National Institute for Health Research

COLLABORATIONS FOR LEADERSHIP IN APPLIED HEALTH AND CARE

SPECIFIC THEME - DETAILS

Host Organisation

1.1 Name of proposed Host Organisation (NHS Trust or Provider of NHS services)

Liverpool CCG

Theme – to be completed for all Themes

2.1 Name of Theme

Delivering Personalised Health and Care

2.2 Percentage of Research and Implementation

Research:	**80%**
Implementation:	**20%**

2.3 Theme specific short (1-2 years), medium (2-3 years), long term (4-5 years) aims and objectives:

The Theme's vision is to deliver the best clinical decision, treatment and monitoring strategies in a number of chronic disease areas using personalised medicine approaches, including the creation and implementation of medical technologies, to reduce health inequalities. Our aim is to improve self-care by patients, improve access to care in the community, and allow its integration in complex chronic conditions with a personalised approach. The Theme will provide NHS practitioners and patients with innovations in personalised medicine, medical devices and diagnostic tools that genuinely add value but not cost, thus satisfying the NHS Quality, Innovation, Productivity and Prevention (QIPP) challenge.

The Theme will *initially* concentrate on five specific projects outlined in section 2.5. The Theme will also have continuous activity to evaluate and optimise the effectiveness of assistive technologies which have the capacity to improve outcomes for patients and to help deliver more efficient healthcare across the wider healthcare system as piloted in the TSB-funded DALLAS programme, and specifically the Liverpool-based "More Independence" (Mi) project.

Short term: (a) realisation of a POC biomarker device, with telehealth facilities, for early identification of sepsis, (b) improving the safety of drug therapy in epilepsy, bipolar depression and trigeminal neuralgia using genetic diagnostics, (c) development of a personalised renal function monitoring plan in heart failure patients on diuretics, (d) improving the detection and reporting of adverse drug reactions, (e) assessment of access and equity in personalised medicine, (f) evaluation of assistive technology use in residential and care homes within the DALLAS-Mi project and engaging with DALLAS project through bringing together the project, their industrial partners, service users, managers and practitioners to develop and commission a bespoke evaluation to complement the national one.

Medium term: (a) widening scope to implement technologies and personalised medicine approaches developed by investigators in the UK and world, (b) assessment of cost-effectiveness of personalised renal function monitoring, (c) assessment of acceptability of personalised approaches to treatment and monitoring, (d) development of predictive tools on glaucoma progression using optical coherence tomography (OCT) images of the optic nerve head.

Long term: (a) clinical assessment of technology developed in years 1-4 within the NW Coastal AHSN geography and with strong involvement of end-users and healthcare services, (b) work with electronic prescribing companies to incorporate personalised monitoring of renal function to computer systems in GP practices, (c) work with MHRA to assess uptake of recommendations produced through our studies into clinical practice, and the impact of these changes on public health, (d) development of generic strategies for improvement and nationwide implementation.

2.4 The strategy for the Theme, providing a description of how the aims and objectives will be achieved:

The Theme Steering Committee (TSC) will shape strategy and operational management. The TSC will oversee the theme's applied research and implementation priorities. Importantly the TSC will integrate new projects in collaboration with our stakeholders supported by the EEE theme: Practitioners, PPI, Commissioners, Managers & Industrial Partners, with Liverpool Health Partners, Lancaster & Cumbria Clinical Research Hub, through links to our translational centres such the MRC Centre for Drug Safety Science and Wolfson Centre for Personalised Medicine, and through national horizon scanning. It will also facilitate implementation by linking closely with the NW Coast AHSN, which has a specific theme dedicated to personalised medicine. In order to ensure the best methodologies are used for our clinical studies, we will have active involvement of the MRC NW Methodology Hub (which has a stratified medicine theme). We will give particular attention to industrial partnerships, and service user groups who will help to identify emergent clinical needs. The TSC will continue the work conducted in the development stage to prioritise R&D projects according to explicit criteria that include strategic fit with (a) NIHR's priorities, (b) the Theme's overarching aims in collaboration with our stakeholders, (c) the nature and scale of the needs to be addressed. For each of the projects to be supported, the SC will bring together a team of academics, clinicians, industrialists with stakeholders including PPI representatives, public health experts, NHS commissioners and relevant charities, to oversee and support progress and to ensure timely production and cost effectiveness of healthcare solutions, and relevance to patient and healthcare needs. Where appropriate, we will also work with the MHRA, particularly when our goal is to lead to a change in the prescribing instructions or improvement in ADR reporting. The TSC will also work with the Theme's industrial and NHS partners and other stakeholders to identify and pursue additional funding resources for projects with exceptional potential, strong industrial interest and longer-term delivery plans. The projects described in 2.3 have been identified at the Theme's development stage with stakeholders, but wider participation will be invited with commencement of the Theme's activities. The theme leader will report to the NWC CLAHRC Management Team on progress as specified in the main part of the application.

2.5 A brief description of proposed projects proposed for first two years of the contract:

The Theme will initially concentrate on 5 projects for which there is significant potential benefit to patients and healthcare services and a clear route to translation into healthcare products.

The **first project** will refine a TSB and Gates foundation-funded point-of-care device for the detection of biomarkers of sepsis (a common presentation in the elderly and children under 5 years of age, and a common complication of diabetes) in order to improve ease of use by end-users. The device will employ microfluidic/electrochemical platforms using aptamers as biorecognition elements and relying on whole blood from finger prick samples. Built in electrochemical biosensors will be used in detection of sepsis with the results transferred via simple technology to common smart phone devices and communicated to practitioners using telehealth. The same PoC device will be further developed for the diagnosis and management of chronic musculoskeletal, cardiovascular and kidney conditions in collaboration with an Industry partner. Future applications will include other biomarkers and fluids. We will explore potential applications and models through our stakeholder engagement, multidisciplinary team and industry partners.

The **second project** will seek to establish whether Carbamazepine, which is used in a number of chronic neuropsychiatric conditions, can be used more safely through the use of HLA-A*31:01 gene screening prior to its use. We showed (NEJM; 2011; 364(12):1134-43) that HLA-A*31:01 predisposes to serious hypersensitivity reactions. In a feasibility study of 100 new CBZ starters, we will determine in primary care (GP or primary care pharmacy) specialist care settings the feasibility of genotyping, and its acceptability to patients and clinicians. This work will be done with an Industry partner such as MC Diagnostics, and the data will assist the design of a national trial where clinical outcome measures will be assessed based on additional funding from the HTA or EME scheme.

The third project will seek to develop personalised renal function monitoring in patients on diuretics for chronic heart failure; the second most common cause of admission to NHS hospitals (*BMJ; 2004: 329:15-19*). There are currently no agreed guidelines for GPs and hospital physicians, leading to inconsistent practices in patient monitoring. We will use primary care databases (CPRD, Farsite, hERC) to identify patients on diuretics, determine how often U&Es are measured, what actions are taken based on the results (if any), how many patients develop renal impairment, monitor drug dosages and types of diuretics used, and patient factors that may influence renal function (underlying disease, severity of heart failure, hypertension, diabetes etc, and concomitant medications). Acceptability of developing renal function monitoring will be assessed through interviews with patients and clinicians. We will ultimately aim to incorporate the decision rules in GP prescribing systems, and utilise the PoC device mentioned above to test near patient monitoring.

The fourth project, an implementation project, seeks to improve detection and reporting of adverse events through use of our Liverpool causality tool (*PLoS One*. 2011;6(12):e28096) and the BMJ/MHRA learning package on spontaneous ADR reporting to improve reporting rates of ADRs from all healthcare sectors. We know that reporting rates vary widely between primary care practices and hospitals, and although all

doctors should report ADRs, very few do. Early detection of ADRs is of obvious patient benefit, while better reporting allows the MHRA to protect public health by undertaking regulatory action when appropriate. An educational programme will train doctors to recognise and report ADRs. Input from the MHRA will be sought at an early stage. Acceptability of the causality tool and ADR education packages will be determined by clinician interviews. Success will be ascertained by the increase in number and quality of ADR reports from the sentinel sites in comparison to historical reporting rates.

The fifth project aims to extend the use of computer-based predictive tools to healthcare in ophthalmology to personalise treatment in glaucoma, a chronic condition. Within the first two years, the project will concentrate on the analysis of optic nerve head (ONH) cupping and its geometry change between clinic visits to provide accurate predictions of glaucoma prognosis and help optimise the patient's medication to lower intraocular pressure. Validation of the predictive tool against clinical data will be conducted before use in future clinical trials.

The sixth rolling project brings the multidisciplinary approach with industry partners and our robust stakeholder engagement to enhance shared development and evaluation of new technologies within DALLAS and Mi to complement the national evaluation led by Prof Mair in Glasgow..

2.6 The Theme's relevance to the health of patients and the public:

The use of personalised medicine approaches and technologies has a high potential to impact on patients and healthcare services in the near term. Our aim is to improve the diagnosis, treatment and monitoring of diseases which are chronic, of public health importance, and lead to the use of secondary and tertiary care services, in order to allow patients to self-care within their home setting, optimise chronic care, prevent hospitalisation, and improve cost-effectiveness, in a manner which does not exacerbate health inequalities. An important focus is on drug safety: we have shown that approximately 8000 NHS beds are occupied by adult patients with ADRs at any one time (70% are avoidable) and at least 25% of children develop ADRs as in-patients. The total cost to the NHS is over £1 billion/year. To improve therapy with existing drugs, as well as develop new drugs, personalised or stratified medicine approaches are important so that the patient's overall treatment is optimised and the benefit-risk profile maximised. We also focus on chronic diseases such as glaucoma which affects more than 500,000 in the UK and costs the NHS £3.7bn annually. Predicting the progression of the disease will help optimise and personalise medication to lower intraocular pressure and improve disease management procedures. The theme will develop a POC device which promises to improve the quality of care by providing low-cost, rapid results at the POC for clinical decision making in the management of chronic conditions. In addition to improving the speed of diagnosis, increased use of POC tests in primary care will save beds and resources at the secondary care level. For example, the use of a POC cardiac panel for 3 biomarkers (*Alere Triage Cardiac Panel- myoglobin, CK-MB and Troponin-I*), which can help differentiate chest pain patients that require admission and those that can be discharged, has saved the NHS over £192M in England (*British In Vitro Diagnostics Association, Technology Brief 13*). With an increasing aging population with multiple co-morbidities, such technologies address an urgent need for a more integrated and personalised approach to management of chronic conditions, and a shift of traditionally hospital-based technologies into patients' homes.

2.7 The proposed Theme Leader:

Prof Munir Pirmohamed will be theme leader. He is an NIHR Senior Investigator (since 2008), recently appointed FMedSci, has an H-index of 54 (Web of Science), and has an international reputation in drug safety and personalised medicine. He is also the NHS Chair of Pharmacogenetics, Chairs the Pharmacovigilance Expert Advisory Group for the MHRA, and is a Commissioner on Human Medicines. He directs the Wolfson Centre for Personalised Medicine, a multidisciplinary centre with 73 individuals where research into personalised medicine spans the whole spectrum from discovery to implementation.

2.8 Three examples over the last ten-year period from the proposed NIHR CLAHRC of how previous research findings in this area have translated into improved outcomes for patients and the NHS:

1. Our work demonstrated the clinical utility and validity of the meningococcal PCR test in a real-life clinical setting, which led to improved diagnosis and thus improved case ascertainment. The diagnostic confirmation rate increased from 31% (before introduction of meningococcal PCR into routine testing) to 88% (A*rch Dis Child, 2002*). The test is now established as the gold standard for diagnosis of meningococcal disease (MCD) and recommended in the 2010 NICE Guidelines for bacterial meningitis and meningococcal septicaemia. Improved diagnosis of MCD leads to appropriate treatment for the correct duration of time, thereby improving quality of life and life-time productivity and reducing complication rates.

2. Our work on HLA and drug hypersensitivity has led to the use of HLA-B*5701 testing before abacavir prescription (Hughes et al, *Pharmacogenetics*. 2004;14(6):335-42) which has virtually eliminated the problem of abacavir hypersensitivity in the NHS. This is now mandated in the abacavir SPC and in international guidelines for HIV. We were also able to show that HLA-B*1502 does not predispose to severe blistering skin reactions in Caucasians (but does in other ethnic groups) (*Pharmacogenomics*. 2006 Sep;7(6):813-8) and have identified a new biomarker (HLA-A*31:01) which predisposes to carbamazepine hypersensitivity in Caucasians (*N Engl J Med*. 2011 Mar 24;364(12):1134-43) – both of these are

mentioned in the SPC in the EU, and also taken up in the US FDA drug label.
3. Spontaneous reporting of ADRs suffers from under-reporting. We were the first to show that nurse-led reporting would add real value to the yellow card system operated by the MHRA (Lancet. 2003 Apr 19;361(9366):1347-8), which resulted in nurses being added to the list of professional who could report ADRs. For certain categories, for example, vaccines, nurse reporting has been key in evaluating the benefit-risk ratio of new approaches, for example, the use of HPV vaccines to prevent cervical cancer.

For Themes containing proposed applied health research

Research Theme Section – for research or mixed model Themes
Please leave blank if implementation-only Theme

3.1 Please describe the proposed applied health research to be undertaken within the Theme using NIHR funding and where appropriate matched funding:

The TSC will be responsible for prioritising the research to be supported by the Theme. A variety of approaches, including feasibility studies, observational and qualitative methodologies, will be used to evaluate different approaches to improve personalisation of therapies and diagnostics with the aim of improving patient outcomes in the near term. Where ever appropriate, we will use expertise within the MRC NW Trials Methodology Hub to ensure that the most efficient design is used to achieve our objectives. Our focus on chronic disease areas, and move towards personalised healthcare is important, but it is equally important that we do not exacerbate health inequalities which can arise because of many factors including communication barriers, location of services, health beliefs and perceptions, and organisation of pathways through the service. An evaluation to assess health inequalities will be embedded within all of the above projects to provide an in depth knowledge base on access and equity issues in personalised medicine, and to build on the findings to consider how service provision can be reconfigured to reduce inequalities. The methodology will include interviews with health care professionals and service users to map the area and scope the issues to form the basis for the subsequent work; examine the pathways and protocols and how service user access is organised; in depth interviews with service users to explore how they perceive the service and what are the barriers and facilitators to participation; and a design phase where users and staff collaborate on designing service change, implementing and reviewing the changes.

3.2 Please outline the key researchers associated with the Theme including how their involvement will add depth and quality to the proposed applied health research to be conducted:

Dr Carrol (Reader in Paediatrics) - experience of both clinical research and in using technologies in patient care. Dr Carrol works closely with **Dr Myers** the Director of MicroLab Devices and the industrial partner and manufacturer of biomarker devices. **Prof Williamson,** UoL – Prof of Medical Statistics and Director of the MRC NW Trials Methodology Hub, with extensive experience of clinical trial design and analysis. **Dr Jorgensen**, UoL – Lecturer in Pharmacogenetic Statistics, knowledge of pharmacogenetics, statistical genetics and application to clinical practice. **Dr Alfirevic**, UoL – Senior Lecturer in Pharmacogenetics – expertise in genotyping and bioinformatics. **Dr Frith**, UoL - Senior Lecturer in Bioethics and Social Science with expertise in qualitative methodologies. Lucy will lead the work on health inequalities in personalised medicine with **Prof Popay**. **Prof Marson**, UoL – Prof of Neurology, will be key in developing personalised approaches in epilepsy. **Prof Peak** (Alder Hey Hospital R&D Director) and **Prof Beresford** (Chair in Paediatrics) will ensure that paediatric expertise is covered, while **Prof Alfirevic (**Prof of Obstetrics) will provide expertise in Women's Health. **Ms Randall**, Senior Pharmacist, NW Regional Medicine Information Centre, with extensive experience of pharmacovigilance, ADR reporting and education in ADRs. **Prof Gabbay**, UoL, Prof of Primary Care, to provide input into the primary care aspects of research. **Prof Elsheikh**, Head of Ocular Biomechanics Group at UoL; **Prof Harding**, Head of Eye and Vision Science at UoL with expertise in glaucoma and diabetic retinopathy, and clinical trials; **Prof Williams**, expertise in biomaterials; **Dr Zheng**, expertise in image processing and OCT map segmentation. This inter-disciplinary grouping has collaborated in translating medical device technology in ophthalmology into clinical pathways. **Drs Wuerger and Meyers**, UoL, background in psychology and expertise in end-user acceptance, contribution to all projects to ensure compliance to patients' needs and acceptance by healthcare services. Health Economics input from Lancaster University will be led by **Prof Bruce Hollingsworth.** Educational expertise and evaluation will be provided by the 3 health and medical schools.

3.3 Please describe the proposed outputs from the research and the impacts anticipated (including the intended audience, how the impacts will be achieved and the likely timeframe):

Outputs: (a) High impact publications, conference presentations, workshops, dissemination of activities via the clinical research networks and AHSN. Throughout the 5 years; (b) Genotyping device for *HLA-A*31:01* (to be developed by Industry partner): year 2. (c) Personalised renal function monitoring protocol for patients on diuretics (2 years). (d) A lightweight POC device for assessment of sepsis. (e) Predictive tool and computer software to estimate progression of glaucoma. (f) Website to highlight achievement of theme – throughout the 5 years. The audience for this will be broad, and should in essence include any

healthcare professional who is involved in the prescribing and administration of drugs.

Impacts

- Changes to prescribing information in the SPC, for example for carbamazepine
- Changes to guidelines in relevant areas of drug prescribing
- Revenue generation and employment creation through the development of novel POC diagnostics and genetic marker assessment
- Health economic benefits through more rapid diagnosis, improved monitoring, better self-care in the community and prevention of hospitalisation.
- Societal impact by improving quality of life of patients and allowing them greater independence in their homes

For Themes containing implementation (to be funded by matched funding only)

Implementation Theme Section – for implementation or mixed model Themes
Please leave blank if research-only Theme

4.1 Please describe the proposed implementation of applied health research into clinical practice across the health community that will be pursued within the proposed Theme using the matched funding, including an overview of how these relate to the overall strategy:

Implementation in different settings including primary and secondary care, in both adults and children, and in women's health will be conducted as appropriate, working in collaboration with the NW Coast AHSN. The NHS Technology Adoption Centre (NTAC), the industry/NHS liaison body TRUSTECH, MHRA and NICE involvement will be sought where necessary, while additional funding will be sought facilitate larger clinical trials (Phase 3). For the education in ADR reporting, we will use the AHSN to implement both the detection and reporting of ADRs, with the involvement of the MHRA, Schools of Pharmacy (Liverpool John Moores University and UCLan), and the Primary Care Pharmacy Network. Our overall approach here is to develop new technology platforms and use existing structures and regulatory procedures to enable implementation and diffusion into clinical practice in a time and cost-efficient manner without exacerbating health inequalities. Health economic analysis and working with Industry will be prioritised whenever possible so that we attain the dual goal of health improvement and wealth creation. All steps will be coordinated by the Theme's Steering Committee, which will ensure continuous consultation with appropriate experts and stakeholders (NICE, patient groups, NHS Trusts, INVOLVE, NWPiRF, NHS National Innovation Centre).

4.2 Please describe the proposals for activities to facilitate the implementation of research findings across the health community, including the rationale and an outline of the process and methodology by which this approach to implementation will be evaluated:

We will disseminate research findings through journals, websites, and conferences, and direct contact with CCGs, NHS England, stakeholder groups (Department of Health, NHS Commissioning Board Special Health Authority, the National Institute for Clinical Excellence, the Royal College of Nursing, the Royal College of Physicians, Age concern UK, British Heart Foundation, Arthritis UK), and across the AHSN footprint to ensure widespread uptake of innovations.

4.3 Please outline the key individuals associated with the implementation, summarising their previous experience in the proposed approach to implementation:

Our implementation strategy will be through the AHSN. Patients increasingly want to be involved in decisions about their own healthcare. Research has shown that when they are, they choose less hospital care and report better experiences. This has given rise to an approach known as "Shared Decision Making" (SDM), in which health care professionals explain all the relevant treatments and alternatives to patients in a planned and systematic way, providing enough of the right kind of information to enable the patient to choose the treatment option that best suits their lifestyle, personal beliefs and values. Combining highly personalised information about the response to given treatments with a systematic framework of high quality information giving takes patient involvement, engagement and influence to a new level. AQuA (the Advancing Quality Alliance) will be one of the CLARHC's key delivery partners. Having been commissioned by Right Care on behalf of the Department of Health as one of the three National providers of the Right Care Shared Decision Making Programme, it has worked with individuals/organisations to develop SDM, in particular the "Ask Three Questions" approach, which has been rolled out across AQuA member organizations. AQuA's SDM team is working with the Centre for Personalised Medicine at UoL to ensure close alignment between the two agendas. Many of the investigators listed above also been involved in the implementation of innovative approaches into the NHS. We will also work closely with Commissioners, R&D Departments, and Medical Directors to ensure that we have the best systems for implementation, and close links with our two overarching themes on Evidence Synthesis, Knowledge Exchange and Implementation will enhance their stakeholders' engagement and involvement with the theme's portfolio.

This form, together with other requested attachments, must be submitted by **1:00pm** on **13 May 2013.** Any questions about the completion of the form should be directed to Claire Vaughan (claire.vaughan@nihr-ccf.org.uk).