NHS
National Institute for Health Research

NIHR Research for Patient Benefit (RfPB) Programme

Final Report Form

IMPORTANT

Final reports are required from all projects funded through the NIHR Research for Patient Benefit Programme. The RfPB Programme requires a final report in order to:

- ensure accountability
- aid in appropriate dissemination of project results
- encourage quality assurance of project outputs
- assess the impact of the research supported by the Programme
- demonstrate the achievements of the Programme

Please keep these aims in mind while completing your final report.

The report needs to offer:

a) a clear summary of the project for practitioners and users of research
b) a record of challenges faced and modifications made to the study
c) a description of experience with patient and public involvement that might help identify lessons for future research
d) an impact assessment both locally and for the NHS more broadly
e) a summary of any outputs, such as publications, from the research (which should be updated as outputs occur). Completion of this report should not pre-empt any publications that have been prepared or are in preparation detailing project results.

This form must be completed in draft prior to peer and lay review. Following review, the final version of the scientific and lay summaries will be displayed on the NIHR CCF website and will be accessible to a wide range of interested parties.

You will be required to submit a final statement of expenditure at the same time as your final report. Please note that the completed final report along with a final statement of expenditure is required prior to release of the final payment.

For further guidance or information on completion of your final report, please contact the regional Programme Manager at NIHR CCF, using the details below:

Samantha Wade
Programme Manager for the North East region
Samantha.wade@nihr-ccf.org.uk
020 8843 8055
NIHR CCF helpline: 020 8843 8057

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Note the maximum field sizes shown include both printing and non-printing characters such as spaces and carriage returns.

Reference Number PB-PG-0407-13039

Region North East

Date submitted

For office use

1. Project Details

Project Title*:	Improving the safety and efficacy of anticoagulation therapy for thromboembolic disease through vitamin K		
NHS Contracting Organisation*:	The Newcastle Upon Tyne Hospitals NHS Foundation Trust		
Project Duration*:	36 months	Grant Value:	£250,844.35
Start Date:	01 November 2009	Agreed Extension:	10 months shortened by 5 due to contract termination
End Date:	31 October 2012	Revised End Date:	13 March 2013

2. Grant Holder's Details

Title*:	Prof		
Surname*:	Kamali	Forename*:	Farhad
Department*:	Institute of Cellular Medicine		
Role in Project*:	Principal Investigator		
Institution*:	Newcastle University		
Street*:	Framlington Place		
Town/City*:	Newcastle upon Tyne	County*:	Tyne & Wear

* Field is mandatory

Post Code*:	NE2 4HH
Telephone*:	0191 2226000 Extension: 8043
Email Address*:	farhad.kamali@ncl.ac.uk

3. Details of the Research Team

Co-applicant 1

Title:	Dr Surname: Wynne Forename: Hilary
Post held:	Consultant Physician and Senior Lecturer
Department:	Elderly Care
Organisation:	Newcastle upon Tyne Hospitals NHS Foundation Trust
Telephone:	0191 233 6161 Extension: 25397
e-mail address:	hilary.wynne@nuth.nhs.uk
Role in project:	Responsible for clinical management of patients

Co-applicant 2

Title:	Dr Surname: Kesteven Forename: Patrick
Post held:	Consultant in Haematology
Department:	Haematology
Organisation:	Newcastle upon Tyne Hospitals NHS Foundation Trust
Telephone:	0191 233 6161 Extension: 37271
e-mail address:	patrick.kesteven@nuth.nhs.uk
Role in project:	In charge of anticoagulant monitoring service and responsible for database

Co-applicant 3

Title:	Dr Surname: Hanley Forename: John
Post held:	Consultant in Haematology
Department:	Haematology
Organisation:	Newcastle upon Tyne Hospitals NHS Foundation Trust
Telephone:	0191 233 6161 Extension: 24773
e-mail address:	john.hanley@nuth.nhs.uk
Role in project:	Responsible for quality assurance of haematological measurements

Co-applicant 4

Title:	Please select.. Surname: Forename:
Post held:	
Department:	
Organisation:	
Telephone:	Extension:

e-mail address:

Role in project:

Co-applicant 5

Title: Please select.. Surname: Forename:

Post held:

Department:

Organisation:

Telephone: Extension:

e-mail address:

Role in project:

Co-applicant 6

Title: Please select.. Surname: Forename:

Post held:

Department:

Organisation:

Telephone: Extension:

e-mail address:

Role in project:

Co-applicant 7

Title: Please select.. Surname: Forename:

Post held:

Department:

Organisation:

Telephone: Extension:

e-mail address:

Role in project:

4. Changes to the Research Team

Please outline any changes that have been made to the research team, including an explanation of why these changes were required.

5. Lay/Plain English Summary*

Please provide a summary of the project, including background, findings and conclusions. It is essential that you make the content of your summary and the implications of your research evident to the lay public. It should avoid technical terms and should be written in an accessible style and emphasise in particular the potential for patient benefit arising from the study.
(Maximum 2,500 characters)

Thinning the blood (anticoagulation) with warfarin is useful for the treatment of blood clotting disorders and for stroke prevention. Anticoagulation response to warfarin can change day to day. People taking the drug need regular blood tests to check that their blood neither clots too easily nor too slowly. This is to ensure that clots are prevented but also to reduce the risk of bleeding. About half of people treated with warfarin fail to have acceptable clotting control resulting in increased risk and worry. Warfarin acts to prevent vitamin K working to produce clotting proteins which stop us bleeding. We have previously shown that a daily supplementation with vitamin K, taken by mouth with warfarin, improves clotting control in patients with unstable control. We suspected that clotting control for the whole anticoagulated patient population could be improved by using this approach. To test this possibility we conducted a clinical trial where patients were allocated, at random, to receive either a small amount of vitamin K as a capsule or a dummy capsule (placebo) for six months. The target was to recruit 180 patients.

The governmental agency, the Medicines and Healthcare products Regulatory Agency (MHRA), ruled that for the trial vitamin K was a medicine. This meant that the vitamin K/placebo capsules had to be manufactured under strict regulations. The stability of vitamin K in the capsules was tested at regular intervals post-manufacture. The tests showed that the vitamin K content in the capsules was within the allowed range (90-110%) for the first 24 months. However, the test results at 35 months showed a catastrophic decline (down to 6.9%) in the vitamin K content of the capsules. For patient safety the trial was stopped immediately. When the trial was stopped only 33 patients had completed it during the first 24 month post capsule manufacture and 39 had completed it after this period. Another 36 patients who were still participating were withdrawn and instructed to stop taking the trial medication. A further 8 patients who had agreed to take part in the trial but had not started taking the trial medication were also withdrawn. Analysis of the limited useful data did not show a clear signal for the effect of vitamin K supplementation on anticoagulation control. The scientific value of the trial is likely to have been significantly affected as data from patients treated beyond 24 months were unreliable.

6. Keywords*

Please provide up to 8 keywords that relate to the research undertaken in this study.

Warfarin, vitamin K, anticoagulation, diet, atrial fibrillation, stroke, DVT, bleeding

7. Summary of Research and Findings*

Please provide a structured summary of the research including background, aims and objectives, methods, key findings, expected impact on the relevant field and conclusions.
(Maximum 10,000 characters)

Background
We had previously established that daily supplementation with vitamin K significantly improved anticoagulation control in patients with unexplained instability of response to warfarin. Very few patients achieve absolute stability of control over an extended period of time. All would benefit from anticoagulation which was more consistent and less susceptible to unpredictable change because this would reduce their risk of thromboembolism or bleeding. Investigation of the effect of long-term vitamin K supplementation upon anticoagulation control on the unselected warfarin treated patient population is therefore warranted. In this project we investigated how much concomitant daily supplementation with vitamin K improves anticoagulation control in an unselected group of patients.

Aims and objectives
The aim of this pilot study was to test our hypotheses that daily supplementation with vitamin K improves the stability of control in an unselected anticoagulated cohort.

Methods
Patients receiving warfarin with target INR 2-3 were recruited from the Newcastle upon Tyne Anticoagulant Monitoring Service. Baseline demographic data were collected. Information on factors which can affect anticoagulation response was also collected. Patients were randomly allocated to two groups in a double-blind fashion. One group received a once daily supplement of vitamin K capsule (150 µg), and the other matching placebo, with their warfarin daily dose. The vitamin K/placebo capsules were dispensed in child-safe bottles for each patient on a monthly basis by the Pharmacy Department at the Royal Victoria Infirmary, Newcastle and recorded in the patients' clinic files (code breaking facility always available).

All patients attended their designated monitoring service for the following six months, where their INR was checked and were supplied with vitamin K and warfarin dosage adjusted if necessary. It was anticipated that the INR of some patients receiving vitamin K would fall; therefore anticoagulation status in all patients was monitored initially on a weekly basis to ensure that target INR in each patient was maintained. When each patient's INR was reached and remained within target value for at least two visits, anticoagulation was monitored less frequently, but at intervals of no longer than 4 weeks.

Patients' perceived health status and quality of life were assessed by the UKSF-36 and Euroqol, and satisfaction with treatment by validated questionnaire designed for face-to-face interview at entry into the study and at its end.

Analyses
Statistical analysis of the data was carried out using the data relating to all the patients who had participated in the trial (irrespective of whether they took part in the trial beyond the first 24 months after vitamin K capsules were manufactured) in an attempt to identify a possible signal for the effect of vitamin K supplementation on the stability of anticoagulation control. Regression analysis was used to evaluate associations between measures of anticoagulation and patient factors.

For the economics analysis, data were collected on costs and effects for the study arms. In terms of the costs element, this study originally intended to take a societal perspective to collect costs that fall on both the NHS and the patient, which includes the costs of treatments and the use of primary and secondary NHS services, as well as participants' out-of-pocket

expenses relating to the condition. However, due to the early termination of the study, there were insufficient data available for analysis. Thus, the average cost per patient includes only costs of the intervention drug and administration of the drug. Effects as measured by Quality of Life (QoL) were obtained through the use of EQ-5D and SF-36 questionnaires that were completed at baseline and at six-month follow-up.

Drug costs- vitamin K
The cost of vitamin K was obtained from the manufacturer which produced the vitamin K capsules for this trial. The cost of each capsule was £1.92. The cost also included periodical stability tests. As these study specific vitamin K capsules are not commercially available, the calculated average cost is likely to overestimate the costs of the drug if it is made available for commercial purchase.

Staff costs
Staff costs related to this intervention primarily related to the drug administration. It is advised that the administration of vitamin K involves the patients spending two minutes with a phlebotomist and then three minutes with a pharmacy technician, and these appointments are usually consecutive, so that the total time spent with health care staff amounts to five minutes in total. No allocation was made for waiting time between appointments although occasionally this may have occurred in practice. Data from Department of Health publication and statistics reference costs were used for staff cost estimation (@£15 for one outpatient visit to the anticoagulant service). A typical outpatient appointment is likely to last for 30 minutes and as such this figure was adjusted to reflect the shorter appointment time of 5 minutes used for this study. This provided a cost of £2.50 for a five minute appointment. The DH reference costs were selected as the most appropriate value for this study as these costs include a contribution of overheads which reflect the cost of providing service at a suitable facility.

Economic analysis
No cost-utility analysis was performed because final end point data were not available for the majority of trial participants; therefore, there were insufficient numbers of participants who had complete data to conduct a full cost-utility analysis. Nevertheless, with completed data that were available for analysis, a range of descriptive statistics for costs and effects were calculated. Average and unit costs of vitamin K and outpatient visits were calculated for each study arm. Utility values were calculated for each arm at both baseline and six months follow-up.

Findings
69 patients with a mean+/-sd age of 72±11 years had received vitamin K and 63 patients with a mean age of 69±10 had received placebo. There were significant differences in mean INR between the vitamin K and placebo groups (2.38±0.03 v 2.60±0.03 respectively; $p<0.001$). Neither age nor sex had an effect on INR. There was no significant effect on percentage time within target INR (%TIR) between the vitamin K (66.9±2.8) and placebo (73.6±2.4) arms. The Median INR after finishing/stopping trial was significantly less in the vitamin K cohort compared to the placebo cohort of patients (2.43±0.05 v 2.63±0.06; $p=0.008$).

The patients receiving vitamin K supplements had a slightly higher mean number of visits than the placebo arm (11.06 v 10.65 visits). The unit cost of each outpatient visit was the same for both the vitamin K arm and placebo arm as they both used the same type of health care professionals for the same length of time.

The cost of providing vitamin K supplements for the duration of the six month period was £322.56 per patient. The mean visit costs was £27.65 for the vitamin K arm and £26.62 for the placebo arm. This difference is attributed to the difference in mean number of visits between the two arms.

The net change in SF-6D for the vitamin K arm over six months was 0.0032, this change was

-0.0190 for the placebo arm. The net change in EQ-5D for the vitamin K arm over six months was -0.0027 and for the placebo arm it was -0.0052. It was not possible to test the significance levels in the findings due to small sample size; therefore, the difference seen was unlikely to have meaningful interpretation. QALYs were calculated from both SF-6D and EQ-5D values using the area under the curve method. When calculated using SF-6D scores the QALY gained by the vitamin K arm was 0.3787 and the QALY gained by the placebo arm was 0.3739. When calculated using EQ-5D scores the QALY gained was 0.4335 for the vitamin K arm and 0.4294 for the placebo arm. The mean difference was not calculated as the sample size was too small for any comparison to be meaningful.

Conclusions
As the study is underpowered it was not possible to carry out a comprehensive statistical analysis. Summary statistics of the data on the 132 patients who had taken part in the study did not result in any meaningful conclusion about the effect of vitamin K supplementation on the stability of anticoagulation control.

The number of clinical appointments was similar between the two arms and any difference is unlikely to be a major factor in the overall cost of the intervention given the relative cost of the drug cost compared to the cost of appointment. There appeared to be higher QALY associated with the intervention arm than the placebo arm when only patients who completed the trial within the first 24 months of capsules manufacture were included in the analysis whereas a different trend was observed when all patients with complete data were analysed. However, the QALY values generated from using patients who completed within the first 24 months of the trial are derived from a very small sample and thus may not be reliable. The inclusion of data from all the patients who took part in the trial reduces the quality of the results due to the ambiguity surrounding the dosage of vitamin K received. The total number of participants was still small in this case, and the sample size was again deemed insufficient. The small differences on costs and effects found in this study between the vitamin K arm and placebo arm could not be meaningfully tested for their statistical significance due to insufficient sample size, therefore, the results from this study are inclusive, and it cannot be ascertained whether the intervention with vitamin K is cost-effective.

8. Changes in the project since initial approval*

Please summarise any changes made to the project as outlined in the original proposal and outline the reasons for these changes. If there were no changes to the original plans write ‘not applicable’. **(Maximum 2,500 characters)**

Aims and objectives:
Not applicable.

Research Plan and Methodology:
Not applicable.

9. Patient and Public Involvement*

The RfPB Programme is particularly keen to learn from the experiences of research teams regarding patient and public involvement (PPI). Please provide comment on your experiences with PPI, any changes made and lessons drawn. Please include detail of PPI with dissemination and with trajectory into practice both in the project and beyond. **(Maximum 5,000 characters)**

This study was very well received in the clinics by patients and their families. The overwhelming feeling from patients was that taking vitamin K orally was a simple way to improve stability of anticoagulation control and thus make them worry less about the risks of having bleeds. The patients who participated in the study were both saddened and disappointed with the outcome of the trial. They are still hopeful that trial can be restarted and completed in some way.

10. Next Steps to Patient Benefit*

Please provide comment on the likely implications for practice which may result from the outcomes of this project and the next steps to be taken to ensure patient benefit both locally and more broadly. Steps already taken and planned for the future should be included. While in funding research, RfPB emphasises a 3-5 year trajectory into practice, it is important not to 'overclaim' and care should be taken to cover the limitations of the study and any risks associated with implementation. Where the project is a pilot, include details of plans for a definitive study, including the likely funder and timetable for its submission. Please give reasons if there is no plan to go forward to a trial at this stage. **(Maximum 5,000 characters)**

No clear conclusions can be drawn on the impact of vitamin K supplementation on the stability of anticoagulation control in patients on chronic therapy with warfarin as the trial was terminated early due to issues relating to the stability of vitamin K in the capsules. To detect a 10% improvement in percentage time within target therapeutic INR range (a measure of anticoagulation control) in patients receiving vitamin K supplementation over that for patients receiving placebo, using a two-sample t-test with 80% power, a sample size of 180 patients was needed. The study is significantly underpowered since only 33 patients completed the trial within the first 24 months that the vitamin K/placebo capsules were manufactured and for whom the data can be considered viable.

11. Key Presentations and Publications*

Please list here any presentations and publications which have resulted from the work. This should include journal articles, conference proceedings, press releases and all publications in the lay and scientific press, including website links to published articles if appropriate. Items that are forthcoming should also be included. **Please note you are contractually obliged to provide 28 days notification prior to any publication.**

Author (s)	Title	Reference/Further Details