Author’s response to reviews

Title: Ambulatory Toxicity Management (AToM) Pilot: Results of a pilot study of a pro-active, telephone-based intervention to improve toxicity management during chemotherapy for breast cancer

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Author’s response to reviews:
Dear Dr. Parpia,

Thank you for reviewing our manuscript and for the feedback from yourself and the reviewers. Below please find a point-by-point response to the comments.

Editor Feedback

1. Please provide details on study design under the methods section

Additional information regarding the study design has been added to the “Study Design and Participants” section of the methods for clarity.

2. Please provide more details on how the sample size was derived

Since the main goals of this pilot study were to determine the feasibility and acceptability of the intervention in our local jurisdiction before considering a larger study, a formal sample size calculation was not performed. Based on guidance from the literature on pilot studies, the project steering group felt that including two centres and up to 100 patients would provide us with enough information on experience with study procedures and to decide whether to proceed with a larger study. The Methods section has been updated to clarify this.

3. Were there pre-defined criteria for determining whether the intervention was acceptable and feasible?

We did not have formal pre-defined criteria for moving forward. The plan was for the project steering group to review the experience with recruitment, delivery of the intervention and feedback from patients and providers to decide whether the intervention was acceptable and feasible. A comment explaining this has been added to the manuscript.

4. Provide CIs for all estimated proportions of acceptability and feasibility, and how they were calculated?

For quantitative measures of feasibility and acceptability, 95% confidence intervals (95% CI) have been added per the editor’s comment. For evaluations of acute care utilization using administrative data, incidence rate ratios with 95% CI are currently reported.
5. Omit p-values as the study was not designed to make statistical comparisons.

We agree that the study was underpowered to provide meaningful estimates on the intervention; we have removed p-values from the acute care utilization findings per the editor’s comment.

6. Provide explanation as to why Centre specific analysis was reported separately? Was this pre-defined?

Contemporaneous control selection was based on cancer center, cancer stage and treatment regimen. As such, we undertook the stratified analysis due to centre differences in regimens, baseline rates of acute care visits, and patient characteristics such as cancer stage and age. Additionally, there were other systematic differences between the populations of two participating centres, such as rural residence, that affect the way patients would receive and seek medical care but could not be adjusted for due to small sample size. Additional information regarding the stratification has been added to the “Analysis of Acute Care Utilization” section of the methods for clarification.

7. Page 10 - L27. No differences in rates of hospitalization - given the wide CI, I suggest to rephrase to suggest that the results are inconclusive rather than "no difference"

Statement has been updated per the editor’s comment.

Reviewer #1:

1. The study design is not explicitly written. It appears that it is a clinical trial with an intervention and a control group; however, clarity is needed. Moreover, if it is a trial, figure 1 can be modified into a CONSORT flow diagram.

This was a prospective, single arm, two-centre pilot study to evaluate feasibility and acceptability of the intervention hence a CONSORT flow diagram would not be appropriate. Inclusion criteria were: diagnosis of early stage breast cancer (stage I-III), plan to initiate adjuvant or neo-adjuvant chemotherapy, adequate command of English to complete questionnaires, and provision of informed consent to participate. The confusion may be coming from the fact that a contemporaneous control cohort was identified at a later date from administrative data to evaluate the feasibility of using administrative data to determine emergency room visits and hospitalizations (versus relying on primary data collection) as we were hoping to use this approach in the larger trial. The control cohort consisted of all other
patients diagnosed with early stage breast cancer who were initiating the same chemotherapy regimens as study participants in the two participating institutions during the study intervention period but who did not participate; details of the cohort creation are summarized in Supplementary Figure 1. This information has been added to the “Study Design and Participants” section of the methods for clarity.

2. On page 4, within the third paragraph, add impact of study on identifying incidence rates of ED and hospitalization visits as one of the purposes.

This information has been added to the introduction per the reviewer’s comment.

3. The article does not state anything about group allocation between intervention and control, nor there is any mention of bias in selecting the participants. Though study participants are mentioned, inclusion and exclusion criteria should be clearly written.

This study prospectively recruited patients to a single arm pilot study to assess feasibility and acceptability. To evaluate the impact of the intervention on acute care utilization, incidence rates in the intervention cohort were compared to contemporaneous controls identified from the administrative data. We included two different centres to improve generalizability of findings and experience with implementation, but since not all patients treated at each of the centres during the intervention period were enrolled, potential for selection bias exists. This information is provided in the fifth paragraph of the discussion.

Patients were eligible to receive the intervention if they were newly diagnosed with early stage breast cancer (stage I-III) who were initiating adjuvant or neo-adjuvant chemotherapy during the accrual period, had adequate command of English to complete questionnaires, and provided individual consent to participate. Patients receiving treatment with an investigational agent were excluded. The contemporaneous control cohort was identified using administrative data, and consisted of all other patients diagnosed with early stage breast cancer who were initiating the same chemotherapy regimens as study participants in the two participating institutions during the study intervention period. The inclusion and exclusion criteria for the study are further described in the “Study Design and Participants” section of the methods.

4. Nurse interventionists should have been trained in both centers to ensure consistency in delivering the intervention. It can be acknowledged in the limitation somewhere.

Participating nurses received training on the study protocol and intervention during a study kick-off meeting prior to initiating the intervention, and participated in monthly study calls to
troubleshoot logistics of delivering the intervention. This information has been added to the “Description of the Intervention” section of the Methods.

Toxicity assessments, management recommendations and documentation were standardized using a form covering the same nine toxicities as the patient symptom self-management guide and a companion provider symptom management guide, consistent with best practices and current evidence. Reactive toxicity management is within the scope of practice for oncology nurses; as such, additional intensive training was not provided.

5. Heading 'recruitment and retention' should come after 'setting and participants' instead of falling under results heading. Moreover, after describing the intervention, it would be nice to describe control participants' and their selection.

Recruitment and retention were collected to assess feasibility of the intervention; this section has now been incorporated into the “Feasibility” section of the Results. Description of the controls, which were identified post-hoc from administrative data in part to demonstrate feasibility of using administrative data to look at healthcare utilization outcomes rather than collecting the data from patient report or by chart abstraction, has been included in the Methods section.

6. Table 1 indicates only study participants' characteristics. The readers may wish to see data of control group participants as well to infer for similarities and differences among the groups. In addition, there are some errors in calculation in the 'total column'. For example, against row "college/university of higher", the total participant count should be 56 instead of 66. Also, total participant count is 76 instead of 77 in 'combined household income', 'stage', 'treatment intent', 'regimen' etcetera. Kindly recheck percentages of all the percentages in the table.

The values in Table 1 have been corrected as per the reviewer’s comments. The contemporaneous control cohort was identified post-hoc from the administrative data so it was not included in Table 1 describing the prospectively enrolled cohort; a description of the contemporaneous control cohort is appended in Supplementary Table 1.

Reviewer #2:

The value of the study would be enhanced if the reason for ED visits and hospitalization were reported so there was more information to link the focus of nurse calls and the relationship to ED visits and hospitalizations in the nurse call group and similarly ED/hospitalization chief
complaints to know how they relate to unresolved chemotherapy related toxicities for the comparison group.

There is significant interest in identifying potentially preventable ED visits in oncology populations. However, there is a lack of formally validated approach. We conducted an exploratory analysis investigating potentially treatment-related ED visits and hospitalizations, using a previously developed algorithm (Krzyzanowska et al, J Oncol Pract, 2018). Among the control patients, 113 of 270 (41.8%) ED+H visits were classified as potentially-related to treatment toxicity. Among the AToM patients, 30 of 54 (64.8%) ED+H visits were classified as related to treatment toxicity.

However, given the small sample size and exploratory nature of the analysis we do not feel we have enough data to more formally evaluate the relationship between the intervention and reasons for visits and we have elected not to include it in the manuscript. However, if the editor and the reviewer feel the data below is of interest, we are happy to add it as supplementary material.

Please see Table 1 in appended reviewer response letter: Table 1. Crude and adjusted toxicity-related event incidence rates, by intervention group and center

We hope that you will find our revised manuscript of interest and we look forward to hearing from you in this regard.

Sincerely,

Monika K. Krzyzanowska, MD MPH