Author's response to reviews

Title: Attainment of Clinical Performance Targets and Improvement in Clinical Outcomes and Resource Use in Hemodialysis Care: A Prospective Cohort Study

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Iratxe Puebla  
Senior Assistant Editor  
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Dear Dr. Puebla:

We are submitting the attached revised manuscript entitled “Attainment of Clinical Performance Targets and Improvement in Clinical Outcomes and Resource Use in Hemodialysis Care: A Prospective Cohort Study” (1199896052112713) for consideration for publication in the *BMC Health Services Research*. After careful consideration of the reviewers’ comments, we have made several substantial changes to the paper.

We have addressed the major compulsory revisions as well as the minor essential revisions. The major changes we have made to manuscript include the following. We have added sensitivity analyses in which individual targets are examined only in those patients who had not already attained the target at baseline. Results from likelihood ratio tests to determine which targets contributed most to variation in the outcomes of interest are also reported. We have also indicated where results did not reach a more strict, Bonferroni-corrected threshold for statistical significance. Finally, we have significantly expanded the limitations section of our manuscript to emphasize the main reviewer concerns. Point-by-point responses to each of the reviewers’ suggested revisions follow.

We thank you, the editorial director, and the referees for your thoughtful review of our manuscript and for providing us the opportunity to improve and resubmit this work.

Sincerely,  
Neil R. Powe, MD, MPH, MBA  
Director, Welch Center
Reviewer 1

Major Compulsory Revisions:

1. Page 5, study design: please describe in the manuscript how the EQUAL patients were derived from CHOICE. Are they the survivors? What is the timing of EQUAL and CHOICE relative to each other? I believe that neither study was an intervention trial and the text should state that.

   - We agree that the description of the EQUAL and CHOICE cohorts may have introduced confusion. Basically, the EQUAL study was a study of processes of care and outcomes in the CHOICE cohort, so the original cohorts were the same; however, a select group of hemodialysis patients who survived at least 6 months comprised the cohort for the study reported here. Thus, on p. 5 (paragraph 1), we have now clarified this relationship: “The ESRD Quality (EQUAL) study was designed to measure processes of care and outcomes in the Choices for Healthy Outcomes in Caring for End-Stage Renal Disease (CHOICE) [25] cohort. The population examined here consisted of 668 incident hemodialysis patients who were treated at 74 U.S. not-for-profit, free-standing outpatient dialysis clinics in 18 states. To be included in this study, patients had to be treated with hemodialysis and survive at least 6 months.” Additionally, we have stated that neither study involved intervention: “Neither the CHOICE nor the EQUAL study involved the use of any intervention.”

2. Page 18: authors include as a limitation: "because most of the factors that we studied here were not the subject of national guidelines at the time we started our study, guideline-directed therapeutic intent cannot be shown”. The authors should be more specific about how the KDOQI guidelines differed at the time (’95-'98) from the present targets which are used to judge the current study cohort.

   - We have now added more specific information about the KDOQI guidelines during the study period (vs. current guidelines) to the limitations on p. 19: “…guideline-directed therapeutic intent cannot be shown. The hemoglobin, dialysis dose, and vascular access targets were in place in 1997 and have not changed since this time, although they were not yet widely implemented by 1998. The albumin and Ca-P targets used here were not introduced until well after the study period.”

3. A major limitation of the study is the use of the word "attain" and inclusion of patients who were at the target at initiation. Healthier patients were already at target values at enrollment and therefore they did not "attain" the targets. These healthier patients would be expected to have fewer hospitalizations, lesser morbidity, etc. This would be a more valuable study if the patients who were NOT at target at enrollment, who experienced changes in albumin, hgb, Kt/V, etc were compared to those with similar baseline values who did not improve.

   - We agree that the use of the term “attain” does not convey that the baseline values were not taken into account; however, our definition of attainment of targets as values at 6 months (pp. 5-6) makes this clear. Additionally, we have performed further sensitivity
analyses for mortality and hospitalization outcomes, in which those patients who were already at the target in question at baseline were excluded. These results have been added (pp. 11-14). The hospitalization results were mostly robust to this exclusion, although we did lose significant numbers of patients who were already at calcium-phosphate (n≈500) and dialysis dose (n≈300) targets at baseline. Mortality results for albumin only remained significant with this exclusion. Note that only ~25 patients had attained zero targets at baseline; only for the analysis of hospital days did we still see a significant trend among this tiny population.

4. The possibility or even likelihood that albumin and hgb are affected by volume status is not entertained here. Patients who "attained" their targets may have been able to achieve them because of better ultrafiltration, achievement of dry weight. Otherwise the achievement of an increase in albumin in a 6 month time period is not easy to accomplishment. Evidence that increases in epo, hgb, Kt/V etc can do this is slight. While the dialysis community made great strides in many clinical performance outcomes in the late years, for albumin "only 39% of patients achieved a serum albumin concentration of >4.0 g/dl in the last quarter of 2003". This is not to dispute that albumin is associated with outcome; but to imply that it is "attainable", unless through ultrafiltration, is too simplified.

-We agree that this possibility should be addressed. Thus, on p. 19, we have added this particular issue to the limitations: “…the biological markers studied may be influenced by other factors than the quality of providers’ care. For example, albumin and hemoglobin levels could be affected in part by the degree of ultrafiltration achieved.”

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Minor Essential Revisions:

1. authors should state method of albumin assay, BCP or BCG, whether all patients had same assay or not.

-All patients had the same assay (BCG method) at the same central laboratory. This information has been added to the top of p. 6: “All serum albumin levels were measured at a central laboratory using the Bromocresol Green method (CV, 1.1%).”

2. page 11, top and again at bottom of page 11, page 12, page 13: "39% (n=133) had attained 0/1 targets at baseline"; this should read "attained 0 OR 1 target out of 5" since it reads as "0 out of 1 target" as later in the sentence you say "attained 2, 3, and 4/5 targets at baseline" which I took to be 2, 3 and 4 OF 5.

-We agree that the use of slashes was confusing. Thus, we have changed all of the wording on pp. 11-15 to read “0 or 1 targets” and “4 or 5 targets,” as we intended.
Reviewer 2

General
The data this relates to predates current quality initiatives but nevertheless I think the conclusions are sound and that the paper provides a useful addition to current knowledge in this area.

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

Was the methodology for albumin measurement uniform across the participating centres?

-All patients had the same assay (BCG method) at the same central laboratory. This information has been added to the top of p. 6: “All serum albumin levels were measured at a central laboratory using the Bromocresol Green method (CV, 1.1%).”

The target level for albumin is given as >= 4mg/dl on page 6, and should be corrected

-Thank you for pointing out this error. This has now been corrected to units of “g/dl” on p. 6.

The quality of Figure 1 should be improved.

-We will assure through the editorial office that our figure is of high enough resolution before publication.

Discretionary Revisions (which the author can choose to ignore)

Whilst accepting the association between target achievement and outcome, it is difficult to judge how much this relates to quality of care and how much relates to the fixed characteristics of the patient. The authors do refer to this in the discussion but this could usefully be amplified. More could also be made of the change in target achievement from baseline to 6 months which might be a route to addressing this issue.

-We agree that the characteristics of the patient which might or might not allow target attainment could be further emphasized. Thus, on p. 19, we have emphasized this point: “…as with any study of clinical performance targets, the biological markers studied may be influenced by other factors than the quality of providers’ care…Importantly, there may be fixed and possibly unmeasurable patient characteristics that might or might not allow target attainment with exposure to same quality of provider care. Such characteristics might also affect the amount of time needed to attain a goal, which may be more or less than 6 months for some patients and some targets.”
Reviewer 3

General Comments: the authors present a manuscript in which they evaluate whether standard clinical performance measures for hemodialysis patients such as adequate albumin and hemoglobin levels, calcium phosphate product, dialysis adequacy as measured by the KT/V > 1.2, and fistula use, are associated with less mortality, fewer hospitalizations, and decreased costs. Attainment of clinical guideline targets was associated with improved survival, fewer hospitalizations, and less overall costs for one of the outcomes (albumin). Using multivariate modeling, the authors found that that with each additional attainment of a guideline target was associated with better survival, fewer hospitalizations and hospital days, however only attainment of albumin goals was associated with improvement in costs. The authors conclude that attainment of core dialysis guideline targets is associated with improved survival and they offer their manuscript as proof of concept. The paper as written suffers from some methodological concerns regarding data analysis and presentation.

Major Comments: The major concern regarding the manuscript is that the authors are performing multiple analyses on the same cohort; however they neither address the need for nor conduct corrections for multiple comparisons. The cohort is sufficiently small that the consideration for Bonferroni or some similar adjustment for the multiple analyses with multiple outcomes might need to be considered.

A second concern is that the authors present multiple, repetitive analyses with little concern or discussion of the clinical consequences of failure to attain guideline goals, or how patient characteristics might influence the ability to attain goals. Guidelines that are easier to control by the treating nephrologist tend to have better attainment compared to those goals that are more under the patient control (i.e. albumin levels which reflect nutritional status or level of inflammation versus attainment of hemoglobin levels that are more easily treated by adjustment of erythropoietin dose). Patients who have diabetes or other chronic co-morbid conditions are also less likely to have attainment of certain guideline goals, but appear more likely to attain others. Prioritization of goals, specifically, an analysis to ascertain which guidelines contribute the most to improved survival would be useful in prioritizing guideline goals. Also, understanding if there are interactions between certain goals would also be useful information as well.

Another concern is that very few patients have attainment of all the guideline goals, which brings up the issue that this study might be underpowered to ascertain all results. This should be listed as a limitation of the data.

Finally, in the discussion the authors state that the data meet criteria for causal influence. The authors should remember that this is a longitudinal observational study, and as such, only associations with outcomes can be ascertain, not cause and effect. The authors also conclude that physicians taking care of dialysis patients should be more willing and less skeptical of current guidelines. The authors should recall that many of the guidelines have some randomized control trial evidence to substantiate the specific guideline; however, some guidelines are by consensus or use very small outdated trials
as the basis for the guideline and have not been fully evaluated in rigorous randomized controlled trials. Given that it would be unethical to randomize patients to low or high albumins or catheters versus fistulas, some guidelines may never be able to be randomized and we are left with observational data. However, the value of observational data should not be overstated.

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

1. The need to adjust for multiple comparisons.

We agree that there is a possibly of random statistically significant results with the examination of multiple outcomes in a small cohort. Thus, we have set a second Bonferroni-corrected threshold P value of 0.01 for the individual target analyses (p. 9): “Statistical significance was set at P<0.05. However, because examining five targets in a small sample might lead to randomly significant results at this cutoff, we decided to also set a Bonferroni-correct threshold P value of 0.05/5=0.01 for the individual target analyses.” In the results, we have noted where originally significant results in the individual target analyses did not reach this significance under this stricter threshold (pp. 11-15). Generally most individual target results were robust to this correction, especially those associations between target and decreased hospitalizations, hospital days, and hospital costs. Dialysis dose and Ca-P product were no longer significantly associated with mortality using this threshold. Interactions were also tested; there were no statistically significant pairwise interactions (with Bonferroni correction for multiple comparisons) between targets in the association with mortality. There was a significant interaction between albumin and dialysis dose for hospital admissions and several interactions between all five targets for hospital days; however, we do not have sufficient power to explore stratified analyses.

2. A model that has all predictors of interest and evaluates which guideline contributes most to the outcomes of interest.

Unfortunately, our sample size does not allow all the comparisons that would be necessary to determine which factor or combination of factors. This limitation has now been emphasized on pp. 18-19: “…this study was underpowered to determine which particular individual targets or combinations among the five performance targets examined yield the most benefit in terms of each outcome.” However, we were able to run likelihood ratio tests in adjusted models to determine which target contributed most to the variation in each outcome. These results are now reported on pp. 11-15. Basically, albumin and hemoglobin contributed most to mortality, with calcium-phosphate contributing slightly less. All targets except dose contributed significantly to hospital admissions, whereas all targets had an equal contribution to hospital days. Albumin and access, to a lesser extent, contributed to hospital costs.

3. Better illucidation of the limitations of the data.
-We have significantly expanded our discussion of the limitations of this study in response to both yours and other reviewers’ comments. First, we have added that patient characteristics might influence ability to attain goals (p. 19): “…there may be fixed and possibly unmeasurable patient characteristics that might or might not allow target attainment with exposure to same quality of provider care.” Additionally, we have emphasized the point that some guidelines are easier to control than others (p. 19): “Of course, some targets may be more easily modified (e.g., hemoglobin through erythropoietin) than others (e.g., albumin, which is influenced by patients’ nutritional and inflammatory states).” As mentioned above, the fact that the study was underpowered to determine which targets contributed most to the outcomes has been emphasized (pp. 18-19): “…this study was underpowered to determine which particular individual targets or combinations among the five performance targets examined yield the most benefit in terms of each outcome.” Finally, we have emphasized in the limitations that conclusions from observational data should not be overstated (p. 19): “…it should be remembered that this is an observational study and that only the associations between target and outcome can be ascertained, not cause and effect. Despite the fact that some clinical performance targets have been chosen based upon observational data and consensus (and could never be part of an ethical randomized trial), the value of observational data should not be overstated.”

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

Abstract: All abbreviations and eponyms should be defined before use (i.e. EQUAL).

-All abbreviations (RH, IRR, CI) and acronyms (EQUAL) have been defined in the abstract.

Table 1: Define all definitions used in the table.

-Abbreviations have either been written out or defined in the tables.