Author’s response to reviews

Title: Standardized Warfarin Monitoring Decreases Adverse Drug Reactions

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Maria Elisabeth Johanna Zalm, Ph.D.
Editor-in-Chief, BMC Family Practice

Dear Dr. Zalm:

We are pleased to submit our revised manuscript entitled “Standardized Warfarin Monitoring Decreases Adverse Drug Reactions” (FAMP-D-18-00252) for publication in BMC Family Practice. Point-by-point responses to the comments are below. All changes are clearly marked in red within the manuscript.

We would like to thank you and the reviewers for your meticulous work and valuable advice. We hope that our manuscript will now be accepted for publication in BMC Family Practice.
Technical Comment: Provide a Cover letter stating the intention of the article and the approval of all authors on submitting this manuscript to the journal.

Response to the Technical Comment: We have included a Cover letter that states the intention of the article and the approval of all authors on submitting this manuscript to the journal, as follows: “The risk of adverse drug reactions (ADRs) associated with the anticoagulant warfarin poses a significant concern. We developed an anticoagulation task force at our Institution to decrease warfarin ADRs and to standardize warfarin monitoring and management. We present a 5-year (2013-2017) study of patients who were prescribed warfarin by their primary care provider (PCP) or cardiologist upon hospital discharge and in the ambulatory setting to determine the international normalized ratio (INR) within 5, 10, and 30 days after discharge, time in therapeutic range (TTR), and the number and total cost change of severe warfarin ADRs. The goals of our study were to decrease warfarin ADRs and to develop an anticoagulation task force aimed at educating PCPs and cardiologists about evidence-based guidelines for warfarin management, increasing the use of our Institution’s electronic warfarin module, and enhancing patient compliance with obtaining INR. All of the authors of this work have read and approve the final version of our manuscript and its submission to BMC Family Practice.”

Reviewer #1, Comment #1: I am still not convinced that Poisson generalised regression is the most appropriate method of analysis but given that other methods of analysis give similar results, I do not insist on a change of analysis.

Response to Reviewer #1, Comment #1: We appreciate that Reviewer #1 does not insist on a change of statistical analysis as the reviewer realized that other methods of analysis give similar results.

Reviewer #1, Comment #2: Only overall p-values are given in the table. Subgroup p-values are only given in the text. I would recommend only discussing significant changes in the text and not mentioning non-significant changes.

Response to Reviewer #1, Comment #2: We have removed the non-significant changes within the Results section (Page 8), as follows:
INR within 5, 10, and 30 days of hospital discharge and time in therapeutic range: The proportion of patients who had an INR within 5, 10, and 30 days of hospital discharge out of the total number of patients who were prescribed warfarin by all PCPs, cardiologists, and other specialties significantly increased over the 5-year period (p<0.01 for each time period) (Table 3). At 5-days post-discharge, the proportion also significantly increased for PCPs and cardiology (p<0.001 for both). The proportion significantly increased for PCPs at 10- and 30-days post-discharge (p<0.001 for both).

Electronic warfarin module usage and time in therapeutic range

Use of the electronic health module significantly increased between baseline in 2013 and 2017 for both PCPs (68.9% to 84.2%, p<0.001) and cardiologists (76.5% to 85.4%, p<0.001). The TTR is represented by a ratio of the number of days the INR was in the therapeutic range for all patients treated with warfarin to the total number of days all patients were treated with warfarin. The TTR was significantly higher for cardiologists compared to PCPs for all 3 years of study (p<0.0001).

Reviewer #1, Comment #3: Line 176. I think it should say 'TTR was significantly higher' not 'the change in TTR was significantly higher'

Response to Reviewer #1, Comment #3: We have revised this sentence as follows: “The TTR was significantly higher for cardiologists compared to PCPs for all 3 years of study (p<0.0001).”

Reviewer #3, Comment #1: Abstract (Lines 37-38): Rewrite the statement 'number and total cost change of severe warfarin ADRs' clearly.

Response to Reviewer #1, Comment #1: We have revised the sentence in the Methods section of the Abstract, as follows: “Between 2013-2017, we analyzed patients who were prescribed warfarin by their PCP or cardiologist upon hospital discharge and in the ambulatory setting to determine the international normalized ratio (INR) within 5, 10, and 30 days after discharge, time in therapeutic range (TTR), number of severe warfarin ADRs, and total and average cost reduction of all severe warfarin ADRs to determine whether there was an organizational cost savings following the implementation of standardized warfarin care.”
Reviewer #3, Comment #2: Background (Line 69): Specify whether 'protime' is generic term or brand version of the procedure. If it is brand version, mention protime®.

Response to Reviewer #3, Comment #2: The word “protime” is a generic term and not a brand version. We have specified this in the Background, as follows: “The generic prothrombin time or protime (PT) historically has been used to monitor warfarin levels.”

Reviewer #3, Comment #3: Methods: Specify the study design very clearly. Table 3 shows that you followed trend analysis or time series study design. Clarify this.

Response to Reviewer #3, Comment #3: We have clarified the study design with the Methods section on Page 5, as follows: “The study design was a trend analysis in which the data were derived from a comprehensive records review involving all prescriptions of anticoagulants at our Institution over this 5-year time period.”

Reviewer #3, Comment #4: Methods: Elaborate upon the basis of sample size calculation for each year and sampling technique employed for each year. These are very crucial for the external validity of your findings.

Response to Reviewer #3, Comment #4: We have detailed the study design within the Methods section on Page 5, as follows: “The study design was a trend analysis in which the data were derived from a comprehensive records review involving all prescriptions of anticoagulants at our Institution over this 5-year time period.” Since our study involved a comprehensive records review at our Institution, there was no basis for a sample size calculation.

Reviewer #3, Comment #5: Statistical analysis: Lines 142-145: Table 3 shows that you performed follow up for 4 years, even adding new patients. This shows you repeatedly measured the INR from the patients taking warfarin and interpreted these for your study purpose. In such scenario of repeated design, chi square test is not better suited; it seems that you tried to compute Bayes factor with the Poisson model as your sampling plan. If this was the condition, row sum or column sum multinomial model would be better. Above all, repeated measure ANOVA (if data
were normally distributed) or Friedman's test (if data were non-normally distributed) or multilevel modeling would be relevant and appropriate statistical test.

Response to Reviewer #3, Comment #5: After extensive discussions with the expert statistician who performed the statistical analysis of our data, the statistician believes that the reviewer has misunderstood our data and, therefore, is not recommending the appropriate statistical analysis. The statistician has written a detailed explanation about why he selected the statistical analysis based on the data, as follows: Our data are cohort-based rather than individual-based. In other words, we have aggregate data for an entire group of patients at a hospital rather than data from individual patients at the hospital. For example, we have the number of warfarin prescriptions per year, but we don't have individual-level data about those individual prescriptions. Because of this, we technically don't have access to repeated measures about those individual prescriptions. Because of this, we technically don't have access to repeated measures ANOVA, Friedman test, or multilevel model for these data. As such, the chi-square test, although fairly simple, is an appropriate way to judge our hypothesis that proportions changed over the years. We implemented the Poisson model for TTR ratios because the denominator - the total time of observation - is aggregated over all patients and itself a random variable [Agresti, A. (2012) Categorical Data Analysis. 3rd Edition. Wiley, NH, USA]. The multinomial model technically presumes a fixed total with counts distributed among categories, which is not the case for these data. Because of this, we implemented the Poisson model. We made no attempts to calculate Bayes factors with our models. We have enhanced our Methods section to detail how the data were collected in hopes of clearing up any issues with regard to our statistical analyses. We have detailed the study design within the Methods section on Page 5, as follows: “The study design was a trend analysis in which the data were derived from a comprehensive records review involving all prescriptions of anticoagulants at our Institution over this 5-year time period.”

Reviewer #3, Comment #6: Table 4: You've only mentioned the numbers of warfarin ADRs. It would be better to show the ADRs exactly in appendix as well.

Response to Reviewer #3, Comment #6: We have added the severe ADRs to Table 4.