# A. Cover Page

## Request for Proposals (RFP): *Improving Care of Patients with Atrial Fibrillation in Order to Reduce Stroke Risk*

**Project Title:** Optimising clinical effectiveness and quality along the Atrial Fibrillation anticoagulation pathway through implementation of personalised care.

**Applicant:** Professor Oliver James, Medical Director. Academic Health Science Network North East and North Cumbria

**Main collaborators:**
Academic Health Science Network North East and North Cumbria (AHSN NENC)
**NHS:** The Newcastle upon Tyne Hospitals NHS Foundation Trust, County Durham and Darlington NHS Foundation Trust, Newcastle Gateshead CCG
**Academic:** Institute of Health & Society, Newcastle University; Institute of Genetic Medicine, Newcastle University
**Commercial:** NewGene Ltd, LGC Ltd, QuantuMDx Ltd, Inhealthcare Ltd.

**Abstract**

**Goal:** To evaluate and disseminate lessons learnt from the optimisation of the entire AF anticoagulation pathway in the Newcastle area. The redesigned pathway will improve the quality of patient care, personalisation and clinical effectiveness.

**Project description:** An innovative new clinical pathway for Atrial Fibrillation will improve patient treatment stratification and personalisation of care. At the start of the pathway, genetic testing will identify warfarin sensitivity and shared decision-making will enable health professionals and patients to make an informed choice of anticoagulant. Two cohorts of individuals (see target population) will be offered INR self-monitoring using point of care coagulometers and telehealth solutions. Project learning will be shared through webinars and workshops, and the creation of an open source economic model that will enable localities across England to quantify potential cost-benefits of pathway optimisation.

**Target population:** The project will focus on two cohorts, the first drawn from the estimated 650 newly diagnosed AF patients in the Newcastle upon Tyne area; the second a stratified sample of existing attendees at Newcastle warfarin clinics in hospital, community settings and in domiciliary care.

**Methods:** Patient's genetic, anthropometric and TTR data will be recorded and analysed. Qualitative data will be collected from patients, clinical staff, healthcare professionals, commissioners and other stakeholders.

**Assessment:** As the new pathway is operationalised, resource use, patient experience and clinical outcomes will be collected. A *de novo* economic model will be developed to allow commissioners across England to calculate the cost-effectiveness of implementing the new pathway in their area.

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# C. Main Section of The Proposal

## 1. Overall Goal and Objectives

**Overall Goal:** ***The project will evaluate and disseminate lessons learnt from the optimisation of the entire atrial fibrillation (AF) anticoagulation pathway in the Newcastle area. The redesigned pathway will aim to improve the quality of patient care, personalisation and clinical effectiveness.***

Newcastle's redesigned AF anticoagulation pathway responds to the internationally recognised need for continued improvement in patient stratification and personalisation of AF care[1] and will be patient-centred, based on peer-reviewed and real world evidence and will deploy both innovative and NICE approved technologies at key points along the pathway.

Steps in the redesigned pathway:

1. Patients starting anticoagulation therapy will be offered genetic testing prior to the commencement of therapy;
2. The genotype result and shared decision-making that reviews clinical and lifestyle factors, will inform anticoagulation choice;
3. Patients with 3 warfarin sensitivity variants and no other contraindications, will be advised they may be best suited to a direct oral anticoagulant (DOAC). Patients without these variants who choose to anticoagulate with warfarin will, if appropriate, receive pharmacogenetic guided initiation and maintenance dosing, which will reduce the time taken to reach therapeutic range, increase time in therapeutic range (TTR) and deliver associated reductions in stroke and bleeding risk.
4. In addition, patients currently receiving warfarin and demonstrating unstable INR will be offered point of care genetic testing. Highly sensitive/sensitive patients will be offered INR self-monitoring or DOACs.
5. Also, patients with stable INR whose lifestyles make clinic attendance problematic will be offered INR self-monitoring.

Taken together we hypothesise that these measures will maximise benefits for AF management through increased capacity in warfarin clinics, increased patient TTR and reduced risk of adverse events.

The project will monitor and assess clinical and economic outcomes through prospective analysis of new AF patients, warfarin clinic activity and prescribing practice. Qualitative research will be carried out during the project's implementation to document the challenges, decision-making structures and potential barriers to service redesign and implementation. System enablers and learning points will be captured and shared to allow anticoagulation services elsewhere in England to quickly adapt and deploy the new pathway in their own services. An open source health economics model will be developed that will allow the interrogation of publicly available prescription trends and AF prevalence data to enable individual localities to explore the potential cost-effectiveness of anticoagulation service redesign in their own area. This project is aligned with the goals of the Academic Health Science Network North East and North Cumbria to improve AF based healthcare alongside effective dissemination of best practice.

The AHSN team will work in partnership with:

- **Newcastle upon Tyne Hospitals NHS Foundation Trust** (CQC 'Outstanding') whose teams have the sole responsibility for deploying and managing the anticoagulation programme for the population of the city through hospital based and outreach facilities;
- **County Durham & Darlington Foundation Trust** who have successfully delivered self-testing to 200 patients, and over a 24 month period have observed an increase in average TTR from 60% to above 75%;
- **Newcastle Gateshead CCG** who commission INR services, and are committed to improving the quality and experience of services for people living in the Newcastle area;
- **The Institute of Health & Society**, **Newcastle University** who have extensive experience in health economic evaluation and health technology assessment;
- **The Institute of Genetic Medicine**, **Newcastle University** who bring expertise in genotype guided anticoagulation policy; and
- **Four commercial partners: Inhealthcare ltd, NewGene ltd, LGC ltd, and QuantuMDx ltd** Inhealthcare has an established track record of providing telehealth solutions to AF clinics, transferring patient data safely and effectively across primary and secondary care IT systems. Newgene Ltd is a wholly owned subsidiary of Newcastle Hospitals NHS FT and Newcastle University, providing molecular genetic testing services using next generation technologies. LGC Ltd. has developed a point of care device, which carries out genotyping in under 50 minutes from sample to result. The device was used in the EU-PACT trial and has also been validated by the team for its genotyping accuracy against laboratory-based technologies. QuantuMDx ltd is a Newcastle based biotechnology company which has developed a low cost point of care testing device which will offer warfarin genotyping in 15 minutes.

**Key Objectives**

- **OBSERVE:** Deploy a lean methodology approach with key stakeholders to evaluate barriers to pathway redesign in a high performing Foundation Trust. Conceive modular strategies for pathway introduction suitable for use across the NHS.
- **EDUCATE:** Deliver online and face-to-face training sessions for clinic staff, biomedical scientists, GPs and hospital clinicians to secure the adoption of the new pathway. Model the pathway to clarify roles and ensure the system can cope.
- **STRATIFY:** Offer an estimated 650 anticoagulation naive patients either warfarin or DOAC treatment following genotyping and shared decision-making. This will provide personalised, safer care for the patient and deliver potential savings in anticoagulation-related costs.
- **EMPOWER:** Offer warfarin patients self-monitoring and, where appropriate, self-management using telehealth to connect to dosing programmes.
- **EVALUATE:** Prospectively map patient journeys through the new anticoagulation pathway as it is operationalised, capturing resource use and patient outcomes.
- **PREDICT:** Configure publicly available health and prescription data into an open source model that forecasts cost and benefits of implementing an optimised anticoagulation pathway in the wider NHS.
- **DISSEMINATE:** Share training and education materials with other trusts/CCGs and organisations in England who share this project's ambition to optimise anticoagulation pathways. Newcastle will be a vanguard for widespread uptake of the pathway across the NHS.

## 2. Current Assessment of need in target area

**Project need**

*A. Describe the need for your project in terms of "what is" versus "what should be".*

**"What is"**

Atrial Fibrillation represents the most common sustained cardiac arrhythmia, affecting more than 6 million people in Europe[2]. Vascular thrombosis and embolism are major avoidable causes of morbidity and mortality. AF prevalence, and its associated service pressures are increasing in part due to a growing proportion of over 65s in the population, but also because actual AF prevalence is likely to be much higher than predicted as many patients with AF remain undiagnosed[3]. In the aged population (65 years and above), it is estimated AF is responsible for a stroke every 15 seconds[4].

The AHSN North East and North Cumbria (AHSN NENC) is currently delivering a comprehensive AF programme to drive up rates of AF detection and increase GPs awareness of symptomatic control and appropriate referral. The GRASP-AF audit tool, and a local business intelligence & information analysis tool RAIDR, are being deployed to identify people likely to be at risk of stroke by assessing GP records. A programme of pulse checking is also being rolled out. Taken together, these actions are likely to create an increase in anticoagulation requests in clinics already running at capacity. Anticoagulation therapy, if used appropriately, is highly effective; lowering stroke risk by about two-thirds in AF patients[5]. However, despite the availability of the $CHADS_2$ and $CHA_2DS_2VASc$ scores to aid patient selection, concerns about safety of anticoagulant treatment leads to poor uptake[6]. An analysis of Newcastle CCG level HES data shows that 57% of patients with AF who were admitted to hospital in 2014/15 for stroke, had not been prescribed anticoagulation therapy prior to stroke.

Two types of oral anticoagulants have been licensed for use in the UK[7]: warfarin and DOACs. Warfarin has a narrow therapeutic window and its impact is vulnerable to variable metabolism; a major reason for the wide variation in optimal dose. In contrast DOACs have a wider therapeutic window than warfarin and are marketed with "no monitoring required" status. DOACs cost the NHS up to 25 times per patient more than warfarin and have not been shown to be substantially superior at stroke risk reduction. Factoring in costs of routine INR surveillance, the cost of managing patients with DOACs is four times higher. NICE has yet to factor self-monitoring and genotype testing into its warfarin cost algorithms due to a perceived lack of data. Analysis of publicly available primary care prescriptions data shows expenditure on DOACs has contributed to an increase of £100 million in NHS England spend on anticoagulation in the year to November 2015. In February 2016 27,002 anticoagulation based prescriptions were issued in the Newcastle area at a cost of £384,803. 64% of prescriptions were for warfarin costing £25,945; 36% were for DOACs costing £358,858. The AHSN NENC AF network has established that clinicians use a wide variety of tools, dosing regimes and stratification to either DOACs or warfarin. Underpinning the variation is a lack of awareness of existing evidence based practice and subjective prescribing practices. County Durham and Darlington FT is the only service provider in the region offering INR self-monitoring. This disparity in the delivery of healthcare across the region, and the potential unnecessary increase in cost, makes this project timely.

**"What should be"**

It has been known for two decades that around 3% of the population with north European ancestry carry two *CYP2C9* variants plus a variant in the vitamin K related *VKORC1* which make them exquisitely sensitive to warfarin and more liable to overdose[8,9,10]. Around a third of the population have one or two of these variants making the choice of warfarin a more finely balanced decision. The EU-PACT trial, where Newcastle was one of the recruitment centres, tested the effect of pharmacogenetic-guided warfarin dosing on anticoagulation outcomes with the aid of point-of-care genetic testing, and demonstrated clinical benefits, improved quality of patient care, increased TTR, and fewer incidents of over-anticoagulation[11]. The trial results showed that genotyping prior to the commencement of warfarin therapy and dosing resulted in patients spending a greater percentage of time within target anticoagulation ($P$<0.001). This improvement was most prominent during the first 90 days of therapy. Stable warfarin dose was achieved a week earlier ($P$<0.001) than traditional slow loading and there were significantly fewer incidences of over-anticoagulation. INR monitoring services have changed little in recent years despite evidence that shows self-monitoring[a] of anticoagulation status is both clinically and cost-effective compared with standard monitoring [12,13]. Self-monitoring has also been shown to increase TTR[14,15]. Compared with primary care or anticoagulation clinics, self-monitoring has been statistically significantly associated with fewer thromboembolic events[16].

By adopting both of these innovations, Newcastle will adopt a "multiple win" approach for both newly diagnosed and existing AF patients. New AF patients will be genotyped prior to commencement of anticoagulation therapy. Health professionals and patients will use shared decision-making, taking into account clinical and lifestyle factors and genetic makeup, to make a more informed choice of anticoagulation treatment. Patients with three warfarin sensitivity variants and no other contraindications, will be advised they may be best suited to a DOAC. Patients with 2 or 3 warfarin sensitivity markers will be advised they may be best suited to INR self-monitoring or a DOAC. Patients without the variants choosing warfarin will be advised they may be best suited to pharmacogenetic guided initiation and maintenance dosing. Patients choosing to self-monitor INR will be able to use a landline telephone and/or a range of mobile devices to send INR readings and receive dosing updates. Patient INR information will be automatically entered into the DAWN dosing management software and made available to the GP electronic patient record.

These same benefits of genotyping and self-monitoring will be extended to cohorts of patients currently attending warfarin clinics. Patients with unstable INR will be offered genotyping and a review of their treatment reflecting the presence of any warfarin sensitivity variants. Existing warfarin clinic patients with stable INR, whose lifestyle choice makes attending clinics inconvenient, will also be offered self-monitoring.

We hypothesise that this redesigned pathway centred upon genotyping and INR self-monitoring will create clinic capacity, increase time in TTR for warfarin patients, provide objective stratification of patients to the two anti-coagulant treatments, improve patient and clinician experience, and minimise cost to the NHS.

[a] Self-testing refers to the user doing the INR test themselves and then contacting their healthcare professional with the reading for advice on any change to the dosage of the anticoagulant that may be needed. Self-managing refers to the user doing the INR test themselves and then adjusting the dosage of their anticoagulant medication by following an agreed care protocol. Together, these methods of care are referred to as self-monitoring. (NICE 2014b)

**Quantitative baseline data summary**

B. *Please include quantitative baseline data summary, initial metrics (e.g., quality measures), or project starting point (please cite data on gap analyses or relevant patient-level data that describes the problem) in **your** target area. Describe the source and method used to collect the data. Describe how the data was analyzed to determine that a gap existed.*

Population Data

Newcastle Gateshead CCG has a membership of 65 GP practices, and is responsible for a local population of approximately half a million people across Newcastle and Gateshead. Prevalence of AF in Newcastle Gateshead CCG is 1.52% (1.63% in England) equating to 7694 people registered on GP systems as having AF (Source: QOF 2014/15). Of these, 4,568 are high risk and of this number 3,455 (75.6%) are receiving treatment. A total of 12% are either contraindicated or have declined treatment, leaving 3,689 (47.9%) untreated and/or never offered treatment.

National AF prevalence data from Public Health England suggests that a proportion of AF patients are undiagnosed. Predicted AF prevalence for Newcastle according to PHE is 2.23% (2.41% in England) equating to 8623 patients. Therefore the gap is 0.71% (0.78% in England) or 929 patients (PHE 2013/14). Taken together, i.e. the number of people known to have AF but not receiving treatment (3,689) and the estimated people with undetected AF (928), gives a potential increased prescribing burden of 4618 patients.

There were 699 stroke admissions in the CCG during 2014/15. 128 (18.3% ) had a previous diagnosis of AF, of which 55 were receiving anticoagulant medication. 49 admissions (38.3%) were on antiplatelets only and a further 24 (18.8%) were on no medication. This provides a figure of 57% of stroke patients in Newcastle with previous AF were not on anticoagulant treatment compared to 58.6% in England. This suggests that in 2014/15 51 strokes were potentially avoidable[b] in Newcastle Gateshead CCG.

Source: *Sentinel Stroke National Audit Programme* (SSNAP) data in 2014/15

Prescribing data

Analysis of primary care prescriptions data (NHS Digital database) show that for the Newcastle area in February 2016, a total of 27,002 anticoagulation based prescriptions cost a total of £384,803; 64% were for warfarin costing £25,945, while 22% were for rivaroxaban at a cost of £219,991. 9% of prescriptions were for Apixaban; 5% dabigatran. Newcastle CCG has a relatively high proportion of prescription items for DOACs summarised below:

| | Newcastle Gateshead CCG | North East & Cumbria AHSN area | NHS Cube Cluster[c] | England |
|---|---|---|---|---|
| Warfarin | 65.11% | 70.25% | 74.16% | 74.50% |
| DOAC | 34.89% | 29.75% | 25.85% | 25.50% |

Table 1. Proportion of prescription items warfarin/DOAC in the period Jan 16 – March 16
Source: http://www.england.nhs/ourwork/pe/mo-dash/

[b] Avoidable strokes assumes effective anticoagulation in AF patients reduces risk of stroke by 70%
[c] Similar traditional communities with deprived areas and poorer health

Current configuration and performance of anticoagulant service (INR/warfarin clinics)

Anticoagulant Services operate in hospital and community settings across Newcastle. Clinics are held at the Freeman Hospital each morning (Monday to Friday) where patients may attend between 9:00 - 11:30am; and at the RVI's Outpatient Department on Monday, Thursday and Friday mornings where patients are allocated timed appointments. Both clinics are operated by the Directorate of Pharmacy and Medicines Management. The Community INR (warfarin) Service, which operates through some of the local GP surgeries, is managed by the Chronic Disease Management Service and is the responsibility of the Community Directorate. In 2011, costs of warfarin and monitoring in Newcastle were calculated at £128 per patient per year for hospital, £126 for general practice and £222 for domiciliary patients[17].

There are currently 3630 patients attending INR clinics across three services in Newcastle:

- 778 patients under the care of the Freeman Warfarin Clinic
- 40 patients under the joint care of Ward 31[d] FRH/Freeman Warfarin Clinic
- 379 patients under the care of the RVI Warfarin Clinic
- 2433 patients under the care of the Community Warfarin Service (661 in Domiciliary Care).
- In the period August 2015 to July 2016 the Freeman Warfarin Clinic received 341 new patients; the RVI Warfarin Clinic received 287 new patients.
- There are currently no patients self-monitoring INR; however the Community Warfarin Service uses point-of-care testing with Roche CoaguChek Plus/Pro for domiciliary visits.
- 10 patients with dangerously high INR have been retrospectively genotyped as part of a small study at Freeman hospital. All 10 patients were found to have one or more risk alleles and this information has been shared with patients to inform discussions on anticoagulation choice.

Clinic data summarised below, shows that overall performance is below the NICE guidance threshold of 65% and significantly lower than the NICE metric of good INR control of TTR of 75% or above[18]. Results from the SPORTIFIII and V Trials showed that people with a TTR less than 60% have a higher rates of annual mortality and major bleeding compared to patients with good INR control[19].

| 2015/16 Data | TTR within ±0.5 of target INR of 2.5 | TTR within ±0.75 of target INR of 2.5 | % of patients with INR 6.0 or over |
|---|---|---|---|
| Freeman Warfarin Clinic | 64% | 79% | 0.5% |
| RVI Warfarin Clinic | 63% | 78% | 0.6% |
| Community Service | 63% | 78% | 0.7% |

Table 2. Newcastle anticoagulant service performance April 2015 – March 2016.

In summary the Newcastle Gateshead CCG area has a high proportion of people with AF currently not receiving optimal healthcare. The proposed pathway redesign has the potential to narrow performance gaps, improve health outcomes and enhance patient quality of life.

[d] Ward 31 is a specialist ward for adults requiring renal dialysis. Patients receive anticoagulation for line patency.

## 3. Target Audience

**Support from Participants**

*a. Describe the level of commitment from the potential participants including your plan for recruitment as necessary.*

**Participant Commitment:**

- **Newcastle Gateshead CCG:** participants across the CCG including the Medical Director, Director of Operations & Delivery and the Medicines Optimisation Pharmacists are committed to championing pathway improvements and working with GP Federations and individual practices to ensure take up of genotyping prior to anticoagulation commencement and shared decision-making on anticoagulant choice.
- **The Newcastle upon Tyne Hospitals NHS Foundation Trust:** enthusiasm and commitment to drive the project forward has been established from individuals representing a broad range of clinical disciplines including Pharmacy and Medicines Optimisation, Chronic Disease Management, Haematology, Cardiology and Medicine for the Elderly.

**Potential to impact project goal**

*b. Demonstrate the scope of your target audience has a potential to impact the goal established in this proposal.*

- **Newcastle Gateshead CCG:** is responsible for commissioning anticoagulation services. The CCG are committed to bringing together GP practices to work at scale, whilst utilising opportunities for innovative models of care and strong partnerships to deliver them.
- **The Newcastle upon Tyne Hospitals NHS Foundation Trust:** The Directorate of Pharmacy and Medicines Management operates the Anticoagulant service (INR Clinic) at the Freeman Hospital and the RVI. The Chronic Disease Management Service delivers the Community INR (warfarin) Service, which operates through some of the local GP surgeries.

**Beneficiaries**

*c. Describe who will directly benefit from the project outcomes. Include in this description whom, beyond the primary target, would potentially benefit from the project in terms of this being a model for others to replicate or expand.*

**Patients benefits include:** shared decision-making and transparency in the choice of anticoagulation therapy, personalisation and medicine optimisation, reduced burden of attending clinic appointments, increased TTR and lower associated risk of stroke and potentially fewer treatment related adverse events.
**Clinicians benefits include:** able to provide an enhanced INR monitoring service, delivering higher TTRs, creating clinic capacity for new referrals and ability to spend more time with complex patients.
**Health Economy benefits include:** commissioners able to demonstrate improvements in clinical effectiveness, good INR control, reduced stroke risk, more efficient use of public money/resources, and increased take up of telehealth. All of these benefits could be replicated in other areas across England.

## 4. Project Design and Methods

*Describe your project design and methods.*

**Strategy, methodology and analysis**

*a. Include a description of the overall strategy, methodology and analysis linking them to the goal of the project.*

**Genotyping**

From April 2017-March 2018 we aim to recruit 650 AF patients who are naïve to anticoagulation at GP clinics and cardiology centres across Newcastle area over 1-year period. Patients will be invited to be genotyped for warfarin sensitivity by the clinician and a blood sample will be collected in an EDTA vacutainer along with patient's information on height, weight, age, gender, amiodarone use and self-reported ethnicity. The sample will be sent to the pathology department at Freeman hospital or NewGene Ltd., where the sample will be processed using LGC's ParaDNA device, with optional validation based on traditional methods. Genotype result will be analysed by Prof. Sir John Burn at IGM, who will then produce a report outlining genotype result, patient's sensitivity to warfarin, proposed stratification to warfarin or DOAC treatment and, if choosing warfarin, the predicted maintenance dose, using a pharmacogenic warfarin dosing algorithm. The report will be sent to the referring clinician, where he/ she will discuss treatment options with the patient. The option of INR self-monitoring will be discussed in particular with patients who are sensitive to warfarin but cannot be placed on DOAC treatment due to renal function impairment.

Prospective assessment of the time to therapeutic range, TTR, any bleeding events and stroke events over the duration of the project for the patients will be analysed using the DAWN database. Assessment of drug prescription trends will be carried out by using primary and secondary care level data. Uptake in the anticoagulation of AF patients will be monitored through the CCG level data available from NHS Digital website.

DNA from the relatively low proportion of local patients of non-European ethnicities, who are wild-type for all 3 variants but are difficult to 'warfarinise' will be analysed further for other warfarin dose associated markers within the *CYP2C9, VKORC1, CYP4F2* and *GGCX* genes using targeted genotyping approach. This will inform continued refinement of the dosing algorithm to better predict initiation and maintenance doses for individuals of non-European ethnicities, an established gap in the current literature[20,21].

**INR Self-monitoring**

The pathways of two cohorts of patients offered self-monitoring will be evaluated; a sample drawn from the 650 AF patients who are naïve to anticoagulation who choose warfarin, and a sample drawn from patients currently attending INR clinics in Newcastle. A stratified sample of this second cohort will ensure participants offered self-monitoring reflect hospital, community and domiciliary settings. Assessment of patient experience, quality of life (EQ5D) and patient activation (PAMS) will be carried out alongside the suite of clinical outcomes described in previous sections relating to TTR and adverse events.

**Qualitative Research: perspectives on pathway optimisation**

A study will be carried out to explore the perspectives of key stakeholders in the pathway redesign process in relation to the introduction of genotyping, their experiences and expectations of anticoagulation management and their views on the potential to improve clinical and cost effectiveness. This qualitative research will use face-to-face semi-structured interviews with GPs, clinicians in cardiology and medicine for the elderly, health professionals working in anticoagulation services, commissioners and AF voluntary sector organisations. Interviews will be transcribed and analysed using constant comparison across interviews. Sampling will try to ensure a spread of participants across gender, ethnicities, age ranges and years of experience in practice, with recruitment continued until theme saturation is broadly achieved.

**Project need and desired results**

*b. Describe the way the project planned addresses the established need and produces the desired results.*

The redesigned anticoagulation pathway provides personalised treatment through genotyping and INR self-monitoring. The pathway stratifies patients to warfarin or DOAC treatment from the outset, which will improve patient safety and provide significant cost savings. Patients treated with genotype guided dosing in the EU-PACT trial showed increased time spent within therapeutic range and reduced risk of bleeding and stroke. Retrospective analysis of ENGAGE-AF TIMI 48 trial showed that stratification of patients to warfarin or DOAC based on the genotype results was associated with reduced risk of bleeding. Studies carried out by InHealthCare with County Durham and Darlington Foundation Trust showed that patients using INR self-monitoring technology spent significantly higher time in therapeutic range compared to patients receiving standard clinical practice.

The qualitative research on pathway redesign will add knowledge and insight to build an understanding of why, despite published evidence supporting both clinical and cost effectiveness of individual elements of an optimised AF pathway, the pathway has yet to be fully implemented in health economies across England. Barriers and enablers to anticoagulation redesign will be identified and shared alongside quantitative results during the project's dissemination, enabling localities considering pathway redesign to understand some of the organisational and cultural barriers to be overcome in addition to key patient, clinical and financial metrics.

**Audience Engagement**

*c. Indicate how you will determine if the target audience was fully engaged in the project.*

Three key measures will assess audience engagement:

- Take up of genotyping tests by GPs and hospital clinicians
- Take up of self-monitoring by patients using warfarin
- Successful recruitment for qualitative research

**Originality**

*d. Include a description of the measures you have taken to assure that this project idea is original and does not duplicate other projects or materials already developed.*

As the next section of this bid demonstrates, individual elements of the proposed pathway are already operating in parts of the NHS in England, however, to our knowledge the optimised pathway in its entirety has yet to be operationalised. The AF lead members of staff from the AHSN-NENC are active members of the national AHSN AF Community, and discussions within this forum have confirmed the originality of this proposal.

**Building on current practice**

*e. If appropriate, show how this project builds upon existing work, pilot projects, or ongoing projects developed either by your institution or other institutions related to this project.*

The proposed project builds on 2.5 decades of warfarin-related research carried out in Newcastle. The team led by Prof. Ann Daly in 1999 published a landmark paper that identified variants in *CYP2C9* gene that were associated with warfarin sensitivity and bleeding risk[22]. Newcastle based researchers developed the first genotype guided dosing algorithm in 2009 which was subsequently tested and used in the EU-PACT trial, where Newcastle was one of the main patient recruitment centres[23]. The EU-PACT trial showed superiority of genotype guided warfarin dosing over clinical dosing, and used the same device made by LGC ltd. that we are proposing to use in this project.

The AHSN NENC currently funds an ongoing pilot project in Newcastle, led by Prof. Sir John Burn, to genotype current unstable warfarin users (with INR>6). The project showed that most of the unstable warfarin patients tested carry 2 to 3 warfarin sensitivity genetic variants, which, if previously identified, would have helped patients and health professionals objectively consider a DOAC at anticoagulation initiation, reducing the risk of bleeding. Experience from this project has highlighted the limitations of taking a small-scale approach to pathway improvement, and has shaped the ambition of this current bid to adopt system wide, whole pathway optimisation.

Introduction of INR self-testing for patients and integration of INR results with the NHS patient database has been pioneered by County Durham and Darlington NHS Foundation Trust in partnership with InHealthCare. Their project, showcased by NICE, showed that the introduction of INR self-testing for warfarin patients increased TTR from 60% to above 75%, as well as delivering enhanced patient experience and staff satisfaction[24].

Professor Richard Thomson has an established track record of research in shared decision-making. This project will draw on learning from his *Making Good Decisions In Collaboration with Patients (MAGIC)*[25], Health Foundation supported programme which tested and evaluated how to translate shared decision making from academia into practical reality.

***Project resources***

*f. If your project includes the development of tools note if they will be made available publically at no cost.*

The economic modelling tool will be made publically available at no cost. Participants attending dissemination workshops will have the opportunity to use the model and work with their own health data to explore the benefits that pathway optimisation could bring to their local health economy. Patient resources and clinic protocols will also be made available at no cost.

## 5. Evaluation Design

**Was the gap addressed for the target group?**

a. *In terms of the metrics used to assess the need for this project, describe how you will determine if the practice gap was addressed for the target group.*
    - *Identify the sources of data that you anticipate using to make the determination.*
    - *Describe how you expect to collect and analyze the data.*
    - *Describe how you will determine if the results evaluated are directly related to the intervention described in this proposal*

Measurements will be taken before, during and after project implementation in line with NICE guidance[26] on diagnostic adoption and will include:

- **Change in anticoagulation prescription trend and cost:** Assessment will be carried out using publicly available primary and CCG level data from the NHS Digital database. Observations will be corroborated with the prescription data housed at the NUTH pharmacies. Analysis will include number of patients being anticoagulated, distribution of different anticoagulation treatments within the 650 new AF patient cohort, and cost of each prescription based on the British National formulary classification.
- **Time in therapeutic range:** Assessment will involve interrogation of DAWN database which calculates TTR based on a peer reviewed algorithm[27]. TTR for the current warfarin patient cohort will be compared with the TTR of another sex and age matched warfarin patient cohort that were treated in Newcastle area.
- **Measuring impact of self-monitoring:** For patients currently attending a warfarin clinic, TTR 3 and 6 month before, and 3 and 6 months after people begin to self-monitor will be measured. Other measures include patient experience (pre-implementation and post-implementation); number of people offered self-monitoring and reasons for not offering it; take up rate of self-monitoring and reasons for people declining; number and percentage of people completing training; number and percentage of people passing the assessment; number and percentage of people continuing to self-monitor at 3 and 6 months; and testing frequency and associated costs.
- **Clinical events:** reported minor and major bleeds, and thrombotic events using hospital admissions data.

The health economics component of the work, carried out by the Institute of Health & Society at Newcastle University, will provide information on the costs and consequences of the new redesigned anticoagulation pathway. Two elements will be presented 1) a cost-consequence analysis of the new pathway based on routine data collected as part of the prospective analysis 2) an economic model comparing the current service with the new anticoagulation pathway.

As the new anticoagulation pathway is operationalised we will prospectively map the new pathway, and collect both resource use and patient outcomes. Due to the short term nature of the project, those patient outcomes collected will focus on the important clinical outcomes highlighted in previous sections.

As part of the initial stages we will develop data collection forms and questionnaires to capture use of anticoagulation services. Relevant data will be collected from both patients and staff. Unit costs will be obtained and combined with resource use to facilitate costing of the new service. Total costs will be estimated and presented alongside the prospectively collected clinical outcome data. In addition, the data collected will be used to facilitate a comparison of the two pathways in stage two.

For stage two, a *de novo* economic model will be developed to allow an estimate of the cost-effectiveness of the alternative anticoagulant pathways to be obtained. The model will be developed in accordance with the NICE reference case. The perspectives will be that of the National Health Service (NHS) and Personal Social Services. A short-term model based on the prospective data collected will allow for a bespoke locally focused cost-consequence analysis to be undertaken. To fully explore the potential longer-term impact of a change in the pathway, we will augment the data collected with 'high quality' published literature and extrapolate the short-term model over a lifetime horizon. We will also extend the model beyond clinical outcomes to incorporate health-related quality-of-life outcomes; estimates for these will be derived from published literature. Uncertainty in the long-term model data will be addressed through the use of well-established deterministic and probabilistic methods.

**Expected change**

*(b) Quantify the amount of change expected from this project in terms of your target audience*

The project is expected to deliver change to three key metrics:

- Increase by 10% the percentage of patients who have an INR within 0.5 of target of 2.5
- Decrease by 20% the percentage of patients with INR above 6
- For the new cohort of patients starting anticoagulation therapy in 2016/17 bring prescribing trends in line with the England average of 75% warfarin, 25% DOACs

Additional performance targets will be set for the two cohorts of patients offered self-monitoring once the precise make up of these cohorts is known, i.e. AF patients may present with a diversity of preferences, social situations and co-morbidities which will need to be factored in to ensure patients receive more individualised care, and that appropriate targets are set. Cohorts will be matched to a group of patients currently in the INR clinic with similar profiles to enable relative change to be quantified.

**Dissemination activity**

(c) Describe how you plan for the project outcomes to be broadly disseminated.

- Hold two workshops and a webinar to share findings and enable participants to use the economic modelling tool with their AF/INR service data;
- Share findings through the AHSN AF Community of Practice;
- Project updates and findings will be published on the AHSN NENC website;
- The team will share project outcomes and learning at national conferences and seminars, and through their own professional networks including medicines optimisation, genetics, patient experience, health economics and system re-design.

## 6. Detailed Workplan and Deliverables Schedule

The project will be delivered in three stages: initiation, delivery and evaluation & dissemination.

| | | |
|---|---|---|
| Stage 1 | Project Initiation | Jan-March 17 |
| Stage 2 | Project Delivery | April 17-March 18 |
| Stage 3 | Project Evaluation & Dissemination | April 18-September 18 |

Although the workplan shows the Project Initiation stage beginning in January 2017, if successful, the project team will start preparatory work in early November. The Project Director and Project Lead (existing employees of the AHSN NENC) working with our partners, will ensure a number of key tasks take place in advance of January 2017. These include liaison with Newcastle Gateshead CCG, GP practices and hospital clinicians, recruitment of the Project Officer, ensuring necessary authorities are in place to begin the project, and capturing lessons from previous similar projects.

**Stage 1: Project Initiation**

The purpose of this first project stage is to ensure solid foundations for the project. Key activities will ensure partners have an agreed understanding of the work that needs to be done before project delivery can start and that equipment and software is procured, configured and tested.

**Stage 2: Project Delivery**

In this stage of the project, genotyping for new AF patients will begin and a cohort of patients in existing warfarin clinics will be offered self-monitoring. As the project moves forward, newly diagnosed AF patients on warfarin and with a stable TTR, will be offered self-monitoring. As the self-monitoring programme progresses, suitable patients will be offered to move to a blended approach of INR self-monitoring and self-management. Data collection and qualitative research will be carried out and project models will be developed.

**Stage 3: Project Evaluation and Dissemination**

In the final stage of the project data collection will be completed, analysis and findings shared and agreed among project participants. Evaluation activity will be carried out. A programme of dissemination will be delivered.

Project personnel *Member of the Project Board

OJ* Project Director, Professor Oliver James AHSN NENC
JS* Project Lead, Joanne Smithson AHSN NENC
PO Project Officer, AHSN NENC
SJB* Professor Sir John Burn, Consultant Clinical Geneticist, Institute of Genetic Medicine, Newcastle University
DC* Dawn Craig, Principal Scientist, Institute of Health and Society, Newcastle University
NW* Neil Watson, Clinical Director of Pharmacy and Medicines Optimisation, NUTH
LC Lorna Clark, Assistant Director of Pharmacy NUTH
SJ Simon Jones, Inhealthcare
RT Professor Richard Thomson, Dean of Patient and Public Engagement, Faculty of Medical Sciences, Newcastle University
JH Jeannie Hardy, Health Call Coaching and Development Manager, County Durham and Darlington NHS Foundation Trust.

## Table of Deliverables and schedule for completion

| Stage 1: Project initiation | | Lead | Jan 17 | | | | | Feb 17 | | | | March 17 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | 2 | 9 | 16 | 23 | 30 | 3 | 10 | 17 | 24 | 1 | 8 | 15 | 22 |
| **1** | **Scoping activity** | | | | | | | | | | | | | | |
| 1.1 | Project officer recruited | OJ | | | | | | | | | | | | | |
| 1.2 | Qualitative research | JS | | | | | | | | | | | | | |
| 1.3 | Liaison with GP practices | OJ/JS/PO | | | | | | | | | | | | | |
| 1.4 | Liaison with hospital clinical staff | OJ/JS/PO | | | | | | | | | | | | | |
| 1.5 | Risk management strategy | JS | | | | | | | | | | | | | |
| 1.6 | Communications strategy | JS | | | | | | | | | | | | | |
| **2** | **Pathway design sign-off** | | | | | | | | | | | | | | |
| 2.1 | Liaison with NUTH | OJ/JS | | | | | | | | | | | | | |
| 2.2 | Liaison with CCG | OJ/JS | | | | | | | | | | | | | |
| 2.3 | Develop pharmacy procedures | NW | | | | | | | | | | | | | |
| 2.4 | Sign off genotyping protocol | NW/SJB | | | | | | | | | | | | | |
| 2.5 | Sign off by NUTH Board | OJ/NW | | | | | | | | | | | | | |
| 2.6 | Sign of by CCG | OJ | | | | | | | | | | | | | |
| **3** | **Preparing for self-testing** | | | | | | | | | | | | | | |
| 3.1 | Procure coagucheck | NW | | | | | | | | | | | | | |
| 3.2 | Procure teleheath solution | NW | | | | | | | | | | | | | |
| 3.3 | Agree procedures | NW | | | | | | | | | | | | | |
| 3.4 | Integrate system with DAWN | NW/PO | | | | | | | | | | | | | |
| 3.5 | Testing | NW/PO | | | | | | | | | | | | | |
| **4** | **Peer Learning** | | | | | | | | | | | | | | |
| 4.1 | Clinic nurse exchange visits | PO/JH | | | | | | | | | | | | | |
| 4.2 | Develop materials for clinicians | LC/JH/SJB /RT | | | | | | | | | | | | | |
| 4.3 | Develop materials for patients | LC/JH/RT | | | | | | | | | | | | | |
| 4.4 | Develop materials on shared decision-making | RT/PO | | | | | | | | | | | | | |
| 4.4 | NUTH INR staff training | LC | | | | | | | | | | | | | |
| 4.5 | Share learning on pharmacoeconomic modelling | SJ | | | | | | | | | | | | | |
| **5** | **Preparation for Genotyping** | | | | | | | | | | | | | | |
| 5.1 | Prepare genotyping protocol | SJB | | | | | | | | | | | | | |
| 5.2 | Continue to genotyping existing clinic patients with INR >6 | SJB | | | | | | | | | | | | | |
| 5.2 | Installation of LGC's genotyping device at Freeman hospital and International Centre for Life | SJB/NW | | | | | | | | | | | | | |
| 5.3 | Upload warfarin sensitivity test to ICE system | SJB | | | | | | | | | | | | | |
| **6** | **Project methods & evaluation** | | | | | | | | | | | | | | |
| 6.1 | Finalise project methods | DC/OJ | | | | | | | | | | | | | |
| 6.2 | Quality and safety measures | DC/JS/NW | | | | | | | | | | | | | |
| 6.3 | Patient experience measures | DC/JS/LC | | | | | | | | | | | | | |
| 6.4 | Productivity measures | DC/JS/LC | | | | | | | | | | | | | |
| 6.5 | Clinical outcome measures | DC/JS/LC | | | | | | | | | | | | | |
| 6.6 | Identify gaps in knowledge | DC/JS/LC | | | | | | | | | | | | | |
| 6.7 | Agree baseline figures | NW | | | | | | | | | | | | | |
| 6.8 | Set up Project Board and identify CCG representative. | JS | | | | | | | | | | | | | |

| Stage 2: Project Delivery | | | Q1 April - June 17 | | | Q2 July - Sep 17 | | | Q3 Oct - Dec 17 | | | Q4 Jan - March 18 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Lead | Apr | May | June | July | Aug | Sept | Oct | Nov | Dec | Jan | Feb | Mar |
| **7** | **Genotyping** | | | | | | | | | | | | | |
| 7.1 | Full deployment of access to genotyping for new patients with AF presenting in primary and secondary care | SJB | | | | | | | | | | | | |
| 7.2 | Targeted sequencing in high INR patients without recognised variants | SJB | | | | | | | | | | | | |
| **8** | **Self monitoring** | | | | | | | | | | | | | |
| 8.1 | Agree procedures for patient monitoring | NW/LC | | | | | | | | | | | | |
| 8.2 | Agree contingency plans | NW/LC | | | | | | | | | | | | |
| 8.3 | Agree procedures for incident reporting | NW/LC | | | | | | | | | | | | |
| 8.4 | Agree procedures for infection control & QA | NW/LC | | | | | | | | | | | | |
| 8.5 | Equality Analysis/Impact Assessment | LC | | | | | | | | | | | | |
| 8.6 | Deliver patient training | LC/JW | | | | | | | | | | | | |
| 8.7 | Offer self-testing | LC | | | | | | | | | | | | |
| 8.8 | Introduce self-management as appropriate | LC | | | | | | | | | | | | |
| **9** | **Health Economics** | | | | | | | | | | | | | |
| 9.1 | Data collection | PO/LC | | | | | | | | | | | | |
| 9.2 | Map current and new pathways | DC/PO | | | | | | | | | | | | |
| 9.3 | Economic model discussion paper | DC/JS | | | | | | | | | | | | |
| 9.4 | Design and build model | DC | | | | | | | | | | | | |
| 9.5 | Test and review model | DC/JS/ SJ | | | | | | | | | | | | |
| 9.6 | Cost-consequence analysis | DC/SJ | | | | | | | | | | | | |
| 9.7 | Model analysis and sensitivity analysis | DC/OJ/ JS/SJ | | | | | | | | | | | | |
| 9.8 | Open source model | DC/PO | | | | | | | | | | | | |
| **10** | **Qualitative Research** | | | | | | | | | | | | | |
| 10.1 | Continue research | JS | | | | | | | | | | | | |
| 10.2 | Prepare draft report | JS | | | | | | | | | | | | |
| 10.3 | Finalise report | OJ | | | | | | | | | | | | |
| 10.4 | Disseminate findings | JS/PO | | | | | | | | | | | | |
| **11** | **Project Management** | | | | | | | | | | | | | |
| 11.1 | Chair Project Board Meeting | OJ | | | | | | | | | | | | |
| 11.2 | Quarterly reporting | ALL | | | | | | | | | | | | |

| Stage 3: Evaluation and dissemination | | Lead | April 18 | | | July 18 | | |
|---|---|---|---|---|---|---|---|---|
| | | | April | May | June | July | Aug | Sept |
| **12** | **Evaluation** | | | | | | | |
| 12.1 | Analysis of key outcome metrics | DC | | | | | | |
| 12.2 | Complete evaluation | DC | | | | | | |
| 12.3 | Prepare project report | JS | | | | | | |
| 12.4 | Continue to collect TTR data | NW | | | | | | |
| 12.5 | Chair Project Board Meeting | OJ | | | | | | |
| | | | | | | | | |
| **13** | **Dissemination Activity** | | | | | | | |
| 13.1 | Design workshops | JS | | | | | | |
| 13.2 | Hold workshops & webinars | JS | | | | | | |
| 13.3 | Information on AHSN Website | JS | | | | | | |
| 13.4 | Share project information with AHSN Networks | JS | | | | | | |
| 13.5 | Identify conference/seminars | JS | | | | | | |
| 13.6 | Project close | OJ | | | | | | |

## D. References

Please see pages 32-33

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