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Economic evaluation of a randomized controlled trial of pharmacist-supervized patient self-testing of warfarin therapy

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SUMMARY

What is known and objective: **The increase in numbers of patients requiring oral anti-coagulation testing in outpatient clinics has focused attention on alternative flexible systems of anti-coagulation management. One option is pharmacist led patient self-testing (PST) of international normalised ratio (INR) levels. PST has demonstrated improvements in anti-coagulation control, but its cost-effectiveness is inconclusive. This study reports the first cost-effectiveness evaluation of a randomized controlled trial of an automated direct-to-patient expert system, enabling remote and effective management of patients on oral anti-coagulation therapy.**

Methods: **We conducted an economic evaluation alongside a randomised controlled trial investigating a pharmacist led PST method. The primary outcome was to determine the cost effectiveness of PST in comparison with usual care (management in a hospital based anti-coagulation clinic). Long term anti-coagulation patients were recruited to a 6 month cross over study between PST and routine care in an anti-coagulation clinic. Economic evaluation was from the healthcare payer perspective.**

Results and discussion: **On a per patient basis over a 6 month period, PST resulted in an incremental cost of €59·08 in comparison with routine care. Patients achieved a significantly higher time in therapeutic range (TTR) during the PST arm in comparison with routine care, (72 ± 19·7% vs. 59 ± 13·5%). Overall cost of managing a patient through pharmacist supervised PST for a 6 month period is €226·45. Additional analysis of strategies from a societal perspective indicated that PST was the dominant strategy.**

What is new and conclusion: **Pharmacist led patient self-testing is a viable method of management. It provides significant increases in anti-coagulation control for a minimal increase in cost.**

WHAT IS KNOWN AND OBJECTIVE

Despite the development of new oral anti-coagulant agents (NOACs), warfarin remains an integral option in anti-coagulation management strategies. In Ireland in 2010, 57 000 patients were in receipt of a prescription for warfarin.[1] This constitutes 1·7% of the population. The majority of patients (55%) required warfarin for treatment of atrial fibrillation.[1]

Warfarin is a well-established medication with a relatively low cost. However, unusually for an oral medication, it has significant expenses associated with the monitoring and management stage of the therapy. Warfarin is a medication with a narrow therapeutic index, requiring close management, and regular dosage adjustments can be necessary. Currently in Ireland, the majority of management is provided by dedicated hospital-based anti-coagulation clinics.[1]

There are documented limitations to hospital-based clinics, especially from a patient's perspective, which include the requirement to make regular and frequently time-consuming visits to the clinic.[2] Furthermore, previous studies have shown that alternative management strategies can improve anti-coagulation control in comparison with hospital-based anti-coagulation clinics.[3] The development of NOACs will decrease the overall proportion of patients dependent on warfarin as a long-term anti-coagulant; however, some patients will remain on warfarin therapy and therefore require an anti-coagulation management service.[4]

Patient self-testing (PST) of warfarin therapy is a concept which allows the management of warfarin therapy to move away from already overburdened hospital-based clinics to management at a primary care level. The PST model involves the patient measuring their international normalized ratio (INR) levels using a portable point-of-care (POC) device. There are clinical benefits associated with the application of PST over usual care in anti-coagulation management. Evidence ranging from randomized controlled trials (RCT), meta-analysis and full systematic reviews indicates that PST is associated with improved outcomes.[5–10] PST of oral anti-coagulation has been proven to be a safe option in all age groups.[11]

Input from healthcare professionals is still a fundamental requirement for the success of any PST strategy. Ryan *et al.*[9] demonstrated that a single pharmacist could favourably oversee the management of a group of patients managing their INR using a PST strategy. Pharmacists have a broad clinical and therapeutic knowledge and are using these skills to diversify into new areas of patient care.[12] With additional training in the area of anti-coagulation management and accreditation of required standards, pharmacists have shown they are capable of providing an anti-coagulation management service.[13]

The method by which results are communicated to the responsible professional is another crucial part of warfarin PST. Telephone-based communication has been proven as a viable method and is widely utilized in the United States.[14] However,

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availing of technological developments can reduce the cost, time and risk of errors associated with verbal communication.[15] 'Expert' software systems have been developed to assist in patient management and data recording. The RCT examined in this evaluation utilizes the CoagCare™ system (ZyCare Inc. Chapel Hill, NC, USA). CoagCare™ combines a direct-to-patient expert system accessed via the internet with PST to provide a novel model of pharmacist-supervized telehealth.[9]

This study is the first cost-effectiveness evaluation of an internet-based, direct-to-patient expert system in anti-coagulation management. The direct-to-patient expert system employs a rule-based algorithm to inform patients how to adjust warfarin therapy based on INR data which has been recorded and inputted by the patient.[9] Previous cost-effectiveness analysis has been inconclusive as to whether similar systems offer 'value for money' to the healthcare payer.[16]

In this study, a cost-effectiveness analysis was undertaken based on the outcomes and resource utilization from a RCT of pharmacist-supervized PST of warfarin therapy using an internet-based system.[9] The primary aim of this study was to determine the incremental cost-effectiveness of PST in comparison with usual care.

METHODS

Trial protocol

This cost-effectiveness analysis was based on data from an RCT which is documented elsewhere.[9] In summary, the trial was a prospective, randomized controlled crossover study. Patients were initially assigned to either 6 months of routine care or 6 months of PST. At the end of the 6-month period, the patient was transferred to the alternative arm. The crossover design of the study eliminated the potential for covariate disparities. The primary outcome was the difference in the time in therapeutic range (TTR) between the two arms. Overall TTR for each arm was calculated using the Rosendaal method.[17] For the purposes of this trial, TTR was defined as the time spent within 0·5 units of the targeted INR value.[9] Patients were required to have been on warfarin therapy for at least 2 months prior to the start of the study and expected to have a requirement for warfarin for the duration of the 12-month study. Patients were excluded from the trial if they were unable to use a POC device, if they missed attending more than two clinic appointments in a 6-month period prior to recruitment screening or if the patient was taking an additional anti-coagulant other than warfarin. Furthermore, patients were excluded if they had experienced a haemorrhagic complication in the preceding 6 months or if they were unable to attend the hospital clinic at short notice. Following recruitment, patients received comprehensive training from the research pharmacist.

Initially, INR levels were measured in the PST arm twice weekly. Following stabilization of INR levels, intervals between tests were increased to a maximum of once every 2 weeks. Management of deviations from the targeted INR value or other patient issues was the responsibility of the research pharmacist, assisted by the CoagCare™ system. During the course of routine care, patients attended the anti-coagulation management service (AMS) for INR measurement every 4–6 weeks. Any necessary dosage adjustments were calculated by a doctor or nurse associated with the clinic.

RCT information

Patient recruitment and provision of routine care were provided at the AMS of Cork University Hospital (CUH). Currently, the AMS has approximately 850 regular patients. Additionally, the clinic is responsible for short-term anti-coagulation patients and the processing of INR tests which are taken at other locations. In 2012, 120 000 INR tests were processed at the medical laboratory in CUH.

The total patient enrolment was 162 patients, 132 of whom completed both the AMS and PST arms of the trial. Only patients who completed both arms of trial were included in the final analysis. The mean age of the patients was 58·7 ± 14·3 years. Indications for oral anti-coagulation therapy consisted of prosthetic heart valve – 49 (37·1%), atrial fibrillation – 43 (32·6%), deep vein thrombosis (DVT)/pulmonary embolism (PE) – 29 (22%) and other – 11 (8·3%). Patients withdrew from the trial for the following reasons: warfarin therapy discontinued (n = 8), patient found PST stressful (n = 5), left the AMS (n = 5), issues with internet access (n = 4), poor correlation between PST meter and laboratory INR results (n = 3), non-anticoagulant-related death (n = 2) and difficulty obtaining sample of blood using lancet (n = 1).

Pharmacoeconomic analysis

The analysis has a time horizon of 6 months which is the duration of the intervention arm. Discounting of costs or outcomes was not required as the time horizon was <1 year. Base case analysis is from the narrower perspective of the healthcare payer. Base case analysis used mean values determined during the RCT. Resource utilization was over a 6-month time period. The effect measurement was TTR in both the routine care and intervention arms. The duration of the trial was unsuitable for the adequate measurement of patient-orientated outcomes such as death and non-fatal thromboembolic events. However, TTR is a documented marker for haemorrhagic and thrombotic complications.[18] Kaatz reasons that TTR should be the standard quality indicator for anti-coagulant control as there are pragmatic issues affecting the completeness and accuracy of adverse event gathering.[19]

Costs associated with the control and intervention groups are described in Table 1. The cost of processing an INR test at the CUH laboratory had previously been calculated as part of an internal CUH evaluation. Costs of staff were calculated based on expert guidance from staff of CUH, internal CUH data and published HSE salary scales.[20] Patients received a 90-min education and training session from the pharmacist. These were carried out in groups of one to three people; the pharmacist conducted 44 separate sessions.[9] Mean daily time required to manage a group of 80 patients was 23·2 min (±9·5 min standard deviation). Therefore, an estimated 20 h per month would be required for management of 132 patients. A cost of €30 per hour was applied to pharmacist time required for the study. The cost of the POC system was sourced from Roche Diagnostics, the manufacturer of the device used in the RCT.

The cost of warfarin therapy was excluded from both arms as significant differences in usage between groups were not anticipated; furthermore, warfarin is a relatively cheap medication. Referenced unit cost prices are from 2012. Value added tax (VAT) was excluded from study costs based on recommendations for conducting health technology assessments in Ireland.[21]

Table 1. Costs associated with anticoagulation management

Anticoagulation management service[a]	€
Cost per laboratory INR test	2·00
Medical staff[b,c]	8·08
Nursing[b,d]	62·67
Clerical officer[b]	8·17
Senior medical scientist[b]	9·43
Phlebotomy [b]	52·51
Healthcare assistant[b]	5·11
Patient self-testing group	**€**
Cost per coaguchek strip	3·66
Lancets (200)	12·62
Pharmacist supervision[b]	27·27
Cost of education session per patient	15·00
Coaguchek® XS Meter (purchase cost)	588·00
CoagCare – 6-month license cost	2500

[a]Mean cost per patient per 6-month period.
[b]Four senior house officer hours and three consultant haematologist hours per week.
[c]One whole time equivalent (WTE) clinical nurse specialist and 2·5 WTE's staff nurse.
[d]Costs calculated based on internal CUH data and expert guidance.

Sensitivity analysis

One-way sensitivity analysis was conducted on all known variables. Standard deviations and confidence intervals were employed where possible. In the absence of any indication of variability, a ±50% variation was applied. Additional evaluations which were inclusive of societal benefits such as travel costs and patient time foregone through attendance at AMS were also included in a supplementary evaluation. An argument for evaluation from a societal perspective can be made as significant costs can be accrued due to patients' requirement to attend an anti-coagulation clinic. Societal benefits were calculated using resource consumption and patient data obtained in the RCT.[9] Cost per kilometre travelled by car was calculated using recommended Irish reimbursement rate for a mid-sized car.[22] Working time sacrificed due to attendance at anti-coagulation clinic was calculated using national average wage per hour (Q3 2013).[23] Leisure time lost through attendance at clinic was valued at 35% of the local average gross wage. This methodology had been used in previously published attempts to calculate cost of attending an anti-coagulation clinic.[2] The cost to the HSE for provision of POC devices to patients was also investigated. Machine costs were spread over a 5-year period using a straight-line depreciation method. This was deemed acceptable as 5 years is recognized as the minimum lifespan of these machines.[24] The year one purchase cost of a CoagChek XS meter was included in this scenario.

RESULTS

Patients achieved a significantly higher TTR during the PST arm in comparison with routine care, (72 ± 19·7% vs. 59 ± 13·5%). Increases in TTR were achieved for both patients who were initially randomized to PST group (16·6%) and AMS group (12·3%). The effect of order of management was non-significant (P = 0·412).

There was a substantial difference in the frequency of testing between the trial groups. The PST group tested their INR almost four times more frequently than the AMS group over a 6-month period (Table 2). The mean frequency of testing days for PST was 4·6 days, which was a considerably shorter time period than the 19·6 days between each test in the control group.

The base case cost-effectiveness analysis indicated that on a per patient basis, PST was slightly more expensive than AMS (Table 2). On a per patient basis over a 6-month period, PST resulted in an incremental cost of €59·08 in comparison with routine care. The overall cost of managing a patient through pharmacist-supervized PST for a 6-month period was €226·45. Difference in overall cost was minimal, and PST was the dominant strategy in some scenarios examined during sensitivity analysis, specifically if analysis was conducted from a societal perspective or at the maximum estimate of the cost of AMS staff, as demonstrated in Table 3. Unsuprisingly, the most expensive scenario evaluated was if the full cost of the POC meter was reimbursed by healthcare payer.

DISCUSSION

Based on the results of this study, on a per test basis, PST is marginally more expensive in comparison with centralized laboratory testing. This is similar to the established trend of previous publications.[25] However, it does offer additional benefits to the healthcare payer in exchange for this extra cost. It is speculative to determine whether this strategy is cost-effective, as no threshold has previously been suggested for an increase in TTR. However, the relatively small value of the incremental cost increases the probability that a healthcare payer would surmize that it is a worthwhile strategy to finance. The fact that multiple scenarios examined in the sensitivity analysis, including an evaluation from a societal perspective, concluded that PST was the dominant strategy, gives further credence to this prospect.

The cost-effectiveness of PST is dependent on the method of evaluation used, choice of comparator and the setting. As far as the authors are aware, this is the first economic evaluation of a pharmacist-supervized direct-to-patient system. Furthermore, this is the first evaluation of PST that has been undertaken in an Irish population. The strategy evaluated in this paper is favourable on a cost per patient basis in comparison to a number of other PST strategies which have undergone economic evaluation. Claes *et al.* evaluated a similar method which involved a CoaguChek device,

Table 2. Cost-effectiveness of 6 months of patient self-testing (PST) vs. anticoagulation management service (AMS) (usual care)

	Patient self-testing	Anticoagulation management service
Mean % TTR (95% CI)	72 (±2·32%)	59 (±3·36%)
Median % TTR (IQR)	74 (64·6–81)	58·6 (45·5–73·1)
Mean INR tests/ patient ± SD (Range)	41·7 ± 6·6 (24–60)	10·7 ± 5·2 (5–35)
Cost of 6 months of patient management	€226·45	€167·38
Incremental cost of 6 months of PST therapy vs. AMS	€59·08	

Table 3. One-way sensitivity analysis on incremental cost of 6 months of patient self-testing (PST) therapy vs. anticoagulation management service (AMS)

	€
Testing frequency	
Minimum value 95% CI	34·92
Maximum value 95% CI	83·23
Point of care device reimbursement	
5 year straight-line depreciation	176·68
AMS staff[a]	
Minimum value (15% of workload)	−13·91 (Dominant)[b]
Maximum value (5% of workload)	132·07
Societal perspective	−13·44 (Dominant)[b]
Excluding pharmacist training	44·08

[a]Based on expert guidance, sensitivity analysis of ±50% was applied.
[b]This scenario was both less costly and more effective in comparison with management at AMS. Therefore, PST is dominant over usual care.

dosing software and GP management in Belgian GP practices; however, this method was more expensive and achieved an inferior TTR level to our study. Perhaps the most comprehensive evaluation of PST strategies was a health technology assessment conducted in Canada. This concluded that PST was not cost-effective based on a threshold of €50 000 (CAN) per quality-adjusted life year (QALY). However, when calculated from a societal perspective, PST was determined to be cost saving.[26] Although QALYs attempt to give an overall measurement of the impact of a therapy or intervention on a patient, they can lack sensitivity when used in the comparison of two similar treatment strategies, as is the case with PST and AMS.

Time in therapeutic range is a reliable indicator of the performance of any method of anti-coagulation management and therefore is a suitable effect measurement for this cost-effectiveness analysis. The current study showed a difference of 13% between the means of both groups and a 15·4% difference between the two median values. The Stroke Prevention Using Oral thrombin Inhibitor in Atrial Fibrillation (SPORTIF) III and SPORTIF V studies suggest that the incidence of death, major bleeding and stroke may be halved by a 15% improvement in TTR.[27] Similar increases were obtained during the course of this study.

Significantly, the TTR levels associated with this study were greater than the 70% range which would be considered a good level of control. A retrospective review of 6108 patients with non-valvular atrial fibrillation showed that patients with INR control of 70% of time in range had a significantly reduced risk of stroke.[28]

The cost of managing a patient using PST based on our trial data was determined to be €226 for a 6-month period. In comparison, the net ingredient cost of 6 months of therapy of either of the two NOACs currently licensed for the prophylaxis of thromboembolic events in Ireland is between €456·06 (Dabigatran 150 mg × 60 capsules per month) and €384·66 (Rivaroxaban 20 mg × 28 tablets per month).[29] Previous studies indicate that these are cost-effective in comparison with conventional warfarin management.[30] However, the comparator used in both of these trials was conventional warfarin management, which is associated with reduced TTR levels and overall poorer patient outcomes. No significant effect has been shown between patients treated with dabigatran and those who are treated with warfarin and have TTR levels >65·5%.[31] The management strategy evaluated in this paper has an overall TTR of 72%. Improvements in warfarin control may force a reappraisal of the cost-effectiveness of NOACs.

Although, the increase in testing frequency has been hypothesized as the reason for the observed benefits of PST,[32] it does not offer a comprehensive explanation. Similar testing frequencies in control and intervention groups resulted in better outcomes in the groups using POC monitoring.[33,34]

Patient self-testing is not a suitable strategy for all patients. This is reflected in the reasons given by patients for dropping out of the trial. Thirteen patients did not complete the trial for reasons which could be attributed to difficulties with PST management. Future research should attempt to investigate which patient groups would benefit most from self-testing or self-monitoring strategies. Some studies have suggested focusing on those with mechanical heart valves or those under 55 years of age; however, conclusive evidence is lacking.[35]

Limitations

The limited duration of the RCT restricts the utility of the data as initial costs such as patient training and purchase costs of the POC devices are loaded into a 6-month time period, even though they will have a longer term benefit to the patient who is not captured during this study. The duration and sample size did not allow for a significant level of haemorrhagic and thromboembolic complications to be detected. Optimal management of warfarin therapy in the form of PST has a long-term benefit to the patient in terms of reduced thromboembolic events and deaths.[5] The benefit is not one that is conclusively detectable after 6 months of data collection.

Some of the costs calculated were based on expert guidance and internal hospital data. Workload of AMS staff was based on expert guidance from senior staff in the anti-coagulation clinic at CUH; however, variation of this estimate had the greatest effect on outcome. Wide variations were employed to any assumptions based on expert guidance during sensitivity analysis. Analysis based on microcosting techniques would considerably reduce uncertainty around outcomes. Additionally, there was a self-selective nature to patient recruitment. Therefore, the group studied may not be representative of the actual population. The estimated percentage of patients who are prescribed warfarin for atrial fibrillation was lower in this study compared with national levels.

As with all economic evaluations based on a single RCT, there are considerable issues associated with the generalizability of the results reported. However, this has been partially addressed through the application of a sensitivity analysis.

WHAT IS NEW AND CONCLUSION

PST provides a significant increase in anti-coagulation control for a modest increase in expenditure. This is maintained in all situations evaluated in sensitivity analysis. The associated increase in INR control for a modest increase in expenditure demonstrated in this study provides further evidence that optimally managed warfarin therapy remains a viable strategy for anti-coagulation management. Therefore, pharmacist-supervized patient self-testing should be considered as an alternative to NOACs which are both more expensive and not established.

AUTHORSHIP AND ACKNOWLEDGEMENTS

J Gallagher was responsible for analysing data from randomized controlled trial and drafted manuscript. S Mc Carthy, N Woods and S Byrne were responsible for designing the research strategy. F Ryan, S O'Shea and S Byrne designed the randomized controlled trial on which economic evaluation was based. F Ryan was responsible for patient management and data collection during original RCT. All authors revised the manuscript and approved the final version of the manuscript. The authors would like to thank staff at the Warfarin Clinic, Directorate of Medicine and Haematology department at CUH for their time and support.

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