PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Observational follow up study following two cohorts of children with severe pneumonia after discharge from day-care clinic/hospital in Dhaka, Bangladesh
AUTHORS	Ashraf, Hasan ; Alam, Nur; Chisti, Md.; Salam, Mohammed; Ahmed, Tahmeed; Gyr, Niklaus

VERSION 1 - REVIEW

REVIEWER	George J. Fuchs, M.D. Professor of Pediatrics University of Arkansas for Medical Sciences Little Rock, AR USA I have no competing interests
REVIEW RETURNED	19-Mar-2012

THE STUDY	Only after reading the entire manuscript did it become clear that it the study focus was the need for subsequent hospital referral after completion of the initial day care vs. hospital management. It initially appeared the manuscript is the report of results of two separate studies when instead it is of long-term post management follow-up of two different populations of children enrolled in two studies rather than the results of two studies. 2. The manuscript needs significant editing by a native English speaker.
GENERAL COMMENTS	General comments: 1. The study results are meaningful and have practical implications. 2. The manuscript needs editing by a native English speaker. Specific Comments 1. Abstract, Description of the setting: this needs to also convey that the study was done in Dhaka, Bangladesh. 2. Abstract, Results: The authors appropriately define the method of group comparison as the OR 95% CI. However, thereafter in the abstract and throughout the manuscript, the authors present the OR and CI in an unusual fashion. For example, instead of 0.9% (95% CI, 0.4-2.4%) the manuscript would be easier to read as 0.9 (0-4-2.4) and eliminate the unnecessary percentage symbols and “95% CI”. 3. Abstract, penultimate sentence of Results and elsewhere: The exact focus of the study is unclear and only after reading the entire manuscript did I understand this sentence. Initially it appeared illogical to compare referral to the hospital of day care management children to hospitalized children because the latter group was already in the hospital. After reading the manuscript it became clear it was the need for hospital referral well after completion of subsequent to the initial day care vs. hospital management. 4. Page 2, first sentence of Strengths of the study and throughout

	the manuscript: The authors compare the results of the current study population to and use as a point of reference the recovery of severe acute malnutrition (SAM). SAM is not relevant to the current study and comparison of the results of the current study population to SAM should be omitted. 5. Page 3, Introduction: In the sentence stating that “an estimated 1.9 million children died from ARI, inclusion of 95% CI is not needed. 6. Page 3, last sentence of the Introduction: The day care model management hopes to provide are curative or case management benefits rather than public health benefits. 7. Page 4, second sentence of Study design: This reads as if the current report is the results of two separate studies when instead it is the long-term post management follow-up of two different populations of children enrolled in two studies rather than the results of two studies. 8. Page 7, Interventions: This should be summarized in a few sentences and the reader can be referred to the report of the cited study for details.

REVIEWER	Phil D. Seidenberg Assistant Professor Boston University Center for Global Health & Development (CGHD) United States
REVIEW RETURNED	25-Mar-2012

THE STUDY	1) Research question- I think the current version lacks consistency in presenting the overall research question the paper is trying to address, i.e., there seems to be descrepancies between the abstract and the main body of the paper. Trying to interpret the results then becomes difficult without a consistent research question being presented. If I were to write the question, I think it can be broken into 3 parts- 1) To describe the features of relapse, morbidity/mortality following successful discharge for severe pneumonia in children under 5 in urban Bangledesh; 2) To compare these features to another commonly presenting diagnosis (SAM)- this can be removed if the authors choose, but then the focus on SAM and its post-discharge complications needs to be either removed or featured less prominently; and 3) to Compare relapse, morbidity, mortality, and re-hospitalization rates between an outpatient-managed group and a hospital-managed group over 3 months. If these aren't clearly stated, and the paper isn't re-worked to focus on these themes, it won't make any sense. 2) Study Design- while it's appropriate, it needs to be better presented in the paper so that the reader can understand. I would also consider removing the data from the observational period from this, thus only compare 3 month post-discharge outcomes of the RCT kids, too much confounding to include the prior kids; or if they are included, we need to see the differences between these groups on the 'intervention' side. The Section on 'Study Design' really doesn't tell the reader much, it instead refers to the main paper and study question of the RCT. It needs work. 3) Description of study participants- I think these are adequately described for the main paper, however this is a follow-on study for those discharged and followed for 3 months post-discharge, thus a

	description of the 'health' status at the time of discharge of these kids need to be presented in a Table (replace Table 1). The reader really needs to see a comparison of these two groups at time of discharge, not at admission, because the whole research question revolves around comparing 3-month follow-up outcomes of severe pneumonia kids. If the two groups are entirely different at discharge (i.e. if the intervention children are discharged 'sicker' than the hospital ones), then we need to see this because it will completely alter our ability to interpret the results. I'm also a bit confused on the inclusion criteria listed (WHO severe pneumonia) and some data presented in Table 4. WHO severe pneumonia definition includes in-drawing (not speaking of very severe), and yet in Table 4 it looks like only 291 (48%) of kids actually had in-drawing. Please explain this. Were kids with WHO very severe pneumonia excluded? Additionally, I think the group of kids enrolled in the uncontrolled out-patient treatment feasability study really need to be excluded from the study and subsequent data analysis, many confounders for this. Because no sample size calculations are presented, would be great to see if they're even needed to interpret overall study question(s). Bottom line, if this paper is going to be re-written, the status of children at discharge needs to be presented and compared in a Table so that the reader can intepret the main study question (3-month follow-up outcomes comparing the intervention vs. hospital groups). This should include discharge vitals, percent hypoxemic on discharge (I assume all are not but we need to see this), median length of hospitalization, etc. If the authors want to continue to explore predictors of 'successes' or 'failures' for 3-months of follow-up (which is a good research question), then they need to add this is a specific objective and outcome measure. 5) Methods Section- while it's great to see the methods focus on the initial study's research question (RCT of day-care kids and hospital-based treatment of severe pneumonia), I think for this paper the methods need to better describe the follow-up evaluation for those children discharged from the main study. There is a section on this (Bolded 'Follow up Study') but it needs better description. Were all data recorded based on historic findings, or did the study physicians record any vitals (O2 sat, Temperature, RR) or observe some of the signs (chest in-drawing, difficulty in breathing)? If the study physicians did not, this needs to be stated in the methods section. The Study Participant section needs to focus more on the kids studied in this comparison, not the main paper. This essentially means that the children surviving to discharge rather than the children entering the main study (not much of a difference based on the Flow Chart presented, but it still needs to be clearly stated). Since this paper really isn't comparing the treatment methods in the original RCT, rather the 3-month outcomes for those kids discharged from the main study, the methodology for the main study interventions can be shortened and the paper in Peds referred for further clarification. It can also be included as an appendix. 6) Outcome measures- these need to be tightened in the main paper and better presented. I think they're all there, but in the main body of the paper (under Data Analysis) they're not clear. Results also

present many additional findings which the abstract and methods sections do not reference (one example, risk factors for treatment failure which is an entire Table).

I've mentioned above a way of better defining the research question(s), the outcomes measures should follow this and be clearly stated. The results section then needs to be a reflection of these outcome measures.

7) Abstract/Summary/Limitations- unfortunately I'm not sure the authors best describe some of the key summary points nor expand well on them in the Discussion. There's a lot of important information presented but the authors actually do the paper a disservice by not focusing on many of these. Part of the problem may be that they need to better present the research question(s) and study design.

Abstract- needs some editing but can be salvaged. Objectives- need to include the comparison between the two treatment arms and the time period followed (3 months). Design- not well stated, the design needs to focus on 3 months follow-up rather than the original RCT and feasability study. Participants- needs to state kids who survived to discharge from severe pneumonia. Interventions- really this paper doesn't have any interventions, so this is confusing. It's an observational study following 2 cohorts discharged from severe pneumonia for 3 months. Conclusions- not sure what the author's are now stating, conclusion should be: 1) there are considerable morbidities in children discharged with severe pneumonia (assuming they're healthy at discharge, reader needs to see this); 2) no differences were found when comparing major outcomes (death, re-hospitalization, hypoxemia) during 3-months of follow-up between 2 groups; and 3) risk factors for poor outpatient outcomes include.....

Discussion- lots of focus on compairing severe pneumonia with SAM, although this isn't poised previously as a research question. If it's a focus, then it needs to be included as a research question and outcomes measure, but as of now it feels misplaced. Again, the discussion focuses on Admin risk factors (and not in adjusted HRs and logistic regression, which it really should be) and poor 3-month outcomes, an interesting question and important but not really presented earlier as a focused research question of this paper.

Limitations- not sure why cost effectiveness is a limitation of the current study, nothing previously mentions the cost of the 'intervention' and follow-up as being a research question. The authors need to focus on the current paper, its data analysis and limitations (such as any objective data rather than historic data for morbidity). Same argument can be said for community follow-up and sustainability, these aren't limitations but other interesting questions to focus.

8) Stats- need to be better explained. Although I'm not a biostatistician, there seems to be a paucity of information for comparing the data in this section, can be expanded.

10) References- I would reference a few of tthe many successful published studies on Community Case Management of severe pneumonia (recently published studies on Lady Healthcare Workers in Pakistan, Appis and No-SHOTS, just to name a few). Because this is what the current study is effectively trying to compare, an out-patient model and hospital-based model AND 3-month follow-up

	outcomes of children with severe pneumonia, I think it would be important to reference.
RESULTS & CONCLUSIONS	1) Results- as mentioned in greater detail in the above section, while I think the results are extremely important and answer a few interesting research questions, these questions need to be better stated, re-organized, and better presented to the reader prior to the Results section. A baseline Table of 'health' status of discharged patients needs to be included in the results, if not it's impossible to interpret the results. The Tables should also be re-organized to reflect the study objectives and outcomes measures presented earlier in the paper. Results section is also too wordy, if the Table can better explain some of the results, the authors should only focus on interesting result findings and refere to greater information/depth in the Tables. 2) Conclusions- apologies for including more information on this in the above section, but I think the discussion needs to focus more on the stated research questions, which should be adjusted and re-presented in the Methods section. For example, if one of the objectives and research questions presented in the Methods section is to compare complications/morbidity/mortality 3-month follow-up outcomes between children discharged after severe pneumonia vs. SAM, then the discussion can continue to focus on this. If not, it seems superfluous and not the focus of the paper. Similarly, if one of the stated objectives of the paper is to identify risk factors upon admission for eventual 3-month follow-up mordibity/re-admission/mortality outcomes, then the discussion can focus on this as well. I know I've mentioned this before but unless the reader can see that the 2 groups at discharge are either equally healthy or sick, then it's extremely difficult to interpret any of the data. Presumably even if the groups differ on presenting severity/hypoxemia, they should be similar upon discharge so that we can evaluate 3-month follow-up outcomes. In the limitations section, there also needs to be a discussion of causality over time for some of the outcomes measured. For example, if a child is discharged and develops fever, in-drawing, cough 2 months after discharge, it's difficult to attribute these symptoms with 100% certainty to an admission which occurred 2 months ago. There is no information presented on the frequency of healthcare workers needing to find families in the community if they missed follow-up visits. This is mentioned in the methods section, and follow-up compliance is discussed at length. However, if there are data available between the 2 groups which presents frequency of community visits to remind families to 'comply' with follow-up, this should be presented and discussed.
REPORTING & ETHICS	There is no section on REC approval, Informed consent, or ethical considerations. This needs to be added.
GENERAL COMMENTS	I think these are really good and important research questions to ask, and I do think data are there to answer them in the current study. However, the paper is really poorly organized and needs to be re-written in sections, tightened in others, and better organized. Major Flaws

	1) Inclusion of the out-patient kids from the feasability study- is this really warranted? To me it introduces too many confounders and in effect is combining a pre/post design with a prospective study. Presenting a sample size calculation, if one were determined prior to the study for the percent difference in 3-month outcomes when comparing 'intervention' and 'control' groups, would be helpful; if not, perhaps the authors should calculate to see if these additional cases are needed, but to me it not only seems confusing but hinders the methodology. 2) Baseline Discharge status- because one of the primary study questions is to compare 3-month follow-up outcomes between the 2 groups, there really needs to be a Table which compares the 2 groups upon discharge so that we can ascertain that the groups were equally 'healthy' or 'sick.' If not, I think the results are too difficult to interpret. 3) Research questions- these should be re-focused on the strengths of the study and clearly stated (see my initial comments above). Once this is done, I think it will be easy to organize the data, tables and conclusions.

VERSION 1 – AUTHOR RESPONSE

Response to Reviewer (s)' Comments
Reviewer No. 1
1. Comment: Only after reading the entire manuscript did it become clear that it the study focus was the need for subsequent hospital referral after completion of the initial day care vs. hospital management. It initially appeared the manuscript is the report of results of two separate studies when instead it is of long-term post management follow-up of two different populations of children enrolled in two studies rather than the results of two studies.
Response: Thanks for the comment.
2. Comment: The manuscript needs significant editing by a native English speaker.
Response: The manuscript has been thoroughly edited by a native UK English speaker, Dr Mark Pietroni (markpietroni@gmail.com), Medical Director of icddr,b.
General comments:
1. Comment: The study results are meaningful and have practical implications.
Response: Thanks for the nice comment.
2. Comment: The manuscript needs editing by a native English speaker.
Response: As stated above, the manuscript has been edited by a native UK English speaker, Dr Mark Pietroni.
Specific Comments
1. Comment: Abstract, Description of the setting: this needs to also convey that the study was done in Dhaka, Bangladesh.
Response: In the abstract, description of the setting: it is now mentioned that the study was done in Dhaka, Bangladesh (page 1).
2. Comment: Abstract, Results: The authors appropriately define the method of group comparison as the OR 95% CI. However, thereafter in the abstract and throughout the manuscript, the authors present the OR and CI in an unusual fashion. For example, instead of 0.9% (95% CI, 0.4-2.4%) the manuscript would be easier to read as 0.9 (0-4-2.4) and eliminate the unnecessary percentage symbols and “95% CI”.
Response: As suggested by the reviewer, we have now eliminated the unnecessary percentage symbols and “95% CI” from the abstract (page 1, 2).
3. Comment: Abstract, penultimate sentence of Results and elsewhere: The exact focus of the study is unclear and only after reading the entire manuscript did I understand this sentence. Initially it

appeared illogical to compare referral to the hospital of day care management children to hospitalized children because the latter group was already in the hospital. After reading the manuscript it became clear it was the need for hospital referral well after completion of subsequent to the initial day care vs. hospital management.
Response: The exact focus of the study is now made clear by changing the statement in the abstract as required re-hospitalization after completion of initial day care vs. hospital-care management (page 1).
4. Comment: Page 2, first sentence of Strengths of the study and throughout the manuscript: The authors compare the results of the current study population to and use as a point of reference the recovery of severe acute malnutrition (SAM). SAM is not relevant to the current study and comparison of the results of the current study population to SAM should be omitted.
Response: As suggested by the reviewer that SAM is not relevant to the current study and comparison of the results of the current study population to SAM is also not relevant, we have omitted this sentence.
5. Comment: Page 3, Introduction: In the sentence stating that "an estimated 1.9 million children died from ARI, inclusion of 95% CI is not needed.
Response: As suggested, in the sentence stating that "an estimated 1.9 million children died from ARI, 95% CI is now excluded (page 3).
6. Comment: Page 3, last sentence of the Introduction: The day care model management hopes to provide are curative or case management benefits rather than public health benefits.
Response: The last sentence of the Introduction has been changed to curative or case management benefits rather than public health benefits (page 4).
7. Comment: Page 4, second sentence of Study design: This reads as if the current report is the results of two separate studies when instead it is the long-term post management follow-up of two different populations of children enrolled in two studies rather than the results of two studies.
Response: The statement of Study design has now been completely changed (page 4).
8. Comment: Page 7, Interventions: This should be summarized in a few sentences and the reader can be referred to the report of the cited study for details.
Response: The Interventions are now summarized in a few sentences (page 5) and the readers are referred to the report of the cited study for details (Reference # 11, page 16).
Reviewer No. 2
1) Comment: Research question- I think the current version lacks consistency in presenting the overall research question the paper is trying to address, i.e., there seems to be discrepancies between the abstract and the main body of the paper. Trying to interpret the results then becomes difficult without a consistent research question being presented. If I were to write the question, I think it can be broken into 3 parts- 1) To describe the features of relapse, morbidity/mortality following successful discharge for severe pneumonia in children under 5 in urban Bangladesh; 2) To compare these features to another commonly presenting diagnosis (SAM)- this can be removed if the authors choose, but then the focus on SAM and its post-discharge complications needs to be either removed or featured less prominently; and 3) to Compare relapse, morbidity, mortality, and re-hospitalization rates between an outpatient-managed group and a hospital-managed group over 3 months. If these aren't clearly stated, and the paper isn't re-worked to focus on these themes, it won't make any sense.
Response: The in-consistency in presenting the overall research question has been addressed and removed from the modified version of the manuscript. The discrepancies between the abstract and the main body of the paper are also removed. Similarly, the focus on SAM and its post-discharge complications are completely removed. The research questions have now been properly addressed in the objectives of the revised version of the manuscript (page 4).
2) Comment: Study Design- while it's appropriate, it needs to be better presented in the paper so that the reader can understand. I would also consider removing the data from the observational period from this, thus only compare 3 month post-discharge outcomes of the RCT kids, too much confounding to include the prior kids; or if they are included, we need to see the differences between these groups on the 'intervention' side.

The Section on 'Study Design' really doesn't tell the reader much; it instead refers to the main paper and study question of the RCT. It needs work.
Response: The data from the observational study is now removed as suggested by the reviewer. The statement of the study design has now been completely changed (page 4).
3) Comment: Description of study participants- I think these are adequately described for the main paper, however this is a follow-on study for those discharged and followed for 3 months post-discharge, thus a description of the 'health' status at the time of discharge of these kids need to be presented in a Table (replace Table 1). The reader really needs to see a comparison of these two groups at time of discharge, not at admission, because the whole research question revolves around comparing 3-month follow-up outcomes of severe pneumonia kids. If the two groups are entirely different at discharge (i.e. if the intervention children are discharged 'sicker' than the hospital ones), then we need to see this because it will completely alter our ability to interpret the results.
I'm also a bit confused on the inclusion criteria listed (WHO severe pneumonia) and some data presented in Table 4. WHO severe pneumonia definition includes in-drawing (not speaking of very severe), and yet in Table 4 it looks like only 291 (48%) of kids actually had in-drawing. Please explain this. Were kids with WHO very severe pneumonia excluded?
Additionally, I think the group of kids enrolled in the uncontrolled out-patient treatment feasibility study really needs to be excluded from the study and subsequent data analysis, many confounders for this. Because no sample size calculations are presented, would be great to see if they're even needed to interpret overall study question(s).
Response: The data of Table 1 is now changed to the ‘health’ status at the time of discharge of study children (page 11). The two groups were comparable at the time of discharge, except significantly more infants receiving hospital-care, as shown in Table 1 (page 11).
The current Table 4 (changed a lot after excluding data from the observational study) has now shown that 127 (35%) of kids had history of in-drawing (page 14), which was noted by the mothers at home. But, 358/360 (99.4%) of the enrolled children actually had chest in-drawing on admission, as shown in Table 1 of the published paper in Pediatrics (Ref # 11, page 16). Yes, kids with WHO very severe pneumonia were excluded from the study. The data of kids enrolled in the uncontrolled out-patient treatment feasibility study are now excluded from the revised version of the manuscript.
4) Comment: Bottom line, if this paper is going to be re-written, the status of children at discharge needs to be presented and compared in a Table so that the reader can interpret the main study question (3-month follow-up outcomes comparing the intervention vs. hospital groups). This should include discharge vitals, percent hypoxemic on discharge (I assume all are not but we need to see this), median length of hospitalization, etc. If the authors want to continue to explore predictors of 'successes' or 'failures' for 3-months of follow-up (which is a good research question), then they need to add this is a specific objective and outcome measure.
Response: As suggested by the reviewer, this paper is now re-written, the status of children at discharge is now presented and compared in Table 1 (page 11), so that the reader can interpret the main study question (i.e. 3-month follow-up outcomes comparing the intervention vs. hospital groups). Table 1 now included discharge vitals such as pulse, respiration, temperature, percent hypoxemic on discharge, and median length of clinic stay/hospitalization (page 11). As the authors now wanted to explore the predictors of 'failures' for 3-months of follow-up, they also added this as a specific objective (page 4) and outcome measure (page 6) in the revised version of the manuscript.
5) Comment: Methods Section- while it's great to see the methods focus on the initial study's research question (RCT of day-care kids and hospital-based treatment of severe pneumonia), I think for this paper the methods need to better describe the follow-up evaluation for those children discharged from the main study. There is a section on this (Bolded 'Follow up Study') but it needs better description. Were all data recorded based on historic findings, or did the study physicians record any vitals (O2 sat, Temperature, RR) or observe some of the signs (chest in-drawing, difficulty in breathing)? If the study physicians did not, this needs to be stated in the methods section. The Study Participant section needs to focus more on the kids studied in this comparison, not the main paper. This essentially means that the children surviving to discharge rather than the children entering the main study (not

much of a difference based on the Flow Chart presented, but it still needs to be clearly stated).
Since this paper really isn't comparing the treatment methods in the original RCT, rather the 3-month outcomes for those kids discharged from the main study, the methodology for the main study interventions can be shortened and the paper in Peds referred for further clarification. It can also be included as an appendix.
Response: Methods Section - As thought by the reviewer, the method section now better described the follow-up evaluation of children discharged from the main RCT study under the Bolded 'Follow up Study' (pages 5, 6). All data recorded are based on historic findings as well as study physician's record of vitals like pulse, RR, Temperature, and O2 saturation, as shown in Table 1 (page 11). The observation made by study physicians like the signs of chest in-drawing, and difficulty in breathing are also shown in Table 1 (page 11). The Study Participant section now focused more on the kids studied in this comparison of follow-up period, not on the main paper. This essentially means that the children surviving to discharge were compared rather than the children entering the main study.
As suggested by the reviewer, the methodology section for the study interventions is shortened (page 5) and the paper in Peds is referred (Reference # 11, page 16).
6) Comment: Outcome measures- these need to be tightened in the main paper and better presented. I think they're all there, but in the main body of the paper (under Data Analysis) they're not clear. Results also present many additional findings which the abstract and methods sections do not reference (one example, risk factors for treatment failure which is an entire Table).
I've mentioned above a way of better defining the research question(s), the outcomes measures should follow this and be clearly stated. The results section then needs to be a reflection of these outcome measures.
Response: The outcome measures are now tightened in the main paper and clearly presented in the main body of the paper (under Data Analysis) (page 6). Results also presented many additional findings which the abstract and methods sections now referenced, such as the exploration of the predictors of "failures" for 3-months of follow-up, which are now presented and discussed in details. Similarly, the differences in the morbidity patterns between the groups are also presented in the abstract, result, and discussed in details in the revised version of the manuscript.
Now, a better defined research question(s) addressed (page 4), the outcome measures followed these research questions (page 6). The results section also reflected these outcome measures (pages 7, 8).
7) Comment: Abstract/Summary/Limitations- unfortunately I'm not sure the authors best describe some of the key summary points nor expand well on them in the Discussion. There's a lot of important information presented but the authors actually do the paper a disservice by not focusing on many of these. Part of the problem may be that they need to better present the research question(s) and study design.
Abstract- needs some editing but can be salvaged. Objectives- need to include the comparison between the two treatment arms and the time period followed (3 months). Design- not well stated, the design needs to focus on 3 months follow-up rather than the original RCT and feasibility study. Participants- needs to state kids who survived to discharge from severe pneumonia. Interventions- really this paper doesn't have any interventions, so this is confusing. It's an observational study following 2 cohorts discharged from severe pneumonia for 3 months. Conclusions- not sure what the author's are now stating, conclusion should be: 1) there are considerable morbidities in children discharged with severe pneumonia (assuming they're healthy at discharge, reader needs to see this); 2) no differences were found when comparing major outcomes (death, re-hospitalization, hypoxemia) during 3-months of follow-up between 2 groups; and 3) risk factors for poor outpatient outcomes include.....
Discussion- lots of focus on comparing severe pneumonia with SAM, although this isn't poised previously as a research question. If it's a focus, then it needs to be included as a research question and outcomes measure, but as of now it feels misplaced. Again, the discussion focuses on Admin risk factors (and not in adjusted HRs and logistic regression, which it really should be) and poor 3-month outcomes, an interesting question and important but not really presented earlier as a focused

research question of this paper.
Limitations- not sure why cost effectiveness is a limitation of the current study, nothing previously mentions the cost of the 'intervention' and follow-up as being a research question. The authors need to focus on the current paper, its data analysis and limitations (such as any objective data rather than historic data for morbidity). Same argument can be said for community follow-up and sustainability, these aren't limitations but other interesting questions to focus.
Response: The authors now best described some of the key summary points (pages 7, 8) by expanding them well in the discussion section (page 9). The important information is presented and the authors now focused on many of these in the revised version of the manuscript. Part of the problem is solved by better presenting the research question(s) and study design (page 4).
Abstract is now thoroughly edited and modified. The objectives now included the comparison between the two treatment arms and the time period of 3 months followed. The design is changed by focusing only on 3 months follow-up rather than the original RCT and removal of the feasibility study (page 1).
Participants are the kids who survived to discharge from severe pneumonia. Interventions are really concentrating of the events that occurred during the 3-months follow-up period. It's really an observational study following two cohorts discharged from severe pneumonia for 3 months.
Conclusions are now changed to: 1) there are considerable morbidities in children discharged with severe pneumonia; 2) the risk factors for poor outpatient outcome include the presence of tachycardia, tachypnoea, and hypoxaemia on admission and prolonged duration of stay (page 2).
In the discussion section, the focus on comparing severe pneumonia with SAM is deleted. The admission risk factors for poor outcomes are now discussed in details (page 9).
The limitations are now modified in the revised version of the manuscript (page 9).
8) Comment: Stats- need to be better explained. Although I'm not a biostatistician, there seems to be a paucity of information for comparing the data in this section, can be expanded.
Response: The statistics are now better explained and the information for comparing the data in this section has been expanded (page 6).
10) Comment: References- I would reference a few of the many successful published studies on Community Case Management of severe pneumonia (recently published studies on Lady Healthcare Workers in Pakistan, Appis and No-SHOTS, just to name a few). Because this is what the current study is effectively trying to compare, an out-patient model and hospital-based model AND 3-month follow-up outcomes of children with severe pneumonia, I think it would be important to reference.
Response: The suggested references are discussed and inserted under the discussion section (page 9) and cited in the modified version of the manuscript (References # 17, 18, page 17).
11) Comment: Results- as mentioned in greater detail in the above section, while I think the results are extremely important and answer a few interesting research questions, these questions need to be better stated, re-organized, and better presented to the reader prior to the Results section. A baseline Table of 'health' status of discharged patients needs to be included in the results, if not it's impossible to interpret the results. The Tables should also be re-organized to reflect the study objectives and outcomes measures presented earlier in the paper. Results section is also too wordy, if the Table can better explain some of the results, the authors should only focus on interesting result findings and refer to greater information/depth in the Tables.
Response: As the results are extremely important and answered a few interesting research questions, these questions are now better stated, re-organized and better presented in the results section of the manuscript (pages 7, 8). A baseline Table of 'health' status of discharged patients has been included in Table 1 (page 11). The Tables are now re-organized to reflect the study objectives and outcomes measures presented earlier in the paper. As the results section appeared too wordy and the Tables can better explain some of the results, the authors now focused only on the interesting result findings (pages 7, 8) and referred to the greater information/depth in the Tables (pages 11-15).
12) Comment: Conclusions- apologies for including more information on this in the above section, but I think the discussion needs to focus more on the stated research questions, which should be adjusted and re-presented in the Methods section. For example, if one of the objectives and research questions presented in the Methods section is to compare complications/morbidity/mortality 3-month

follow-up outcomes between children discharged after severe pneumonia vs. SAM, then the discussion can continue to focus on this. If not, it seems superfluous and not the focus of the paper.
Similarly, if one of the stated objectives of the paper is to identify risk factors upon admission for eventual 3-month follow-up mordibity/re-admission/mortality outcomes, then the discussion can focus on this as well.I know I've mentioned this before but unless the reader can see that the 2 groups at discharge are either equally healthy or sick, then it's extremely difficult to interpret any of the data. Presumably even if the groups differ on presenting severity/hypoxemia, they should be similar upon discharge so that we can evaluate 3-month follow-up outcomes.
In the limitations section, there also needs to be a discussion of causality over time for some of the outcomes measured. For example, if a child is discharged and develops fever, in-drawing, cough 2 months after discharge, it's difficult to attribute these symptoms with 100% certainty to an admission which occurred 2 months ago.
There is no information presented on the frequency of healthcare workers needing to find families in the community if they missed follow-up visits. This is mentioned in the methods section, and follow-up compliance is discussed at length. However, if there are data available between the 2 groups which present frequency of community visits to remind families to 'comply' with follow-up, this should be presented and discussed.
There is no section on REC approval, Informed consent, or ethical considerations. This needs to be added. I think these are really good and important research questions to ask, and I do think data are there to answer them in the current study. However, the paper is really poorly organized and needs to be re-written in sections, tightened in others, and better organized.
Response: Conclusions- The discussion section now focused more on stated research questions, which was adjusted and re-presented in the Methods section (page 4). The comparison between the outcomes of children discharged after severe pneumonia vs. SAM, are now deleted from the paper, as suggested by the reviewer. As one of the objectives of the paper is to identify risk factors upon admission for eventual 3-month follow-up mordibity/re-admission/mortality outcomes, the discussion now focused on this as well (page 9). As the 2 groups at discharge are equally healthy as shown in Table 1 (page 11), it is not difficult to interpret any of the data. As the groups differed on presenting severity/hypoxemia, they were found to be similar upon discharge (Table 1) and thus we evaluated 3-month follow-up outcomes easily.
The statement made for the limitations section was not considered as it was not clear to the authors and the native English speaker, who edited the manuscript.
There is now some information presented on the frequency of healthcare workers needing to find families in the community as they missed follow-up visits. About 5% of the patients came to the day-care clinic/hospital after the health care workers made home visits encouraging them to come (page 9).
There is now a section on REC approval, informed consent, or ethical considerations in the revised version of the manuscript (page 5). However, the paper is now well organized and re-written in sections.
Major Flaws
1) Comment: Inclusion of the out-patient kids from the feasibility study- is this really warranted? To me it introduces too many confounders and in effect is combining a pre/post design with a prospective study. Presenting a sample size calculation, if one were determined prior to the study for the percent difference in 3-month outcomes when comparing 'intervention' and 'control' groups, would be helpful; if not, perhaps the authors should calculate to see if these additional cases are needed, but to me it not only seems confusing but hinders the methodology.
Response: As already discussed, the inclusion of the out-patient kids from the feasibility study is already deleted, as it introduces too many confounders.
2) Comment: Baseline Discharge status- because one of the primary study questions is to compare 3-month follow-up outcomes between the 2 groups, there really needs to be a Table which compares the 2 groups upon discharge so that we can ascertain that the groups were equally 'healthy' or 'sick.' If not, I think the results are too difficult to interpret.

Response: As baseline discharge status comparing 3-month follow-up outcomes between the 2 groups are necessary, we really needed a Table (Table 1), which now compares the 2 groups upon discharge.
3) Comment: Research questions- these should be re-focused on the strengths of the study and clearly stated (see my initial comments above). Once this is done, I think it will be easy to organize the data, tables and conclusions.
Response: All the research questions are now re-focused on the strengths of the study and clearly stated. Similarly, all the data are well organized, tables and conclusions are modified in the revised version of the manuscript.

VERSION 2 – REVIEW

REVIEWER	Seidenberg, Philip (R0) Boston University, Center for Global Health & Development
REVIEW RETURNED	24-May-2012

THE STUDY	1) Methods Section- I think that the authors need to include more specifics on the methods of follow-up performed by healthcare providers as well as the data collection at the follow-up visits during the 3month period. Most of the methods are used to describe the original RCT, which has already been published and therefore can be much briefer. What needs a bit greater attention is the current paper and its focus on the follow-up observational cohort and the methods for conducting this. Easy repair. 2) Abstract- I think it needs to be refocused and the outcomes measures re-written to parallel those presented in the study's objective in the main body. Additionally, there are no interventions in this current observational cohort, thus this section is completely false. Another easy fix but the abstract needs to follow the main paper. As currently written, the primary and secondary outcomes measures really say the same thing, there's no focus on predicting failure as described in the main paper, as well as the others. 3) Key Messages- I think these can be better stated. While I appreciate that the authors feel the take-home message is that close follow-up of children with severe pneumonia needs to occur, the authors should really expand on the main outcomes measure focused in the paper and results- compliance, predictors of treatment failure, comparison between the 2 cohorts, rather than simply saying that we need to follow-up. If this were their true focus, they really should have done a study looking at vital status and outcomes of kids comparing a group with close follow-up and one without; as it stands, both groups were followed closely, so this isn't even compared. Again, I think this is a very simple fix to the paper but needs to be come across prior to publication. 4) Main Outcome Measure- again, a very easy fix for the authors but there needs to be a clear definition of 'success' and 'failure' written and expressed in the main body of the paper, this is one of the main outcomes measures and yet we don't get these definitions anywhere. Table 5 is the first place this is inferred, failure means either re-hospitalization, development of hypoxemia or death. This clearly needs to be stated earlier.
RESULTS & CONCLUSIONS	Presentation of results- I mentioned this above, but my suggestion is not to focus on the importance of follow-up for kids discharged with severe pneumonia. While this may be inferred, this was not the objective of the study; if it were, one group would have been

	followed closely and the other not, and then vital status and outcomes compared. Instead, the authors do a good job defining their primary and secondary outcomes, presenting these in the results as well as the tables, then they should deliver the take-home message according to their analysis. Again, I think this is a very easy fix. 2) Conclusions derived from data- very closely linked to comment above. It's hard to make the conclusion that close follow-up prevented deaths, as the authors claim, when this wasn't studied (close follow-up vs. not close follow-up). Many of the other conclusions are fine, although it does appear mixed when comparing the two groups for some morbidity data. This will be easy to read once the author's clearly state their definitions of 'success' and 'failure' somewhere in the body of the paper.
REPORTING & ETHICS	Quick comment- there's a reference to Informed Consent on Page 4, Lines 54-56, but because much of this section is focused on the methodology of the original study, it's not completely clear whether any additional Informed Consent was sought for inclusion in the 3month follow-up. Please make this clearer in this section; easiest would be to make most of the Methods section focused on the follow-up study not the original RCT.
GENERAL COMMENTS	Here are a few specific comments/edit suggestions: 1) Introduction- I think reference to additional literature supporting Community Case Management of childhood severe/non-severe pneumonia needs to be mentioned (even if just references), there is a growing body of literature for these types of programs. But the novelty of the current study is to compare some 3-month outcomes post-discharge, not to report on the original findings. There are also limited data on morbidity and mortality for severe pneumonia post-discharge, so this should be better developed in the intro. This will set the stage for some of the important conclusions. 2) Settings- much of this is focused on the original RCT, perhaps a couple of sentences on the setting of the follow-up would be nice. 3) Methods- too much focus and re-printing of the original study. I would reference it and the published paper, briefly include a synopse, then develop the methods for the observational cohort in greater detail. 4) Page 6, Line 3- with reference to those mothers and caregivers missing follow-up appointments, and HCWs pursuing into the community, it's unclear in this sentence whether the HCWs went there to collect data or simply to remind moms for returning. Please clarify. 5) Data Analysis- may be the best space to define 'failure' and 'success.' If not here, it needs to be done prior to presenting the results. Simple fix but the paper really needs it. 6) Results Section, Page 7, Line 40- curious that you all define tachypnea evenly over all the ages of kids in the study. As you're aware, WHO considers this age-dependent with different reference ranges, not sure why you all just chose 60 particularly for the older kids. 7) Results with Odds Ratios- I always prefer reading CIs when presenting ORs rather than p values, you may want to consider

	changing all of these both in the results as well as the Tables. 8) Results, Page 7 Line 52- what is the definition of 'severe hypoxemia?' You mention it but don't define it, you do present the definition of hypoxemia well. Following up on this, your Ns for hypoxemia in LIne 54 and 56 don't really make sense, in the methods you state that you measure O2 sats on all follow-up visits, but here you're only presenting data on 33 kids (25 hypoxic, 8 not). Please review. 9) Table 3- please review and re-calculate ORs for cough, feeding difficulty and diarrhea. From my read all of these should have values less than one since you're comparing to the hospitalized group.

VERSION 2 – AUTHOR RESPONSE

Response to Reviewer's Comments

Comment 1) Methods Section- I think that the authors need to include more specifics on the methods of follow-up performed by healthcare providers as well as the data collection at the follow-up visits during the 3month period. Most of the methods are used to describe the original RCT, which has already been published and therefore can be much briefer. What needs a bit greater attention is the current paper and its focus on the follow-up observational cohort and the methods for conducting this. Easy repair.

Response: The methods section including settings, participants, and follow up study sections have been modified in the revised version of the manuscript according to the reviewer's suggestion (pages 4-6). The part of the methods used to describe the original RCT was deleted and referenced only (page 5). Now, greater attention is given to the current paper with focus on the follow-up observational cohort and the methods for conducting this (pages 5, 6).

Comment 2) Abstract- I think it needs to be refocused and the outcomes measures re-written to parallel those presented in the study's objective in the main body. Additionally, there are no interventions in this current observational cohort, thus this section is completely false. Another easy fix but the abstract needs to follow the main paper. As currently written, the primary and secondary outcomes measures really say the same thing, there's no focus on predicting failure as described in the main paper, as well as the others.

Response: The Abstract now refocused and the outcomes measures re-written to parallel those presented in the study's objective in the main body. As there are no interventions in this current observational cohort, this section is also modified (page 1). The abstract now followed the main paper. As the primary and secondary outcomes measures really say the same thing, the secondary outcome measures were removed from the abstract (page 1) and the body of the revised version of the manuscript (page 6). There is also focus on predicting failure in the abstract section of the manuscript (page 1), as described in the main paper.

Comment 3) Key Messages- I think these can be better stated. While I appreciate that the authors feel the take-home message is that close follow-up of children with severe pneumonia needs to occur, the authors should really expand on the main outcomes measure focused in the paper and results- compliance, predictors of treatment failure, comparison between the 2 cohorts, rather than simply saying that we need to follow-up. If this were their true focus, they really should have done a study looking at vital status and outcomes of kids comparing a group with close follow-up and one without; as it stands, both groups were followed closely, so this isn't even compared. Again, I think this is a very simple fix to the paper but needs to be come across prior to publication.

Response: The key messages are now better stated with take-home message that close follow-up of children with severe pneumonia needs to occur, the authors now expanded on the main outcomes measures focused in the paper and results, such as the compliance, predictors of treatment failure, comparison between the 2 cohorts (page 2).

Comment 4) Main Outcome Measure- again, a very easy fix for the authors but there needs to be a

clear definition of 'success' and 'failure' written and expressed in the main body of the paper, this is one of the main outcomes measures and yet we don't get these definitions anywhere. Table 5 is the first place this is inferred, failure means either re-hospitalization, development of hypoxemia or death. This clearly needs to be stated earlier.
Response: ‘Success’ and ‘failure’ are now clearly defined in the main outcome measures section of the manuscript (page 6). Success of day-care/hospital care management at follow-up visits, defined as compliance with each of the scheduled follow up visits for three months either spontaneously or brought by the health care workers, without the need for re-hospitalization, or development of hypoxaemia, and not dying during the whole follow up period. As correctly stated by the reviewer, failure of day-care/hospital care management means either re-hospitalization, or development of hypoxaemia, or death at any time during the three months follow up period (page 6).
Comment 5) Presentation of results- I mentioned this above, but my suggestion is not to focus on the importance of follow-up for kids discharged with severe pneumonia. While this may be inferred, this was not the objective of the study; if it were, one group would have been followed closely and the other not, and then vital status and outcomes compared. Instead, the authors do a good job defining their primary and secondary outcomes, presenting these in the results as well as the tables, then they should deliver the take-home message according to their analysis. Again, I think this is a very easy fix.
Response: The results section has now been modified with the definition of success and failures (page 6) and then presenting these in the results (pages 7, 8) as well as the tables (pages 14, 15), then delivering the take-home message in the conclusion (page 10).
Comment 6) Conclusions derived from data- very closely linked to comment above. It's hard to make the conclusion that close follow-up prevented deaths, as the authors claim, when this wasn't studied (close follow-up vs. not close follow-up). Many of the other conclusions are fine, although it does appear mixed when comparing the two groups for some morbidity data. This will be easy to read once the author's clearly state their definitions of 'success' and 'failure' somewhere in the body of the paper.
Response: As suggested by the reviewer, the conclusions are now changed after clearly defining 'success' and 'failure' (page 6) in the primary outcome measures section and then modifying the conclusions accordingly (page 10).
Quick comment- there's a reference to Informed Consent on Page 4, Lines 54-56, but because much of this section is focused on the methodology of the original study, it's not completely clear whether any additional Informed Consent was sought for inclusion in the 3month follow-up. Please make this clearer in this section; easiest would be to make most of the Methods section focused on the follow-up study not the original RCT.
Response: As there's a reference to Informed Consent on Page 4, Lines 54-56, but because much of this section is focused on the methodology of the original study, it's now completely clear that Informed Consent was also sought for inclusion in the 3 month follow-up (page 5). This is now clearly stated in the “Participants” section of the modified version of the manuscript (page 5). Most of the Methods section now focused on the follow-up study, not the original RCT (pages 5, 6), as suggested by the reviewer.
Here are a few specific comments/edit suggestions:
Specific comment 1) Introduction- I think reference to additional literature supporting Community Case Management of childhood severe/non-severe pneumonia needs to be mentioned (even if just references), there is a growing body of literature for these types of programs. But the novelty of the current study is to compare some 3-month outcomes post-discharge, not to report on the original findings. There are also limited data on morbidity and mortality for severe pneumonia post-discharge, so this should be better developed in the intro. This will set the stage for some of the important conclusions.
Response: As suggested by the reviewer, the community case management of childhood severe/non-severe pneumonia has been mentioned in the introduction section of the revised version of the manuscript with references (pages 3, 16). A statement on the novelty of the current study by comparing three months outcomes post-discharge and also by providing some limited data on

morbidity and mortality for severe pneumonia post-discharge has also been inserted in the introduction section of the revised manuscript (page 4).
Specific comment 2) Settings- much of this is focused on the original RCT, perhaps a couple of sentences on the setting of the follow-up would be nice.
Response: The “Settings” section now paid less focus on the original RCT, and a couple of sentences on the setting of the follow-up are now added (pages 4, 5).
Specific comment 3) Methods- too much focus and re-printing of the original study. I would reference it and the published paper, briefly include a synopse, then develop the methods for the observational cohort in greater detail.
Response: The “Methods” section now paid less focus on the original study. It is now referenced, the published paper briefly synopsed, and finally developed the methods for the observational cohort in greater detail (pages 5, 6).
Specific comment 4) Page 6, Line 3- with reference to those mothers and caregivers missing follow-up appointments, and HCWs pursuing into the community, it's unclear in this sentence whether the HCWs went there to collect data or simply to remind moms for returning. Please clarify.
Response: In page 6, Line 3 with reference to those mothers and caregivers missing follow-up appointments, and HCWs pursuing into the community, it's now clearly stated that HCWs went home of the missing children on the very next morning of the scheduled follow-up dates and accompanied them back to the clinic/hospital for collecting detailed data by the study physician (page 6).
Specific comment 5) Data Analysis- may be the best space to define 'failure' and 'success.' If not here, it needs to be done prior to presenting the results. Simple fix but the paper really needs it.
Response: As suggested by the reviewer, the data analysis section now clearly defined 'failure' and 'success' (page 6).
Specific comment 6) Results Section, Page 7, Line 40- curious that you all define tachypnea evenly over all the ages of kids in the study. As you're aware, WHO considers this age-dependent with different reference ranges, not sure why you all just chose 60 particularly for the older kids.
Response: In the Results Section, Page 7, Line 40- we have defined tachypnea evenly over all the ages of kids in the study to correlate with kids who were severely ill and who might have either hypoxaemia, or increased work of breathing and for this, we have considered only one cut off value to simplify by just choosing 60 for all kids (page 8). But, during the inclusion into the study, we have taken the cut off values of WHO criteria with ≥40/min for children ≥ 1 year and ≥ 50/min for infants <1 year of age.
Specific comment 7) Results with Odds Ratios- I always prefer reading CIs when presenting ORs rather than p values, you may want to consider changing all of these both in the results as well as the Tables.
Response: In Results with Odds Ratios, according to the preference of the reviewer, OR with 95% CIs were added in addition to p values in the results as well as the Tables (pages 8, 13, 15).
Specific comment 8) Results, Page 7 Line 52- what is the definition of 'severe hypoxemia?' You mention it but don't define it, you do present the definition of hypoxemia well. Following up on this, your Ns for hypoxemia in LIne 54 and 56 don't really make sense, in the methods you state that you measure O2 sats on all follow-up visits, but here you're only presenting data on 33 kids (25 hypoxic, 8 not). Please review.
Response: In the above mentioned statement, the term will be hypoxaemia which was defined as the oxygen saturation of less than 95% as recorded by pulse oximetry (page 8), not severe hypoxaemia. There is also a problem in understanding as Ns for hypoxemia in Line 54 and 56 really make sense as these are hypoxaemia present during the acute phase of illness presented in the original RCT, which was already referenced there (15). In the methods we stated that we measured O2 sats on all follow-up visits (page 5). On further review, it was found that we measured oxygen saturation in all kids during the follow up visits, but we found hypoxaemia in only 16 children (Table 5). All other children had no hypoxaemia during the follow up visits.
Specific comment 9) Table 3- please review and re-calculate ORs for cough, feeding difficulty and diarrhea. From my read all of these should have values less than one since you're comparing to the

hospitalized group.
Response: We have reviewed Table 3 and re-calculated the ORs for cough, feeding difficulty, diarrhea as well as medicine taken (page 13). It was found that all of these values are less than one, as correctly stated by the reviewer. We are really sorry for these unintentional mistakes.
Specific comment 10) Would you be willing to share your data? Cast your vote in our Online Poll
Response: We would be willing to share our data in near future.

VERSION 3 – REVIEW

REVIEWER	Philip Seidenberg MD Assistant Professor of International Health Boston University School of Public Health Center for Global Health & Development USA I do not have any competing interests to declare.
REVIEW RETURNED	27-Jun-2012

THE STUDY	Much improved with latest edits, particularly on the methods section.
RESULTS & CONCLUSIONS	Again, very good job of editing from most recent review.