Successful delivery will herald a coordinated strategy to prevent RA and, by extension, other immune-mediated inflammatory diseases (IMIDs).

3. Background and Rationale

The burden of RA. Rheumatoid arthritis (RA) is a disease of immune dysregulation in which joint inflammation causes pain, structural damage and disability(1). It affects approximately 1% of the adult population, being the commonest inflammatory cause of disability worldwide, and is a major socioeconomic burden with an annual cost to the UK taxpayer in excess of £5bn(2). Current management paradigms have improved outcomes considerably in recent years(3). Nonetheless, long-term treatment incurs side effects/toxicity for many, and true remission rates are low(4).

The opportunity for RA prevention. Recent research developments converge on the potential to intercept RA before clinically manifest arthritis occurs, raising the possibility of delaying or even preventing disease(5). The first of these has been a revolution in our understanding of its pathogenesis as a stepwise process that maps to an evolving clinical phenotype(6-8). Environmental factors including smoking, dietary and microbial exposures may provoke a phase of autoimmunity characterized by anti-citrullinated peptide antibody (ACPA) formation many years before clinically overt joint inflammation occurs(9). Some individuals on this pathway develop joint pain (arthralgia), fatigue and/or other musculoskeletal symptoms, becoming identifiable as *at risk* of RA development without joint inflammation(8). A second important development has been the

increasing availability of rational therapeutic candidates for interception studies. As well as licensed biologic drugs(10, 11), these range from lifestyle interventions such as smoking cessation(12) and short chain fatty acid (SCFA)-enriched dietary supplementation(13) through to experimental approaches aimed at promoting autoantigen-*specific* therapeutic tolerance – for example by administering autologous tolerogenic dendritic cells (14).

Balancing risks: the need for a precision medicine platform for people at risk of RA. A favourable benefit-harm trade-off must be perceived by at-risk individuals and their physicians to justify predictive testing and therapeutic interception. Key factors determining the balance of risks include current symptom burden, likelihood of RA progression, and whether a lifestyle, licensed or unlicensed pharmacological intervention is being contemplated. For example, asymptomatic at-risk individuals with only modest progression risk are less likely to accept "intensive" interventions (such as early phase drug trial participation) than highly symptomatic individuals at high progression risk (15-17). These considerations are of critical importance when designing trials, being increasingly informed by observational cohort data and consensus definitions. Hence, symptom-free members of the public who test positive for rheumatoid factor (RF) or ACPAs at screening have ~9% risk of developing RA over three years(18), but this increases to 20-34% over 1 year in the presence of musculoskeletal symptoms(19, 20). Widespread adoption of a recent EULAR definition of arthralgia suspicious for RA progression(21) allows disease prediction with high sensitivity (84%)(22), and the positive predictive value of ACPAs amongst those fulfilling the definition reaches 65% over 1 year(23), increasing to >80% in the presence of accompanying radiological findings(24). The value of clinical predictors to define risk strata against which the selection of interventions can be appropriately calibrated during trial design may be further enhanced by robust biomarkers of auto-antigen-specific immunity in the future.

A number of placebo-controlled interventional studies aimed at delaying or preventing RA have been initiated to date, with some encouraging preliminary results already in the public domain. However, heterogeneous and overlapping enrolment criteria, a lack of consensus in determining primary endpoints and limited or varying follow-up periods all present challenges to their interpretation, particularly in respect of comparisons between interventions. This will continue to be compounded by the logistical challenges of identifying sufficient people at risk of RA, naïve to immunomodulation, for enrolment into potentially competing studies. Having realised "proof-of-concept," there is therefore now an urgent need for the field to develop a coordinated strategy that addresses these challenges and accelerates progress towards RA prevention.

Existing expertise and infrastructure. The lead applicant is embedded within a well-established network of collaborating investigators across the UK and EU whose focus is on unravelling risk-to-disease transition mechanisms and their means of disruption in RA. In the ongoing *Rheuma-Tolerance for a Cure* (RT-Cure) project (EU IMI2, CI Klareskog, Karolinska; co-PIs PRATT and ISAACS; 2017-23), Newcastle leads a Clinical Studies work package, integrating delivery of several high profile prevention studies including the APIPPRA study (CI Cope, KCL – to which Pratt oversaw substantial recruitment as Newcastle PI)(10), as well as ARIAA, TREAT-EARLIER and ASCARA. As CI of the Northeast Early Arthritis Cohort (NEAC), PRATT has also contributed to the development of a Europe-wide registry of people at risk of RA (*European Risk RA Registry*) in collaboration with Danish SME Zitelab (see letter of support from Steen Krogh), now comprising longitudinal data on >1000 individuals(25). Recognising the need to engage regulatory agencies due to the paradigm-shifting implications of their endeavours, and in collaboration with EFPIA and academic partners within RT-Cure, ISAACS participated in preliminary discussions with MHRA and, with PRATT, also contributed to a Briefing Document proposing novel clinical development and regulatory approaches in terms of eligibility criteria, study design, and endpoints for RA prevention trials, presented to the Swedish Medical Products Agency in May 2021. This establishes important steps towards establishing such strategies for purposes of early phase trial and clinical guideline development as part of a prospective platform trial. WASON will bring widely recognised expertise in platform trial design, including a particular application of innovative approaches in immune-mediated disease (26, 27). PRATT, ISAACS and

WASON are also co-applicants on a recently submitted proposal entitled *New options to restore more appropriate levels of immunity: scientifically explored* (NORMALISE; EU Horizon 2022, CI van Vollenhoven, AUMC). If awarded, they will lead a work package from Newcastle entitled, "Intervening in Pre-RA," whose goals are distinct from, but entirely aligned with those of the current proposal: NORMALISE, combined with funding from other UK and EU partners and the existing RT-Cure consortium, will provide the network, trial participants and underpinning science needed to set up a platform trial and establish a pipeline of interventions for its continuation. Indeed, recognising the MRC-NIHR EME Programme does not typically support international recruitment, such funding streams will be explored as means to do so, leveraging the recently established EULAR Network of Trials (ENTRI) to streamline enrolment(28).

4. Aims and objectives.

The overarching **aim** is of our work is to deliver a pan-European precision medicine platform for preventative interventions in people at risk of RA whose outputs directly impact policy. To achieve this, a key output from the current Acceleration Award project will be submission of a successful Programme award application for International Platform Studies in Precision Medicine during 2023. Objectives for the proposed 12-month project to this end are as follows:

a) Convene an international *At Risk RA Precision Platform Trial Management Group* (TMG) with representation from expert UK/EU units, the Newcastle Clinical Trials Unit (NCTU), individuals with experience of living at risk of RA and the European Risk RA Registry – to plan and submit a multi-centre application to the anticipated *International Platform Studies in Precision Medicine* call in May (Stage 1) / September (Stage 2) 2023.
b) Undertake a systematic literature review synthesising evidence to understand optimal sponsorship, governance and funding models for international platform trials that directly informs the TMG's development of suitable strategy, is acceptable to participants and compatible with NHS and EU healthcare infrastructures.
c) Convene a RAPPORT Public Advisory Group, steered by the PPI Lead, comprising PPI co-applicants with local patient partners and reporting to the TMG, with a remit to advise regarding elements of a Master Protocol and/or intervention arm development.
d) Refine and achieve consensus across academic and industry stakeholders on optimal clinical and/or immunological biomarkers for participant stratification in platform studies.
e) Engage with our existing industry partners to secure initial interventional arms through written letters of intent, with sample sizes and feasibility to be finalised in each case by modelling real-life *European Risk RA Registry* data.
f) Produce advanced drafts of a RAPPORT Master Protocol and Consortium Agreement.

5. Research Plan / Methods

At Risk RA Precision Platform Trial Management Group (TMG). An early priority of our proposed project will be to convene an international TMG whose membership will shape its long-term delivery during and beyond its "Accelerator" phase. Chaired by PRATT, the TMG will comprise (i) membership of existing and proposed RT-Cure and NORMALISE membership as a strong basis for recruitment, (ii) nominated representatives informed by lived experience of RA risk from Newcastle *Patient and public Involvement in Musculoskeletal reSearch* (PIMS) and EULAR *People with Arthritis and Rheumatism in Europe* (PARE) communities, (iii) expert IT input from ZiteLab, and (iv) representation from Newcastle Clinical Trials Unit (NCTU) and Newcastle upon Tyne Hospitals (NuTH) R&D/Contracting/Pharmacy Departments, as summarised in *Table 1* (see also letters of support from *Klareskog*, *van Vollenhoven*, *EULAR PARE* and *Steen-Krogh*). To guarantee substantive UK recruitment (and hence applicability of long-term findings to the NHS), engagement of additional UK sites for recruitment will be solicited during the Accelerator project, discussions having already been initiated via the NIHR Musculoskeletal Translational Research Collaboration (MSK TRC), upon whose Inflammatory Arthritis Steering Committee PRATT sits (see letter of support from *Buch & Siebert*).

Monthly virtual TMG meetings during the lifetime of the Accelerator Project will ensure milestone delivery (see also *Sections 7* and *8*), with concurrent, contributory work strands guiding progress:

- **Evidence synthesis**. Newcastle researchers will lead a systematic literature review of learnings on implementation of international platform studies during the first six months. Whilst design *methodologies* have previously been reviewed in this way(29), a landscape analysis of their *practical implementation* across international borders is timely in the SARS-CoV era, promising outputs of broad interest that will directly inform RAPPORT's delivery strategy. In parallel, and with expert contracting, oversight and pharmacy input from NuTH, the NCTU team will engage relevant UK/EU counterparts, refining optimal recruitment pathways that leverage the *European Risk RA Registry* as a basis for participant identification within local ethical frameworks.
- **Public Advisory Group** A PAG, co-led by PPI Lead ROMANIUK and PPI co-applicant USHERWOOD, will be convened of up to seven Newcastle PIMS members who have expressed interest in this topic, PPI co-applicants ARMSTRONG and JONES and EULAR PARE membership. This will provide a critical *ad hoc* advisory forum to address issues articulated by the TMG in depth, for example in relation to Master Protocol development (participant identification, study visit scheduling, questionnaire burden, digital inclusion) or case-by-case calibrations of RA progression risk that render emergent interventions acceptable for potential participants. Lay person review of public-facing documentation (PAG agendas, patient information sheets, posters) will be reviewed by PPI co-applicant ARMSTRONG with PPI Lead.
- **Biomarker refinement**. Clinical biomarkers (family history, EULAR definition of arthralgia suspicious for progression to RA, ACPA/RF serology, MRI/ultrasound imaging readouts and combinations thereof) together represent the state of the art for purposes of calculating RA progression risk, and so will likely form the basis of participant stratification at platform launch, but the detail will be determined through TMG consensus. A number of putative theragnostic bio-assays are the subject of ongoing refinement by applicants and partners, including measures of autoreactivity or non-specific immune activation. As with the proposed interventions themselves, prospectively measured biomarkers of this nature are expected to be revised during the trial's evolution, informed by emerging science.

Institution / consortium		Expertise / contribution	Delegates, where confirmed
Newcastle University, UK		Project management, lead master protocol development, trial management, Governance/ IT/Pharmacy/Contracts, public representation.	Pratt (chair), Isaacs, Wason, Bardgett. PPI Lead: Romaniuk; PPI Co-Applicants NCTU & NuTH representatives.
Newcastle PIMS & EULAR PARE		Public representation including master protocol development	Leigh Romaniuk (PPI Lead), PARE.
ZiteLab (SME)		*European Risk RA Registry* integration.	Niels Steen Krogh
Karolinska Institute, Sweden		Trial participation*, master protocol development, RT-Cure Consortium CI; *European Risk RA Registry* integration.	Prof Lars Klareskog
Amsterdam University Medical Centre, The Netherlands		Trial participation*, master protocol development, NORMALISE Consortium lead.	Prof Ronald van Vollenhoven
RT-Cure Consortium		Trial participation, master protocol development.	University of Birmingham, UK (TBC)
		Trial participation*, master protocol development.	Deutsches Rheuma-Forschungszentrum Berlin (TBC)
	NORMALISE Consortium	Trial participation*, master protocol development, *Risk RA Registry* integration.	Medical University of Vienna, Austria (TBC)
		Trial participation*, master protocol development.	University of Erlangen, Germany (TBC)
		Trial participation, master protocol development.	University of Glasgow, UK (TBC)
		Trial participation, master protocol development.	Kings College London, UK (TBC)
		Trial participation*, master protocol development.	Leiden University Medical Centre, The Netherlands (TBC)
		Trial participation*, master protocol.	Semmelweis University, Hungary (TBC)
		Trial participation*, master protocol development.	Instituto de Medicina Molecular João Lobo Antunes, Portugal (TBC)
		Trial participation*, master protocol development.	VIB Center for Inflammation Research, Belgium (TBC)
Additional UK sites TBC		Trial participation, master protocol development.	Via MSK TRC (Leeds, Manchester) TBC

***Table 1**. Collaborator network; *EU sites: local & Horizon 2022 funding options for recruitment.*

A single in-person meeting will coincide with Stage 1 submission of the MRC-NIHR EME award (and completion of the systematic review), kick-starting the Stage 2 application.

Engagement with Industry. We will engage early with potential industry partners to ensure 'buy-in' to the platform trial concept, including those who have already contributed to discussions as participants in RT-Cure. We anticipate these companies may wish to contribute assets in-kind to

an initial trial, and firm commitments to implement *at least* two interventions will be sought within the lifetime of the 12 month Accelerator award. Tailored according to RA progression risk (*Figure 1*), these are expected to include at least one non-pharmacologic approach (such as lifestyle change, dietary modification and/or direct targeting of the microbiome) and one existing, licensed immune modulator. The feasibility of proposed initiator arms within the platform design will be evaluated, being modelled using pilot data obtained directly from the *European Risk RA Registry* with appropriate IT support in Newcastle and via RT-Cure. This will directly inform power calculations to determine sample size, and recruitment planning, de-risking subsequent multicentre implementation as part of a fully funded trial. Thereafter, accruing intervention arms will continue to map intervention "potency" to the probability of RA progression.

Master Protocol development and feasibility modelling. Workshops conducted as part of the RT-Cure Consortium highlighted a platform design, in which different interventions could be compared, as optimum means to address unmet needs (*Figure 1*). The master protocol concept allows testing of multiple treatments, with inclusion tailored to individuals' level of RA risk and/or immune dysregulation. Precision trials of this nature require considerable development (both statistical and more broadly) to ensure a deliverable design.

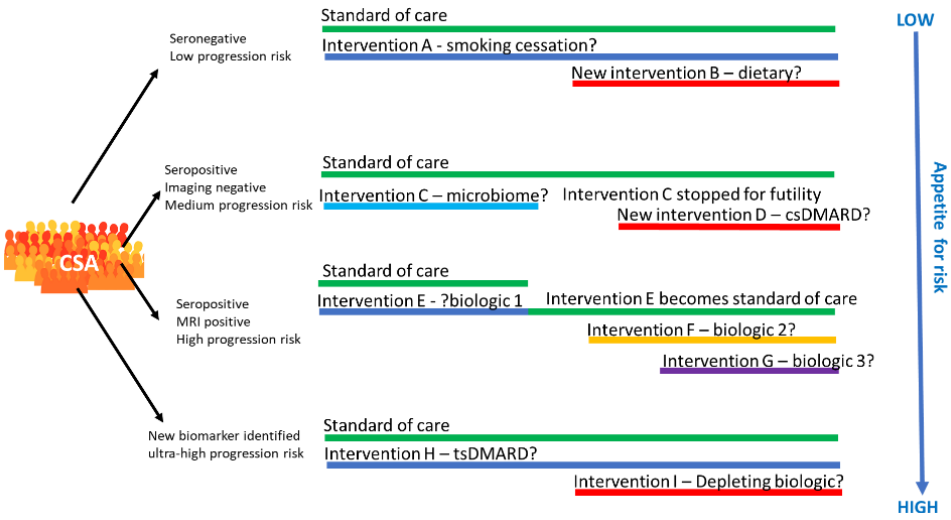

***Figure 1**. Stratified platform design. Multiple intervention arms, ranging from lifestyle to pharmacological, are deployed against standard of care (SoC) with participants stratified at baseline according to predicted risk of RA, and actual RA development being the ultimate trial endpoint. "Appetite for risk" of adverse reactions is thereby matched to risk of progression. New arms may be introduced or existing one terminated due to futility or adoption as SoC as the trial progresses.*

This includes ensuring the most appropriate interim analyses are proposed for an adaptive platform trial. As well as affording an intrinsic participant identification and enrolment strategy, the *European Risk RA Registry* will provide a natural standard-of-care "back-drop," harmonising the care pathway between centres. Classifiable RA development will be its primary endpoint. It is envisaged that "light touch" follow-up will be responsive to evolving symptomatology amongst participants, with outcome measures centring on *time-to-RA* in comparator arms alongside a range of subsidiary clinical, radiological and immunological readouts. Informed by all the preceding elements, delivery of an advanced Master Protocol ready for HRA submission will accompany systematic review, sharing of a draft Collaboration Agreement between sites and NIHR-MRC EME Programme funding application and as substantive outputs of our project.

6. Dissemination, Outputs and anticipated Impact.

The primary output of the current proposal will be a Stage 2 application for an MRC-NIHR (EME) International Platform Studies in Precision Medicine award in collaboration with UK/EU partners and NCTU. Underpinned by recently awarded Newcastle NIHR Biomedical Research Centre infrastructural support explicitly designated for prevention studies, successful delivery of that project will ultimately deliver a novel, preventative management paradigm for RA through implementation of guidelines and recommendations to arise directly from peer-reviewed and published at-risk precision platform outputs, with learnings potentially transferrable to other IMIDs. In the nearer term, the systematic landscape analysis of international platform trial implementation is likely to form a highly-cited reference for similar endeavours. Aside from high-impact publications, dissemination will be via national and international scientific fora and

Newcastle's active in-house and EULAR PARE PPI/E networks and social media. The latter will be overseen by PPI co-applicant JONES in partnership with ROMANIUK.

7. Project timetable and milestones.

Rheumatoid Arthritis Prevention: catalysing PlatfORm Trial delivery (RAPPORT).

Objectives, Activities and Milestones	Month: 1	2	3	4	5	6	7	8	9	10	11	12
Objective a - R*APPORT funding application.*												
Monthly virtual TMG meetings & in-person Workshop	X	X	X	X	X	X	X	X	X	X	X	X
Governance, contracting, pharmacy framework development.												
Milestone ai - Appoint local PIs at collaborating sites.			*									
Milestone aii & aiii - Stage 1 & 2 application									Stage 1			Stage 2
Objective b - *Systematic literature review*												
Milestone bi - Submission of manuscript for publication						*						
Objective c - *Public Advisory Group input* *(ad hoc meetings)*												
Milestone ci - PAG launch event		*										
Objective d - *Biomarker Refinement* ***(clinical, immunological)***												
Ongoing immunological biomarker development												
Milestone di - Clinical stratification criteria for platform arms									*			
Objective e - *Industry engagement*												
Statistical modelling, feasibility, contract discussions												
Milestone ei - Confirmation of 2 initiator intervention arms.											*	
Objective f - *Master Protocol development*												
Milestone fi - Draft Master Protocol & Collaboration Agreement												*

Figure 2 *depicts a Gantt chart for the current proposal.*

8. Project management

Project management overseen by PRATT is supported by experienced Senior Trial Manager/co-applicant BARDGETT, who, with appropriately costed NCTU administrative and database support, will ensure timely milestone delivery and coordinate stakeholder involvement via TMGs

9. Ethics / Regulatory Approvals

No regulatory or ethical approvals are required at the Accelerator stage, but these will be key considerations during the project; ethics for entering data from international sites into the At Risk Registry exist, with adaptations required to align to clinical trial ambition going forwards.

10. Project / research expertise

The project team are ideally poised to implement the proposed work. PRATT is a Clinician Scientist and CI of the Newcastle Early Arthritis Clinic with a track record in the delivery of high impact translational research, including early and late phase clinical trials for people with, and at risk of, RA. Based within the EULAR Centre of Excellence in Musculoskeletal Disease at Newcastle, he will be mentored by ISAACS, an NIHR Senior Investigator with whom he has participated in the aforementioned international consortia, and whose international reputation in the development and delivery of immune modulatory therapeutics is unrivalled. WASON is an NIHR Research Professor whose primary interest is innovative trial methodology for immune-mediated inflammatory diseases; his team's input, together with that of experienced Senior Trial Manager BARDGETT, assures Master Protocol deliverability. Critical (and appropriately costed) expertise in respect of sponsorship, contracting, information governance and investigational product management will be coordinated from the Newcastle University/NuTH Joint Research Office (see also Justification of Costs). The Accelerator phase of our project will benefit throughout from appropriately resourced and remunerated input from Lay Co-applicants ARMSTRONG, JONES and USHERWOOD, supported by PPI Lead ROMANIUK - melding unique skills with lived experience of the RA at-risk state and interventional study participation.

11. Success criteria and barriers to proposed work.

Rapid appointment of the staff needed to deliver the proposed 12-month project is assured, with statistics trial management and NuTH staff already available for engagement in this work, pending award. Its primary success criterion will be award of the aforementioned NuTH-sponsored MRC-NIHR (EME) International Platform Studies in Precision Medicine award.