Author’s response to reviews

Title: Customized Registry Tool for Tracking Adherence to Clinical Guidelines for Head and Neck Cancers: Protocol for a Pilot Study

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Author’s response to reviews:

Geetha Gopalan, PhD
Associate Editor
Pilot and Feasibility Studies

Dear Dr. Gopalan and the Editorial Board at Pilot and Feasibility Studies,

Thank you for giving us the opportunity to submit a revision of our manuscript (PAFS-D-19-00114R1) entitled “Customized Registry Tool for Tracking Adherence to Clinical Guidelines for Head and Neck Cancer: Protocol for a Pilot Study” for consideration as a study protocol in Pilot and Feasibility Studies.

We are pleased to address the reviewer comments below. We have revised our manuscript by incorporating your recommendations throughout. Included in our revision is a clean version of the revised manuscript along with a track changes version of the revised manuscript. Reviewer comments are reproduced in bold with our response following and updated text in italics. We have indicated precisely where in the clean version of the revised manuscript we have addressed reviewer comments and suggestions.

All authors have read and approved submission of the manuscript. Authors claim no conflicts of interest. The manuscript has not been published and is not being considered for publication elsewhere.

Thank you for considering our manuscript for publication in Pilot and Feasibility Studies.

Sincerely yours,
(electronically submitted on behalf of all authors)
Urmimala Sarkar, MD, MPH
Reviewer #1: Comments and Responses

Thanks for the opportunity to review this paper, please consider the following, there is a mix of main points and pedantry in this:

Background

1. Line 71 I would argue these reports should be referenced, this is a US report, which I am aware of because of the field I work in. I don't think this would apply to all readers, particularly those from an international audience.

Thank you for this suggestion. Our manuscript now includes references to these reports.

Previous version:

Since publication of ‘To Err is Human’ and other subsequent reports by the Institute of Medicine, there has been increasing focus on harms caused by medical care.

Revised version: (page 5, lines 71-72)

Since publication of ‘To Err is Human’ and other subsequent reports by the Institute of Medicine, there has been increasing focus on harms caused by medical care.(1-3)

2. Line 79 'high risk' should be hyphenated. I won't repeat this but it does occur throughout.

We edited the manuscript so that ‘high-risk’ is hyphenated on Line 79 and throughout the manuscript.

3. Line 98 review syntax, 'updating needed monitoring....' this doesn't make sense to me. Possibly reword to 'updating necessary (recommended?) monitoring'.

We agree and made the following revisions accordingly:

Previous version:

Traditionally, face-to-face visits have been the primary means of updating needed monitoring and ensuring completion of treatment steps.

Revised version: (page 6, lines 99-100)

Traditionally, face-to-face visits have been the primary means of monitoring patients and ensuring completion of treatment steps.

4. Line 99 you talk about the frequency of errors of omission but haven't included any data from the literature to help the reader frame the magnitude of this particular type of error. I would argue this
would add to your arguments.

Thank you for this point. We now cite data from the literature to demonstrate the magnitude of errors of omission.

Previous version:

However, given the frequency of errors of omission, solutions to systematically identify upcoming and overdue monitoring across a population of patients are needed.

Revised version: (page X, lines XX)

However, given the frequency of errors of omission – missed cancer diagnoses constitute the leading cause of paid medical malpractice claims among outpatients - solutions to systematically identify upcoming and overdue monitoring across a population of patients are needed.(12, 13)

5. Line 116 should read 'diagnoses' given the plural that follows in 'plans'

We refer to plans for a single diagnosis rather than multiple diagnoses in this sentence. We have edited the text as follows for clarity.

Previous version:

This tool enables the clinic to develop custom diagnosis and treatment plans for patients with head and neck cancer, and facilitates subsequent population level tracking of completion of needed diagnostic or treatment steps.

Revised version: (page 7, lines 118-120)

This tool enables the clinic to develop custom diagnostic and treatment plans for patients with head and neck cancer, and facilitates subsequent population level tracking of completion of needed diagnostic or treatment steps.

6. Line 121, what is a 'safety net hospital'? I am not familiar with that term, it is certainly not something used in the UK.

Thank you for suggesting this clarification. We define safety net settings where the term first appears in the text rather than on line 121 to introduce readers to its definition at the earliest opportunity.

Previous version:

Perhaps more concerning, the proportion of patients receiving guideline-based care has decreased over time, and patients in safety net settings and with lower socioeconomic status appear to be most vulnerable.[3, 7]

Revised version: (page X, lines XX)

Perhaps more concerning, the proportion of patients receiving guideline-based care has decreased over time, and patients with lower socioeconomic status who receive care regardless of insurance status or
their ability to pay in safety net settings appear to be most vulnerable.\(^{(6, 10)}\)

Methods

7. The reference to measurement of the effect of the tool in line 131 and the comments in the reply to the initial review under point 2 around the primary aim. This appears to be suggesting that you will look to measure the effect of the tool in improving adherence to guidelines. You also suggest that the adherence to guidelines is a complex thing and is confounded by other issues beyond simple awareness and adherence to guidelines. I don't believe the outcomes have been properly addressed. If this is a pilot study then it should have pilot study outcomes and I'm not sure this is clear. Essentially what are you piloting? On line 215 you mention an effect estimate but this is the first reference I can see to an estimate in the paper and in the repose. I would agree an estimate is possible. That said there is then a discussion of a power calculation in line 220.

Thank you for raising this point. As mentioned in lines 94-97, guideline adherence is complex, but a frequent problem in complex chronic illness management is the inability to conduct ‘population level management’ outside of individual visits. We hypothesize that the health IT tool that we propose to study will allow the pilot clinic to address, and proactively prevent, lapses in delivering guideline-concordant care. We are conducting this pilot study to gain preliminary evidence for effectiveness and to provide an opportunity to revise the intervention, prior to undertaking a large-scale cluster randomized implementation study at multiple sites. Your comments highlight the important point that we have neglected to include implementation outcomes in this study to help understand how the tool is used and to guide further implementation at scale. We have included this in the methods section (pages 11-12, lines 221-228).

Implementation Outcomes

To understand how the health IT tool is used in practice during this study, we will also measure several components of tool utilization to better understand the actor, dose, temporality, and action target of the intervention.\(^{(16)}\) Data collection on these parameters will occur through a quarterly survey of clinic staff using the tool and through five randomly selected clinic days when the investigators will observe clinic staff and any use of the tool that occurs. The survey will ask staff to report their role in the clinic and recall for the prior week the amount of time that the tool was used, timing of use, and number of patients outreached through use of the tool.

8. Why undertake a pilot study and include 300 patients? This really doesn't make sense, what are you piloting that requires that sample size? In terms of a substantive study, what would change in terms of sample between the pilot and eventual trial?

Our goal is to understand how the tool is used, and what effect it has, within a single site prior to moving on to a multi-site trial. Since the tool will be implemented clinic-wide, recruiting a larger number of patients does not require the same level of effort that individual patient recruitment would require. We chose a sample of 300 patients because it is feasible in the time we anticipate it to take to fully implement the tool and have it integrated into clinic workflows, and because this would give us sufficient power to detect clinically significant effect sizes that the tool may have on important care processes.

9. Line 152 insert a comma after 'database'
Thank you for this suggestion, however inserting a comma after ‘database’ would unnecessarily separate the noun (‘database’) from the essential relative clause starting with ‘that.’

Current version: (page 8, lines 156-158)

Prior to development of this tool, the clinic relied on tracking methods requiring intensive manual data entry to populate a database that was not integrated with the medical record.

10. Line 189 insert a comma after 'cancer'

We agree that this sentence can be clarified. Rather than insert an additional comma before this nonessential clause (‘who have not yet initiated treatment’), we propose to adjust the wording to remove the need for an additional comma, which we believe makes the sentence easier to read.

Previous version:

Patients included in the study will be divided into two separate cohorts: cohort 1, patients with a confirmed diagnosis of head and neck cancer but who have not yet initiated treatment, and cohort 2, patients who have initiated treatment.

Revised version: (page 10, lines 196-199)

Patients included in the study will be divided into two separate cohorts. The pre-treatment cohort will include patients with a confirmed diagnosis of head and neck cancer but who have not yet initiated treatment. The post-treatment cohort will include patients who have initiated treatment and are undergoing additional treatment modalities and monitoring.

11. Line 190 sentence starting 'Outcomes...' syntax is poor, sentence is very repetitive and should be reviewed.

Thank you for your comment. We revised this sentence accordingly.

Previous version:

Outcomes consist of completion of sub-steps of each phase of treatment workup and treatment, as well as timely initiation of treatment and completion of treatment.

Revised version: (page 10, lines 201-202)

Outcomes for each cohort consist of completion of key steps in the evaluation and treatment process, and are summarized in Table 2

12. Line 194 'follow up' should be hyphenated

We appreciate your close read. In this revised version we hyphenate ‘follow-up’ in line 194 and throughout the manuscript.

13. Line 205 insert a comma after 'implementation'
We agree that this sentence could be improved. We have revised it as follows in accordance with both your and the other reviewers’ comments.

Previous version:

Patients who started a stage prior to implementation but completed it after implementation will be excluded from analysis for that particular stage.

Revised version: (Page 11, lines 212-215)

Patients who entered a cohort less than six months prior to implementation of the intervention will be excluded from that cohort. All patients entering a cohort after implementation of the tool will be considered exposed to the intervention for that cohort.

Reviewer #2: Comments and Responses

This protocol manuscript describes a planned, pilot observational study to assess the worth of using an information technology (IT) tool for tracking adherence to clinical guidelines in the clinical care of patients with head and neck cancer. The manuscript is well written, and the below comments aim at improving comprehension by the reader.

14. One key element of the analysis is the comparison based on information collected manually (in the preimplementation period) and information collected using a structured, IT tool. I believe authors should specify how they can ensure that the simple difference in data collection method cannot account for some of the eventual differences in outcomes between periods. For example, can manual collection lead to missing data and exclusion of patients from the preimplementation period in a manner that is non-random, thus introducing bias?

This is an excellent point. We have clarified on page 10, lines 191-193 that all data will be collected using chart review, rather than collecting post-intervention data from the health IT tool. The tool will be used in clinical care, but not for research purposes. The notable exception is that we will extract data from the tool on frequency and type of patient outreach conducted; this has been added as a footnote in Table 1 (page 20, lines 370-372) and this data will be used to describe tool implementation, rather than for comparative purposes.

Though it is possible that older charts may be less complete than newer charts, the nature of our chosen outcomes as completion of discrete events that are documented in the medical record in a standard way (e.g. CT scans, appointment dates, treatment initiation, tumor board meeting), makes it less likely that capturing these outcomes will be impacted by the retrospective nature of our data collection. It is possible that older clinical charts may be less likely to record some of the predictor variables of interest (e.g. history of substance use disorder, housing status), however given the importance of these factors in caring for our patient population, it is unlikely that retrospective chart review will be less likely to capture these factors.

New text (page 10, lines 191-193)

Unless noted, all clinical data will be collected from the medical record for both the intervention and control time periods, to minimize differential data collection methods that may influence comparisons.
15. I believe authors need to improve the explanation on "cohorts". Since they say that "patients included in the study will be divided into two separate cohorts: cohort 1, patients with a confirmed diagnosis of head and neck cancer but who have not yet initiated treatment, and cohort 2, patients who have initiated treatment", it isn't clear how it is that "patients who received a diagnosis of head and neck cancer and initiated any treatment will thus be present in both cohorts". Moreover, it is unclear what the relationship is between cohorts (1 and 2) and periods (before and after implementation of the IT tool).

Since this is unclear, we eliminated the use of ‘cohort 1’ and ‘cohort 2’ and instead used more descriptive names – ‘pre-treatment cohort’ and ‘post-treatment cohort’ (lines 132-135, 196-206, Table 2). Essentially, we are conducting two separate cohort studies where the time of cohort entry for the pre-treatment cohort is the time of diagnosis and the time of entry for the post-treatment cohort is the time of treatment initiation. There are some patients who had a diagnosis of head and neck cancer prior to the beginning of the control period, but who initiated treatment during the control period – these patients would be followed as part of the post-treatment cohort only. We have also clarified the language in the section entitled ‘Classification of exposure to the intervention’ to clarify how intervention exposure is determined (page 11, lines 210-219). For example, a patient is considered unexposed to the intervention for the pre-treatment cohort if they were diagnosed with head and neck cancer and initiated treatment prior to implementation of the tool.

16. The following paragraph in the manuscript also requires clarification. Authors say that "Patients will be included in the pre-treatment arm if they entered and completed a stage prior to implementation of the tool". Consequently, "patients who started a stage prior to implementation but completed it after implementation will be excluded from analysis for that particular stage", even though "patients who started a stage before implementation but never completed that stage will only be included if they started the stage more than 6 months prior to implementation". Isn't this likely to introduce bias, arguably this bias may go in favor of the IT tool (i.e., by excluding some patients failing to reach milestones)?

We agree that the restriction “patients who started a stage before implementation but never completed that stage will only be included if they started the stage more than six months prior to implementation” may be problematic, though the direction of bias introduced would likely be in favor of the control condition. The intention was to exclude patients who entered a cohort in the time immediately prior to tool implementation, however since milestones should be completed in substantially less time than six months, exclusion of patients with treatment delays that are less than six months may bias our estimates (again, in favor of control). We have revised our study design to include a more conservative approach – excluding all patients who enter a cohort within the six months prior to implementation of the health IT tool. This ensures that we have uniform inclusion criteria that are more interpretable and less likely to be biased.

Previous version:

Patients will be included in the pre-treatment arm if they entered and completed a stage prior to implementation of the tool (e.g. started and completed treatment prior to tool implementation). Patients who started a stage prior to implementation but completed it after implementation will be excluded from analysis for that particular stage. Patients who started a stage before implementation but never completed that stage will only be included if they started the stage more than 6 months prior to implementation. All patients starting a stage after implementation will be included in the post-treatment arm.
Revised version (page 10, lines 210-219):

Patients will be considered unexposed to the intervention if they entered one of the cohorts at least six months prior to implementation of the health IT tool intervention. Patients who entered a cohort less than six months prior to implementation of the intervention will be excluded from that cohort. All patients entering a cohort after implementation of the tool will be considered exposed to the intervention for that cohort. For example, if a patient was diagnosed with head and neck cancer three months prior to implementation of the intervention and initiated treatment one week after implementation of the intervention, they would be excluded from the pre-treatment cohort and would be included in the post-treatment cohort and considered exposed to the intervention.

17. On a semantic note, I suggest replacing the term "arm", both in the above sentence and in "all patients starting a stage after implementation will be included in the post-treatment arm", by another term, to avoid the connotation of a clinical trial. Also, perhaps the term "pre-treatment" in the first excerpted sentence above is not well suited to the intended meaning.

We agree with these points. Therefore, we have eliminated the use ‘arm’ with to make it clear to readers that we do not intend to conduct a clinical trial. We have instead referred to pre-and post-intervention periods as unexposed and exposed to the intervention, respectively. Lines 211-219 help clarify this point.

18. Can authors please elaborate a bit on which "models controlling for secular trend will be used for the primary and secondary outcomes for each cohort"? Again on a semantic note, this sentence implies that the comparison is between cohorts, when in fact--unless I misunderstand--the comparison is between periods, yet another reason to clarify the terminology.

This statement means that we plan to include a term for calendar year to allow adjustment for secular trend. As in many before-and-after designs, natural trend towards improvement over time is a major threat to validity. Without this adjustment, we may observe improvement associated with exposure to the health IT tool that is, in reality, due to steady improvement over time, rather than the tool itself. We have clarified the language in lines 231-233 to explain this reasoning. We have eliminated the phrase “for each cohort” to avoid any confusion that we are comparing between cohorts. As the reviewer mentioned, we are comparing between exposure to the health IT tool, as defined by time period. We hope that the above clarifications to points 15-17 also help clarify this further.

Previous version:

Models controlling for secular trend will be used for the primary and secondary outcomes for each cohort.

Updated version (page 12, lines 231-233):

Incorporation of a term for calendar time into our models for primary and secondary outcomes will allow us to control for secular trend. This strengthens the analysis by eliminating temporal improvements in clinical care processes that are unrelated to the intervention.

19. By "relative hazard", do authors mean "hazard ratio"?
Yes, these terms are synonymous. We have modified this to read ‘hazard ratio’ for clarity.

Previous text:

In Cox models for time to event, the sample of 300 will provide 80% power with in two-sided tests with alpha of 0.05 to detect a relative hazard of 2.25 for the effect of the intervention, after adjusting for a linear temporal trend as well as confounders.

Updated text (page 12, lines 240-242):

In Cox models for time to event, the sample of 300 will provide 80% power with in two-sided tests with alpha of 0.05 to detect a hazard ratio of 2.25 for the effect of the intervention, after adjusting for a linear temporal trend as well as confounders.