Advantages of a Warfarin Protocol for Long-term Care Pharmacists: a Retrospective Cohort Study

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ABSTRACT

Background

Warfarin is an anticoagulant prescribed to 12% of long-term care residents to reduce the risk of thrombo-embolism. This study used indicators to compare warfarin management by pharmacists to usual care.

Methods

This was a retrospective cohort study comparing a pharmacist-managed warfarin protocol with usual care of qualified warfarin recipients at long-term care facilities (two protocol, one control) in Calgary, Alberta. We compared the proportion of international normalized ratio (INR) tests in the range 2.0 to 3.0, time in range, number of tests, and frequency of bleeding at protocol and control sites. Our primary outcome, time in INR therapeutic range, is an indicator for assuring care quality. A cross-sectional survey at these sites compared health professionals’ perceptions of workload and effectiveness of warfarin management.

Results

Of the 197 residents’ charts reviewed in the study period, those on protocol had 45.0 INR tests while those on usual care had 52.7 tests (p = .034, 95% CI for the difference: 0.6 to 14.6 INR tests). No significant difference was found for time in therapeutic range, number of tests in range, or major bleeding events. Of 178 health professionals surveyed, those from protocol facilities were more satisfied with warfarin management (p = .013). Workload and safety were perceived similarly at all sites.

Interpretation

Our results suggest that a pharmacist-managed warfarin protocol is as effective as usual care and has advantages pertaining to work satisfaction, knowledge of drug interactions, consistent documentation, and fewer INR tests. Further research on teamwork and coagulation management in long-term care facilities is recommended.

Key words: continuing care, pharmacy, warfarin, anticoagulation, international normalized ratio (INR), protocol

INTRODUCTION

In long-term care, the scope of practice for pharmacists may involve warfarin dose management. A warfarin dosing protocol can be a useful tool for consistent antithrombotic care that allows the physician and pharmacist to work together with confidence. The American College of Chest Physicians Clinical Practice Guideline recommends antithrombotic therapy for atrial fibrillation, among other indications such as pulmonary embolus, and supports the use of a protocol.(1) Warfarin is one management choice for atrial fibrillation, and atrial fibrillation is the most common antithrombotic indication at long-term care sites in this study.

Motycka et al.(2) reported on benefits of pharmacist management, which has been shown in hospital settings to improve warfarin therapy,(3,4) reduce health care cost,(5) and improve quality of patient care.(5,6) Use of a warfarin dosing protocol by pharmacists and the effect on quality of long-term care, however, has not been studied. In Alberta, Canada, pharmacists have been able to prescribe warfarin since 2007. This study compared the effectiveness and safety (days within INR range 2.0–3.0) of pharmacist-managed warfarin dosing
using a printed nomogram to that of conventional physician-managed dosing in long-term care. We also compared long-term care health professionals’ perceptions of warfarin management. From this work we have drawn conclusions regarding quality indicators, effectiveness of a protocol, and choices in thrombus risk management in long-term care. We undertook this study to contribute evidence in support of increasing scopes of practice of non-physician professionals in long-term care settings.

Alberta is a good choice of study location since it has 14,500 long-term care beds with two administrative models: public and private-for-profit, but a single-entry model of patient access to the 160 care sites. The Alberta population includes 11.1% over 65 years (Canada is 14.8% overall). Provincial funding for each long-term care bed is based on professional care hours per week.

METHODS

Setting

This study was conducted at three comparable long-term care sites in Calgary, Alberta (Table 1). Two of the sites (comprising 1,059 beds) had implemented the Calgary Warfarin Protocol (“the Protocol”) in 2008 and the control site (629 beds) had not. The three long-term care sites operated under supervision by Alberta Health Services, had similar management regimes, and were comparable in terms of the composition of their nurse, physician, and pharmacist workforces (Table 1). All sites provide standard care for approximately 1,700 Alberta long-term care patients of 65 years and older, excluding patients in specialty care units, such as brain injury, who were not considered for participation in this study.

At all sites, the pharmacist’s role included reviewing prescribed medications for risk of drug interaction and risk of bleeding (see Table 1). Registered nurses and licensed practical nurses shared responsibility for patient assessment and warfarin administration. Physicians were responsible for warfarin management as part of their patient care plan. Most of the physicians at each site cared for at least 10 patients, since community physicians tend not to follow the patient when admitted to long-term care. Physicians visited at least monthly and medications were reviewed quarterly by physician and pharmacist. Team roles and administration at each site remained stable throughout the study period of mid-2010 to late 2011.

The Calgary Warfarin Protocol was adapted from the validated protocol of Hirsch et al. and from the Calgary Anticoagulation Management Service warfarin nomogram. Designed to support warfarin dosing decisions, it was introduced in 2008, shortly after Alberta pharmacists were granted prescribing privileges. Where the Protocol was adopted, pharmacists were trained by a managing pharmacist from Alberta Health Services Seniors Health Division. At protocol sites, once the INR is stable in the range 2.0 to 3.0 for at least two weeks, the patient’s INR report is sent to the delegated pharmacist, who consults the dosing algorithm (plus calculator) and determines the dose to be dispensed. Testing INR is at the discretion of the physician or, if ordered by a pharmacist, as indicated by the Protocol. When the INR is reported above 5.0, warfarin dosing is transferred to the physician, since such management is difficult to incorporate into a protocol; below an INR of 2.0 the physician may be consulted, but the protocol does address the scenario. Since our study was conducted in 2010 and 2011 and the Protocol was introduced in 2008, there was adequate time for familiarization of pharmacists with the Protocol.

For the purposes of this study, “safe warfarin management” means the INR is in the range 2.0 to 3.0 more than half the times tested. A “major” drug interaction is characterized by a change in INR following introduction of a drug that requires alteration of the warfarin dose to avoid adverse effects (e.g., amiodarone). “Major bleeding” is defined by the International Society of Thrombosis and Hemostasis (ISTH) as including fatal bleeding in non-surgical patients, symptomatic bleeding, bleeding causing a fall in hemoglobin level of 20 g/L, or need for transfusion.

Study Design

This two-part study was approved by the University of Calgary’s Conjoint Health Research Ethics Board. The first part (2010–2011) employed a retrospective cohort design comparing warfarin management at two study sites that had implemented the Calgary Warfarin Protocol for at least the past year, to a control site with no protocol in place. The second part of the study (2010–2011) was a cross-sectional survey comparing the long-term care professionals’ perceptions of ongoing warfarin management safety, satisfaction, and workload at their respective sites. In order to avoid confounding results, we ensured that none of the three sites had employed any type of warfarin protocol before the 2008 introduction date.

The charts of all patients prescribed warfarin were analyzed for study eligibility. When reviewing each chart, we collected data on medication management and risk of harm. Charts included in the study documented warfarin therapy of at least four weeks’ duration (suggesting stability) and INR 2.0 to 3.0 in a two-week or greater period from September 2008 to September 2010. Across the three sites, 197 patients were eligible (45 and 71 from population 446 and 620, respectively, at protocol sites and 81 from a population of 629 at the control site). A preliminary chart audit of the three long-term care facilities (1,900 patients) confirmed that 10% of patients in our study sites were receiving warfarin (n = 190), in line with the existing literature. Verhovsek et al. also found that patients are on INR target 54% of the time. Since a patient’s INR was tested 20 times, on average, over a two-year study period, a sample of 190 patient chart reviews provides
in excess of 90% power to detect a difference of 10% in the on-target time, at the 5% level of significance.

Data abstracted from patients’ charts (INR values, lab testing, and bleeding risk) were recorded on standardized sheets by two trained assistants and reviewed for consistency by a third assistant and the lead investigator (RS). A single blinded reviewer (RS) audited participants’ chart data to identify incidents of bleeding and categorized them according to the ISTH definition. A separate category of “clinically relevant non-major bleeding”, defined by ISTH as requiring some form of medical intervention, was identified for future study.\(^{(13,14)}\)

The cross-sectional survey of long-term care professionals’ perceptions of warfarin management safety, satisfaction, and workload at their respective sites was based on the NASA (National Aeronautics and Space Administration) Task Load Index Instrument,\(^{(15)}\) which has been validated in estimating differences in workload.\(^{(16)}\) It consisted of the NASA workload questions, the demographic questions, and the six survey Likert-type scale questions (see Appendix A). The expected time for completion was 5 minutes. For the survey, 147 staff at the two protocol sites and 107 staff at the control site were eligible. In keeping with our inclusion criteria, all were proficient in English and had worked at the site throughout the previous month and were actively involved in warfarin management.

**Outcomes**

Our primary outcome measure was the proportion of time (days in range/total observation days) within INR range 2.0 to 3.0. Secondary outcomes included incidence of major bleeding (including referral to emergency department), proportion of INR measures above 5.0, mean number of INR tests per patient at each site, proportion of INR measures in the 2.0 to 3.0 range, and the number of major drug interactions. The outcome of the health professionals’ survey was the distribution (Likert scale) of each profession’s perceptions of warfarin management safety, satisfaction, and workload at control and protocol sites.

**Statistical Analysis**

In accordance with the method of Rosendaal et al.,\(^{(17)}\) INR measurements were analyzed by the proportion of time in INR range 2.0 to 3.0 for each patient chart, and categorized by their status as protocol or control. The Rosendaal calculation is as follows:

1. Interpolate between adjacent INR values, daily INR increments result.
2. Calculate the number of days from first to last INR measured.
3. Estimate the number of days in INR range 2.0 to 3.0 for that individual.
4. Group the individual days in range for all site participants and calculate the mean.
5. Determine if the mean scores were different between Protocol and control groups.

The cross-sectional survey workload data were collected on continuous scales (NASA Task Load Index) and compared by two sample t-tests; skewed data was assessed with a Wilcoxon ranked-sum (Mann-Whitney) test. Worker perception data (Table 2) lists the five-point Likert-type scale survey questions, which were interpreted using a two sample test of proportion. Responses were analyzed for sensitivity by combining missing (no answered offered) and “neither” responses in ordinal data, then compared using chi-square tests. Five-point Likert-type scale results were combined (0=“very satisfied,” 1=“neither,” and 2=“dissatisfied” and “very dissatisfied”) at the two ends because of low end numbers. Stratified analysis was conducted based on profession type. Stata software (version 11.2) (StataCorp LP, College Station, TX) was utilized for all statistical analysis.

RESULTS

The demographic character of the three sites was comparable (see Table 1). Of the 197 (protocol 116 and control 81) patients, 135 (68.5% overall; 63.8% protocol vs. 75.3% control) were female, and 170 (86.5% overall; 87.1% protocol vs. 85.2% control) were alive at the time of chart review. The age of 188 patients (overall 95.4%; 98.3% protocol vs. 91.4% control) was 65 years or older. All patients’ charts documented anti-coagulation therapy for at least 28 days, with 135 (68.5% overall; 69.0% protocol vs. 67.9% control) having received it for more than one year. Atrial fibrillation was a diagnosis in 142 charts (72.0% overall; 73.3% protocol vs. 70.4% control), deep vein thrombosis in 28 charts (14.2% overall; 14.7% protocol vs. 13.6% control), and pulmonary embolism in 11 charts (5.6% overall; 6.0% protocol vs. 4.9% control).

INR

The overall proportion of time INR was between 2.0 and 3.0 was not significantly different between protocol (71.3%) and control (66.2%) groups ($p = .447$, 95% CI of the difference: -18.3% to 8.1%). Overall, INR was within target range 69.2% of the time, regardless of protocol status. There was no significant difference in the number of INR test results within therapeutic range (protocol 63.9%; control 61.3%, $p = .703$, 95% CI of the difference: -16.4% to 11.1%). The proportion of INR values greater than 5.0 was not significantly different for the groups (0.7% in protocol; 1.8% in control, $p = .486$, 95% CI of the difference 2.2% to 4.3%). In total, 9476 INR tests were reported for 197 patients. On average, patients at protocol sites had 45.0 INR tests compared to 52.7 INR tests for those at the control site ($p = .034$, 95% CI for the difference: 0.6 to 14.6 INR tests) (See Table 3). This represents a significant difference in the number of INR tests.

Interacting Medications

The majority (168, 85.3%) of the 197 charts documented at least one prescription known to interact with warfarin. Of these, 100 (50.8%, 63 protocol and 37 control) were known to have “major” drug interaction with warfarin. (See Appendix B)

Bleeding Events

Five major bleeds (four protocol, one control) and seven clinically relevant non-major bleeds (five from the protocol group) were identified. Three bleeding events occurred when the INR was above target range, one event when it was below target range, and eight events when it was within range. One bleeding event (protocol) correlated with a known major interacting medication (sulfamethoxazole/trimethoprim). There was no significant difference in the number of bleeding events at protocol and control sites ($p = .112$). All major bleeds were referred to the emergency department of acute care.

Survey Results

Of the 178 professionals surveyed, responses were received from 132 nurses (78% of registered and licensed practical nurses), 19 pharmacists (7% response rate), and 27 physicians (43% response rate). This represented a 72% response rate from protocol sites (106 respondents) and 67% from control (72 respondents). Dissatisfaction with warfarin management at the control site was significantly greater (0.0% at protocol vs. .5% at control dissatisfied or very dissatisfied, $p < .001$, see Table 2). No difference was found in the protocol and control groups’ perceptions of workload or warfarin management effectiveness.

DISCUSSION

We found no difference in the time within INR therapeutic range between protocol and control groups, and no statistical difference in frequency of bleeding (Table 3). These results indicate that pharmacist-managed warfarin dosing using the Protocol is as effective and safe as physician management, since amount of time in INR range 2.0 to 3.0 is equivalent and more than half the INR measures fall in that range.

Pharmacist-managed dosing with the Protocol required fewer INR tests, likely because the Protocol directs INR ordering, suggesting potential savings in staff time and laboratory utilization. Other advantages include the availability of INR records, dose records, and the focus on pharmacist decision-making instead of the other care team professionals.
Health-care professionals at protocol sites were more satisfied with warfarin management than those at the control site, though there were no differences in perceptions of safety and workload. We suspect that nurses and physicians experienced reduced workload with management by protocol but did not report it as a significant factor. Further study would require validation of the new survey questions. Overall, these findings are consistent with those of other published accounts, and indicate long-term care teams’ acceptance of the warfarin management by pharmacists.

We have identified no other study in which pharmacists were trained to use a warfarin protocol in long-term care settings. Motycka et al. reported that pharmacists’ warfarin management is more often in the therapeutic range than usual practice (we found equal time in range). Other studies reported that pharmacists improve warfarin therapy, reduce healthcare costs, and improve the quality of patient care. Our finding of fewer lab tests associated with use of the Protocol demonstrates it is effective warfarin management with systematic laboratory testing. While Gurwitz et al. stated that pharmacists prevent adverse drug events in nursing homes, major interacting drugs were identified in both study groups, so it is difficult to know the effect on adverse events. Major bleeding numbers were low in both groups and thus not statistically significantly different. Further study of this issue specifically will require a larger study population.

Neidecker et al. acknowledging risk of adverse events with warfarin therapy, stated that the drug’s low cost,

| Survey Question | Provider | Control (n) | Protocol (n) | Control % | Protocol % | Control % | Protocol % | p-Value |
|-----------------|----------|-------------|-------------|-----------|------------|-----------|------------|---------|
| Safe            |          |             |             |           |            |           |            |         |
| How safe are the patients on your unit from overtreatment (bleeding events e.g. gastrointestinal or intracranial) or undertreatment (e.g. embolic or thrombotic stroke) with warfarin? | Nurses | 50 | 81 | 88.0 | 93.8 | 12.0 | 5.0 | 0.0 | 1.2 | 0.253 |
| Safety          | Physicians | 11 | 15 | 90.9 | 86.7 | 9.1 | 13.3 | 0.0 | 0.0 | 0.738 |
| Safety          | Pharmacists | 10 | 8 | 60.0 | 62.5 | 30.0 | 37.5 | 10.0 | 0.0 | 0.644 |
| Safety          | Overall | 71 | 104 | 84.5 | 90.4 | 14.1 | 8.7 | 1.4 | 1.0 | 0.500 |
| Satisfied       |          |             |             |           |            |           |            |         |
| How satisfied are you with the management of warfarin dosing (INR control) in your facility? | Nurses | 48 | 79 | 79.2 | 98.7 | 18.8 | 1.3 | 2.1 | 0.0 | 0.001 |
| Satisfaction    | Physicians | 11 | 16 | 90.9 | 81.3 | 0.0 | 18.8 | 9.1 | 0.0 | 0.166 |
| Satisfaction    | Pharmacists | 9 | 8 | 22.2 | 100.0 | 55.6 | 0.0 | 22.2 | 0.0 | 0.005 |
| Satisfaction    | Overall | 68 | 103 | 73.5 | 96.1 | 20.6 | 3.9 | 5.9 | 0.0 | <0.001 |
| Low             |          |             |             |           |            |           |            |         |
| Defining workload as: “Professional time spent preparing for and discussing results and orders with other colleagues,” overall, how would you rate your workload in relation to warfarin therapy? | Nurses | 48 | 78 | 27.1 | 14.1 | 27.1 | 42.3 | 45.8 | 43.6 | 0.103 |
| Lowness         | Physicians | 11 | 16 | 36.4 | 18.8 | 45.5 | 56.3 | 18.2 | 25.0 | 0.588 |
| Lowness         | Pharmacists | 10 | 8 | 10.0 | 0.0 | 30.0 | 37.5 | 60.0 | 62.5 | 0.644 |
| Lowness         | Overall | 69 | 102 | 26.1 | 13.7 | 30.4 | 44.1 | 43.5 | 42.2 | 0.068 |
| Agree           |          |             |             |           |            |           |            |         |
| Consider this statement: “A pharmacist-managed warfarin protocol is an asset in INR control.” (for respondents that have used the protocol) | Nurses | 14 | 72 | 100.0 | 97.2 | 0.0 | 2.8 | 0.0 | 0.0 | 0.528 |
| Agreement       | Physicians | 7 | 15 | 85.7 | 60.0 | 0.0 | 40.0 | 14.3 | 0.0 | 0.067 |
| Agreement       | Pharmacists | 10 | 8 | 100.0 | 100.0 | 0.0 | 0.0 | 0.0 | 0.0 | n/a |
| Agreement       | Overall | 31 | 95 | 96.8 | 91.6 | 0.0 | 8.4 | 3.2 | 0.0 | 0.057 |
| Disagree        |          |             |             |           |            |           |            |         |
| Consider this statement: “A pharmacist-managed warfarin protocol is the best method for INR control in most patients.” (for respondents that have used the protocol) | Nurses | 14 | 72 | 57.1 | 86.1 | 35.7 | 12.5 | 7.1 | 1.4 | 0.034 |
| Disagreement    | Physicians | 7 | 15 | 71.4 | 40.0 | 14.3 | 33.3 | 14.3 | 26.7 | 0.387 |
| Disagreement    | Pharmacists | 10 | 8 | 70.0 | 87.5 | 30.0 | 12.5 | 0.0 | 0.0 | 0.375 |
| Disagreement    | Overall | 31 | 95 | 64.5 | 79.0 | 29.0 | 15.8 | 6.5 | 5.3 | 0.240 |

n = total number of respondents for a particular item in the questionnaire.
CONCLUSIONS

This study concludes that delegating warfarin management to pharmacists using the Calgary Warfarin Protocol and a printed nomogram is as effective and safe as management by physicians in long-term care. It frees physicians and nurses to focus on other aspects of care, and makes use of a pharmacist’s knowledge of drug interactions and dose monitoring while offering opportunities for quality assurance activities. Given the pace of change in health care, it is advantageous to have measurement tools and guidelines such as protocols. Studies such as this suggest indicators of quality and measures of team function that can assure safe care for patients. Prospective research focused on individual bleeding risk is a natural follow-up to this study, and direct comparison of antithrombotic management where other health professionals have access to the Protocol would be welcome.

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CONFLICT OF INTEREST DISCLOSURES

The authors declare that no conflicts of interest exist.

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TABLE 3.
INR outcomes among protocol and control groups living in long-term care facilities (95% CI)

| INR Outcome | Protocol Group (n=116) | Control Group (n=81) | p-Value | CI        |
|-------------|------------------------|----------------------|---------|----------|
| Proportion of time within INR target range | 71.3% | 66.2% | 0.447 | -18.3% to 8.1% |
| Proportion of INR test values in target range | 63.9% | 61.3% | 0.703 | -16.4% to 11.1% |
| Proportion of INR test values greater than 5.0 | 0.7% | 1.8% | 0.486 | -2.2% to 4.3% |
| Average number of INR tests done during study period | 45.0 INR tests | 52.7 INR tests | 0.034 | 0.6 to 14.6 INR tests |

INR = International Normalized Ratio.
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APPENDICES

Appendix A. Staff Questionnaire

Please complete the following questions in relation to warfarin therapy to the best of your knowledge. Your responses will be kept anonymous. Your participation in this survey is greatly appreciated.

1. Have you worked at this institution for more than 1 month? (choose one)
   - Yes
   - No

2. What is your profession? (choose one)
   - Pharmacist
   - Registered Nurse
   - Licensed Practical Nurse
   - Physician

3. How safe are the patients on your unit from overtreatment (bleeding events e.g. gastrointestinal or intracranial) or undertreatment (e.g. embolic or thrombotic stroke) with warfarin? (choose one)
   - Very safe
   - Safe
   - Neither safe nor unsafe
   - Unsafe
   - Very unsafe

4. Defining workload as: “Professional time spent preparing for and discussing results and orders with other colleagues,” overall, how would you rate your workload? (choose one)
   - Very high
   - High
   - Neither high nor low
   - Low
   - Very low

5. How satisfied are you with the management of warfarin dosing (INR control) in your facility? (choose one)
   - Very satisfied
   - Satisfied
   - Neither satisfied nor dissatisfied
   - Dissatisfied
   - Very dissatisfied

6. Have you ever used a pharmacist-managed warfarin protocol in INR control? (choose one)
   - No
   - Yes (Please complete questions 7 and 8)

7. Consider this statement: “A pharmacist-managed warfarin protocol is an asset in INR control.” (choose one)
   - Strongly Agree
   - Agree
   - Neither Agree nor Disagree
   - Disagree
   - Strongly Disagree

8. Consider this statement: “A pharmacist-managed warfarin protocol is the best method for INR control in most patients.” (choose one)
   - Strongly Agree
   - Agree
   - Neither Agree nor Disagree
   - Disagree
   - Strongly Disagree

9. The scales below describe six key aspects of workload. Please indicate with an “X” on each scale the point that corresponds to your perception of your workload in relation to warfarin therapy and maintaining target INR (2-3) values (referred to as the “task” on each scale).

   For definitions of any the following categories please refer to the table on page 3.

   How mentally demanding was the task?
   - Very Low
   - Very High

   How physically demanding was the task?
   - Very Low
   - Very High

   How hurried or rushed was the pace of the task?
   - Very Low
   - Very High

   How successful were you in accomplishing what you were asked to do?
   - Very Low
   - Very High

   How hard did you have to work to accomplish your level of performance?
   - Very Low
   - Very High

   How insecure, discouraged, irritated, stressed, and annoyed were you?
   - Very Low
   - Very High
### NASA-TLX Rating Scale Definitions

| Title                  | Endpoints | Descriptions                                                                 |
|------------------------|-----------|-----------------------------------------------------------------------------|
| MENTAL DEMAND          | Low/High  | How much mental and perceptual activity was required                        |
|                        |           | (e.g. thinking, deciding, calculating, remembering, looking, searching, etc.)? |
|                        |           | Was the task easy or demanding, simple or complex, exacting or forgiving?    |
| PHYSICAL DEMAND        | Low/High  | How much physical activity was required                                     |
|                        |           | (e.g. pushing pulling, turning, controlling, activating, etc.)?              |
|                        |           | Was the task easy or demanding, slow or brisk, slack or strenuous, restful or laborious? |
| TEMPORAL DEMAND        | Low/High  | How much time pressure did you feel due to the rate or pace at which the tasks or task elements occurred? |
|                        |           | Was the pace slow and leisurely or rapid and frantic?                       |
| PERFORMANCE            | Good/Poor | How successful do you think you were in accomplishing the goals of the task |
|                        |           | (In this case meaning the maintenance of patients’ INR values within an acceptable range)? |
|                        |           | How satisfied were you in accomplishing these goals?                        |
| EFFORT                 | Low/High  | How hard did you have to work (mentally and physically)                     |
|                        |           | to accomplish your level of performance?                                    |
| FRUSTRATION LEVEL      | Low/High  | How insecure, discouraged, irritated, stressed and annoyed versus secure, gratified, content, relaxed and complacent did you feel during the task? |

Table adapted from: Hart and Staveland (1988). *Development of NASA-TLX (Task Load Index): Results of Empirical and Theoretical Research*

Please use the space below to write additional comments:

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Thank you for taking part in this study
## Appendix B: Number of Residents Prescribed Major Warfarin-Interacting Medications

| Medication                    | Number of Residents and LTC Protocol Status |
|-------------------------------|--------------------------------------------|
|                              | Control Group | On Protocol |
| Amiodarone                   | 3             | 3           |
| Azithromycin                 | 0             | 12          |
| Carbamazepine                | 3             | 0           |
| Celecoxib                    | 1             | 3           |
| Clarithromycin               | 0             | 1           |
| Clopidogrel                  | 4             | 2           |
| Erythromycin                 | 1             | 6           |
| Fenofibrate                  | 1             | 1           |
| Fluconazole                  | 0             | 1           |
| Levofloxacin                 | 13            | 23          |
| Metronidazole                | 2             | 6           |
| Phenytoin                    | 4             | 7           |
| Propafenone                  | 0             | 1           |
| Tramadol                     | 0             | 1           |
| Trimethoprim/Sulfamethoxazole| 16            | 27          |