PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

Title (Provisional)

IMPACT-ICU Feasibility Study: Pragmatic Mixed-Methods Randomized Controlled Trial of a Follow-Up Care Intervention for Survivors of Critical Illness and Caregivers

Authors

Jawa, Natasha Arianne; Maslove, David M; Sibley, Stephanie; Muscedere, John; Hunt, Miranda; Hanley, Michaela; Boyd, Tracy; Westphal, Robin; Mathur, Sunita; Fakolade, Afolasade; Tryon, Michelle; Boyd, John Gordon

VERSION 1 - REVIEW

Reviewer	**1**
Name	**Kiwanuka, Frank**
Affiliation	**University of Eastern Finland, Department of Nursing Science**
Date	**22-Apr-2024**
COI	**none**

Title:

- The title is very long, it can be shortened to max.20 words.

Abstract:

- the abstract is well written but could include the estimated samples to be included in the study.

Introduction:

- The introduction is well-written. The authors have provided a background to the complex intervention package that they will explore in their pilot study.

- The study objectives are clear.

Methods:

The authors have stated patient and public involvement. I feel that this part needs to be elaborated. How will the ICU survivors and caregivers inform knowledge acquisition, translation, and dissemination in practical terms?

- What is the rationale for including only high-risk participants? I feel that this might influence on the outcomes of the intervention that will be examined. possibly providing a rationale is necessary.

- The authors mentioned that "failure to consent" will be an exclusion criteria. However, on page 14, line 1-3, they mention that " if participants do not have capacity to consent for themselves, consent will be obtained from the participant´s substitute decision maker. I feel that there is some confusion regarding the exclusion criteria that considered failure to consent at least on the part of the patient.

- What was the choice of the follow-up period of 1 and 3 months. Because some of the disorders in the spectrum of PICS and PICS-F may come up before or after 1-3 months. So providing a rationale might strengthen the choice of the follow-up periods.

- It is not clear to me what will be included in follow-up clinical care. What makes it different? Providing such information can enable replication of the study by other researchers.

What could be some the anticipated limitations of the study?

Reviewer	**2**
Name	**González-Seguel, Felipe**
Affiliation	**Universidad del Desarrollo Facultad de Medicina, School of Physical Therapy**
Date	**02-May-2024**
COI	**None**

Manuscript: **bmjopen-2024-086799**
Title: **Protocol for the IMPACT-ICU pilot study: Improving medical and psychological outcomes after discharge - Feasibility study for a pragmatic, mixed methods, open-label randomized controlled trial examining the effectiveness of a follow-up clinic for ICU survivors and caregivers**

Reviewer Comments:
GENERAL COMMENTS
The authors are presenting a study protocol mainly to assess the feasibility of a randomized controlled trial (RCT) evaluating an ICU follow-up care bundle vs. standard-of-care for ICU patients and their caregivers. I congratulate the authors for this work that should be carried out. It is very likely that it will be comparable to other similar studies in progress and that will enrich the findings. Compatibility is given by the standardized use of measuring instruments widely used worldwide. I have some comments that could help improve the protocol.

SPECIFIC COMMENTS

Major comments:

1. The introduction could be better ordered, maintaining a better flow of information to define the problem and the gaps. Although I think it contains everything important, it should be rearranged.
2. Primary objectives: I would like to suggest adding the rate of adverse events of survivors/caregivers as a primary feasibility outcome. Safety is part of feasibility (review and possibly cite: https://pubmed.ncbi.nlm.nih.gov/26594739; https://pubmed.ncbi.nlm.nih.gov/31608150)
3. Could the authors detail the characteristics, reliability, and experience of the evaluator(s) with the instruments that depend on the rater? For example, MOCA test, 30s STS?

Minor comments:

4. Title: It looks very complete; however it is very long. Are there possibilities of shortening it to make reading more attractive?
5. General: Try to avoid "ICU survivors" or "critically ill patients" by putting the patient first. Use "survivors from the ICU" or "from critical illness" or patients with critical illness", for example.
6. Abstract: “Tertiary outcomes will be a battery of cognitive, functional, and psychiatric outcomes”. What does authors mean with “functional”. May be physical? There are also cognitive and mental outcomes that are “functional”. Functional is not limited to physical, so it is not the same. Consider this point for the rest of the manuscript.
7. Introduction: I don't understand how to separate the paragraphs in the introduction, dedicating paragraphs manly to cognitive outcomes, some to mental outcomes, and almost no physical outcomes. Could this be balanced?
8. Tertiary objectives: I would like to suggest replacing the 30-s sit to stand with the 60-s sit to stand. There are already some articles that demonstrate its superiority. If not, the authors could argue why they would use 30s over 60s. See:

   https://journals.lww.com/ajpmr/abstract/9900/which_sit_to_stand_test_best_differentiates.459.aspx
9. Study design: “30 ICU survivors and 30 associated informal caregivers (1 caregiver per patient) will be enrolled as dyads to participate in this study” This information should be in the sample size considerations and describe details of the calculation/estimation of the sample size for both caregivers and survivors. Authors should use previous literature to replicate sample size or similar.
10. Although no substantial contribution has been demonstrated, the presence of COVID-19 in patients with critical illness still has long-term consequences that could confound PICS results. The authors could address this COVID-19 factor as confounding. Authors could also consider PICS literature on COVID-19 (i.e., https://pubmed.ncbi.nlm.nih.gov/37972091) to justify the presence of physical, cognitive, and mental impairments.
11. Blinding: I understand that blinding is not possible for treatment, but is it possible for the 6-month evaluations to be performed by a blind evaluator? Depending on the ICU recovery clinic, this might be possible.
12. Stats analysis: For the evaluation of consent rate, enrollment rate, follow-up rate, and assessment rate, could the authors add the report of the reasons for the lack of these

points? (rate and details of the reasons for non-consent, enrollment, follow-up, and evaluation).

13. Please, add relevant references related to PICS outcomes of survivors from critical illness.

Overall, I liked reading this protocol and hope to see the results soon. My congratulations to the authors. I hope my comments are useful.

Reviewer **3**

Name **White, Paul**

Affiliation **University of the West of England, College of Arts, Technology and Enironment**

Date **09-Aug-2024**

COI **None**

The study is well described, relevant with a clear need established. There is a comprehensive set of patient and caregiver measures.

The description of Patient and Public Involvement is quite brief and generic. A little more detail would be useful.

There is some confusion over sample size. The first mention of sample size indicates n = 15 dyads per arm. Under sample size considerations the protocol aims to have 10 dyads per am. This requires clarification as it impacts on feasibility. Feasibility criteria are given as percentages and it is unclear how these will translate to absolute numbers given the lack of clarity over sample size.

The length of the supplementary material could possibly be reduced (although it is very useful and informative).

Reviewer **4**

Name **Belletti, Alessandro**

Affiliation **IRCCS San Raffaele Scientific Institute, Department of Anaesthesia and Intensive Care**

Date **14-Aug-2024**

COI **None**

In this manuscript, prof. Boyd and colleagues present the protocol for a pilot RCT investigating feasibility of systematic following up ICU survivors in a dedicated clinic

The topic is of great importance for both patients and caregiver, has always been underinvestigated, and prospective high-quality studies in this setting are needed.

The protocol is interesting, and overall well-written. The Authors plan this pilot study to assess feasibility of a larger study. I congratulate the Authors for this methodological rigor.

I have few suggestion/comments for the Authors:

1. Please describe study current status: is enrolment started?

2. As a related point, it seems that the study is still awaiting ClinicalTrials.gov registration. I therefore assume enrolment is not yest started. Please state this explicilty. please remember to update ClinicalTrials.gov status, should registration be completed before publication of this protocol

3. If still possible, I would suggest the Authors to include also long-term mortality among exploratory outcomes.

4. From the first paragraph of the Methods section, it is unclear whether patients/caregiver were involved also in study design or simply as part of the study subjects. If such figures were involved in study design, please state this cleraly, and please describe how they were selected, contacted and inited

5. Criteria for high-risk of long-term functional sequelae: are these criteria validated7described in literature, or were they selected by the Authors?

6. I suggest to track the number of patients who will have consent provided by substitute decision maker, and how many of them will ultimately be excluded from the trial

7. As a related point, I sugegst also to record if and how many patients in the control group will attend any post-ICU/psychological follow-up visit by themselves, independently from the study protocol,

8. Minor comment: on page 12, last two lines, the abbreviation KHSC should be expanded

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VERSION 1 - AUTHOR RESPONSE

Reviewer: 1

1. Title: The title is very long, it can be shortened to max. 20 words.

Thank you for your comment. We have shortened the title to ensure it adheres to the 20-word limit, and it now reads as follows: “IMPACT-ICU Feasibility Study: Pragmatic Mixed-Methods Randomized Controlled Trial of a Follow-Up Care Intervention for Survivors of Critical Illness and Caregivers”.

2. Abstract: The abstract is well written but could include the estimated samples to be included in the study.

   Thank you for the positive feedback on the abstract. We have updated the abstract to include the estimated sample size for clarity: “20 ICU survivor-primary caregiver dyads will be enrolled (n=10 dyads per group) and randomized 1:1 to the intervention vs. control group.”

3. Introduction: The introduction is well-written. The authors have provided a background to the complex intervention package that they will explore in their pilot study. The study objectives are clear.

   Thank you for this feedback.

4. Methods:
   a. The authors have stated patient and public involvement. I feel that this part needs to be elaborated. How will the ICU survivors and caregivers inform knowledge acquisition, translation, and dissemination in practical terms?

      We appreciate your feedback. We have expanded the section on patient and public involvement to clarify the practical ways ICU survivors and caregivers will contribute to knowledge acquisition, translation, and dissemination:

      “Specifically, ICU survivors and caregivers in earlier focus groups will participate in the co-design of the study questions used in subsequent focus groups, and all participants will co-design the final resources and tools used to ensure they reflect real-life experiences and concerns of the target population. At the conclusion of the study, all participants will be offered the opportunity to participate in a community outreach event to share the overall findings and final resources developed through the study, helping to translate findings into usable resources for the community.”

   b. What is the rationale for including only high-risk participants? I feel that this might influence on the outcomes of the intervention that will be examined. possibly providing a rationale is necessary.

      Thank you for this insightful comment. We have now provided a rationale for focusing on high-risk participants, explaining how this subset is expected to experience the most pronounced benefit from the intervention, which justifies their inclusion: “As the purpose of this study is primarily to evaluate feasibility, we are targeting high-risk participants only as this subset of ICU survivors is expected to experience the most pronounced benefit from the intervention.”

c. The authors mentioned that "failure to consent" will be an exclusion criteria. However, on page 14, line 1-3, they mention that " if participants do not have capacity to consent for themselves, consent will be obtained from the participant's substitute decision maker. I feel that there is some confusion regarding the exclusion criteria that considered failure to consent at least on the part of the patient.

Thank you for highlighting this point. We have clarified the exclusion criteria and revised the text to better explain the process of obtaining consent from substitute decision makers in cases where patients are incapacitated:

Exclusion criteria: "...or failure to provide consent/failure to have consent provided by a substitute decision maker."

d. What was the choice of the follow-up period of 1 and 3 months. Because some of the disorders in the spectrum of PICS and PICS-F may come up before or after 1-3 months. So providing a rationale might strengthen the choice of the follow-up periods.

We appreciate your suggestion. The early time point of 1-month post-ICU discharge was selected as, prior to this time, in our experience with other ICU follow-up studies at our centre we have found that patients are still admitted to hospital or rehabilitation and consequently unable to return for follow-up. 3- and 6-month time points were selected as the project is being conducted as part of a PhD thesis, and these time points permitted completion of data collection and analysis prior to the trainee's expected program completion date. We have now included the rationale as follows: "These time points were selected to maximize the potential benefit of the post-ICU care bundle for participants, as prior to 1-month we expect that many ICU survivors will still be admitted to hospital or undergoing rehabilitation services and would therefore be unable to attend, or benefit from, follow-up visits."

e. It is not clear to me what will be included in follow-up clinical care. What makes it different? Providing such information can enable replication of the study by other researchers.

Thank you for this point. We have added further details on the specific components of follow-up clinical care to ensure that it can be replicated by other researchers: "During the follow-up clinic visit, ICU survivors and caregivers will meet with three healthcare providers: 1) ICU physician, 2) social worker, and 3) pharmacist. The appointment will cover the patient and caregiver's progress through their recovery, discuss and develop mitigation strategies for barriers to recovery, contextualize the patient's ICU stay, provide therapeutic support and resources for physical and

psychological impairments, arrange necessary referrals for specialist care, provide return-to-work guidance, and review medications. Patients and caregivers will also have the opportunity to revisit the ICU and their specific room to further contextualize their ICU admission. The specific elements of these visits will be evaluated throughout this study and ultimately refined as part of the development of the final standardized clinic protocol."

f. What could be some the anticipated limitations of the study?

We have revised the manuscript to include a discussion on potential limitations:

"Limitations
The primary limitations of this study include its single-center design, which may limit the generalizability of the findings to other healthcare settings. Additionally, the small sample size and relatively short follow-up duration may not capture longer-term outcomes or provide statistically significant results for secondary and tertiary outcomes. The study focuses on ICU survivors at high risk for long-term sequelae, which may reduce the applicability of the findings to a broader ICU population. Furthermore, blinding was not possible due to the nature of the intervention, which could introduce bias in the responses of participants during follow-up assessments."

Reviewer: 2

1. GENERAL COMMENTS
   The authors are presenting a study protocol mainly to assess the feasibility of a randomized controlled trial (RCT) evaluating an ICU follow-up care bundle vs. standard-of-care for ICU patients and their caregivers. I congratulate the authors for this work that should be carried out. It is very likely that it will be comparable to other similar studies in progress and that will enrich the findings. Compatibility is given by the standardized use of measuring instruments widely used worldwide. I have some comments that could help improve the protocol.

2. SPECIFIC COMMENTS
   a. Major comments:
      i. The introduction could be better ordered, maintaining a better flow of information to define the problem and the gaps. Although I think it contains everything important, it should be rearranged.

      Thank you for the feedback. We have reorganized the introduction to improve the flow of the information presented and have added subheadings to each section for additional clarity.

      ii. Primary objectives: I would like to suggest adding the rate of adverse events of survivors/caregivers as a primary feasibility

outcome. Safety is part of feasibility (review and possibly cite: https://pubmed.ncbi.nlm.nih.gov/26594739; https://pubmed.ncbi.nlm.nih.gov/31608150)

Thank you for this suggestion. We have included the rate of adverse events as a primary feasibility outcome and referenced relevant literature, including the suggested articles: Rate of adverse events[39 40], assessed using the number of hospital and ICU readmissions, as well as the number of visits to the emergency department at 6-months.

iii. Could the authors detail the characteristics, reliability, and experience of the evaluator(s) with the instruments that depend on the rater? For example, MOCA test, 30s STS?

Thank you for the suggestion. These assessments will be performed by a trained evaluator who is a member of the research study team (JGB or NAJ). This has been outlined in the Clinical assessments section of the manuscript: "MoCA and 30/60s Sit-to-Stand tests will be performed by a trained evaluator for all participants (JGB or NAJ)."

b. Minor comments:

i. Title: It looks very complete; however it is very long. Are there possibilities of shortening it to make reading more attractive?

Thank you for your feedback. We have revised the title as follows: "IMPACT-ICU Feasibility Study: Pragmatic Mixed-Methods Randomized Controlled Trial of a Follow-Up Care Intervention for Survivors of Critical Illness and Caregivers".

ii. General: Try to avoid "ICU survivors" or "critically ill patients" by putting the patient first. Use "survivors from the ICU" or "from critical illness" or patients with critical illness", for example.

Thank you for this suggestion. We have changed all occurrences of "ICU survivors" to "survivors of critical illness" throughout.

iii. Abstract: "Tertiary outcomes will be a battery of cognitive, functional, and psychiatric outcomes". What does authors mean with "functional". May be physical? There are also cognitive and mental outcomes that are "functional". Functional is not limited to physical, so it is not the same. Consider this point for the rest of the manuscript.

We have clarified the term "functional" in the abstract and throughout the manuscript, specifying that it refers to physical functioning.

iv. Introduction: I don't understand how to separate the paragraphs in the introduction, dedicating paragraphs manly to cognitive outcomes, some to mental outcomes, and almost no physical outcomes. Could this be balanced?

Thank you for your comment. We have added a paragraph in the introduction on the physical functioning changes that occur with PICS as well: “Survivors of critical illness often additionally face functional and physical impairments as part of PICS, including muscle weakness, reduced mobility, and chronic pain[14 15]. Up to 50% develop ICU-acquired weakness, which can persist for months or years, limiting daily activities, contributing to long-term disability, and hindering return to work[13 16]. Chronic fatigue and reduced endurance further exacerbate these limitations[14].”

v. Tertiary objectives: I would like to suggest replacing the 30-s sit to stand with the 60-s sit to stand. There are already some articles that demonstrate its superiority. If not, the authors could argue why they would use 30s over 60s.
See: https://journals.lww.com/ajpmr/abstract/9900/which_sit_to_stand_test_best_differentiates.459.aspx

We appreciate your suggestion and have updated the protocol to include the use of the 60s sit to stand test. We have also retained the use of the 30s sit to stand test in order to enable comparisons with the extensive existing literature on the 30s sit to stand test in ICU populations.

vi. Study design: “30 ICU survivors and 30 associated informal caregivers (1 caregiver per patient) will be enrolled as dyads to participate in this study” This information should be in the sample size considerations and describe details of the calculation/estimation of the sample size for both caregivers and survivors. Authors should use previous literature to replicate sample size or similar.

Thank you for this important feedback. We have added the justification of our sample size to the Sample size considerations section of the manuscript: “This sample size was chosen as it is in line with prior literature in a similar population suggesting that 10-20 participants per group is sufficient to evaluate feasibility outcomes[47-49], and also provides the necessary number of

participants to adequately assess our secondary outcomes for this study."

vii. Although no substantial contribution has been demonstrated, the presence of COVID-19 in patients with critical illness still has long-term consequences that could confound PICS results. The authors could address this COVID-19 factor as confounding. Authors could also consider PICS literature on COVID-19 (i.e., https://pubmed.ncbi.nlm.nih.gov/37972091) to justify the presence of physical, cognitive, and mental impairments.

Thank you for this suggestion. This information (indication for admission) will be collected as part of each patient's ICU admission history, as outlined in Table 1: Schedule of assessments.

viii. Blinding: I understand that blinding is not possible for treatment, but is it possible for the 6-month evaluations to be performed by a blind evaluator? Depending on the ICU recovery clinic, this might be possible.

Thank you for this comment. As the set of questions during focus groups differs for participants randomized to the control group vs. the intervention group (since we need to evaluate the specific components of the intervention that were/were not useful for participants in order to make improvements to the resources), it is not possible for the 6-month visits to be blinded.

ix. Stats analysis: For the evaluation of consent rate, enrollment rate, follow-up rate, and assessment rate, could the authors add the report of the reasons for the lack of these points? (rate and details of the reasons for non-consent, enrollment, follow-up, and evaluation).

Thank you for this important comment. We have added these details to the Statistical methods section: "Details of the reasons for non-consent, enrollment, follow-up, or evaluation will also be described."

x. Please, add relevant references related to PICS outcomes of survivors from critical illness.

Thank you for this suggestion. We have added a paragraph to the Introduction that outlines the outcomes of PICS for survivors of critical illness and their caregivers: " The long-term prognosis for PICS is highly variable, with physical impairments often improving through therapy between 3- and 12-months post-discharge, while

cognitive and mental health issues persist[2 22]. The psychological impacts of PICS-family tend to wane over time, particularly with therapy[23]."

xi. Overall, I liked reading this protocol and hope to see the results soon. My congratulations to the authors. I hope my comments are useful.

Thank you so much for your kind feedback, we appreciate all of your suggestions.

Reviewer: 3

1. The study is well described, relevant with a clear need established. There is a comprehensive set of patient and caregiver measures.

2. The description of Patient and Public Involvement is quite brief and generic. A little more detail would be useful.

   Thank you for this observation. We have expanded the section on Patient and Public Involvement, providing specific details on how patients and caregivers contributed to the study design: "Specifically, survivors of critical illness and caregivers in earlier focus groups will participate in the co-design of the study questions used in subsequent focus groups, and all participants will co-design the final resources and tools used to ensure they reflect real-life experiences and concerns of the target population. At the conclusion of the study, all participants will be offered the opportunity to participate in a community outreach event to share the overall findings and final resources developed through the study, helping to translate findings into usable resources for the community."

3. There is some confusion over sample size. The first mention of sample size indicates n = 15 dyads per arm. Under sample size considerations the protocol aims to have 10 dyads per arm. This requires clarification as it impacts on feasibility. Feasibility criteria are given as percentages and it is unclear how these will translate to absolute numbers given the lack of clarity over sample size.

   Thank you for pointing this out. We have revised the manuscript to clarify that the study will aim to enroll 10 dyads per arm, and we have updated the feasibility criteria and sample size calculation information accordingly.

4. The length of the supplementary material could possibly be reduced (although it is very useful and informative).

   Thank you for this suggestion. We have eliminated repeated occurrences of the pages of the diary and now display only the first instance of each page type as an example to reduce the overall length of the supplementary material.

Reviewer: 4

1. In this manuscript, prof. Boyd and colleagues present the protocol for a pilot RCT investigating feasibility of systematic following up ICU survivors in a dedicated clinic. The topic is of great importance for both patients and caregiver, has always been under investigated, and prospective high-quality studies in this setting are needed. The protocol is interesting, and overall well-written. The Authors plan this pilot study to assess feasibility of a larger study. I congratulate the Authors for this methodological rigor. I have few suggestion/comments for the Authors:
    a. Please describe study current status: is enrolment started?

    Thank you for your comment. We have now explicitly stated that enrolment has not yet started and will provide the trial registration number once available.

    b. As a related point, it seems that the study is still awaiting ClinicalTrials.gov registration. I therefore assume enrolment is not yest started. Please state this explicitly. please remember to update ClinicalTrials.gov status, should registration be completed before publication of this protocol.

    Thank you for this astute observation. Since our original submission of this manuscript, the study has been registered with ClinicalTrials.gov and we have added the registration number to the end of the Abstract. Enrollment is ongoing.

    c. If still possible, I would suggest the Authors to include also long-term mortality among exploratory outcomes.

    We appreciate your suggestion and have added mortality as an exploratory outcome at 6 months.

    d. From the first paragraph of the Methods section, it is unclear whether patients/caregiver were involved also in study design or simply as part of the study subjects. If such figures were involved in study design, please state this clearly, and please describe how they were selected, contacted and invited.

    Thank you for your comment. We have clarified this point in the Patient and public involvement section as follows: “ICU survivor and caregiver representatives will inform knowledge acquisition, translation, and dissemination efforts throughout this study as active participants in the research process. Specifically, survivors of critical illness and caregivers in earlier focus groups will participate in the co-design of the study questions used in subsequent focus groups, and all participants will co-design the final resources and tools used to ensure they reflect real-life experiences and concerns of the target population. At the conclusion of

the study, all participants will be offered the opportunity to participate in a community outreach event to share the overall findings and final resources developed through the study, helping to translate findings into usable resources for the community."

e. Criteria for high-risk of long-term functional sequelae: are these criteria validated/described in literature, or were they selected by the Authors?

These criteria were determined via consensus among ICU healthcare providers at our institution as well as pertinent literature on risk factors for PICS. We have added a paragraph to describe these studies to the introduction: "Factors predisposing an individual towards the development of PICS include prolonged ICU stays, mechanical ventilation, sepsis, ICU delirium, deep sedation, immobility, pre-existing comorbidities (such as diabetes or cardiovascular disease), female sex, and older age[14 17-21]. Delirium during the ICU stay is a particularly strong predictor of long-term cognitive dysfunction[8].

f. I suggest to track the number of patients who will have consent provided by substitute decision maker, and how many of them will ultimately be excluded from the trial.

Thank you for this suggestion. This information is all tracked as part of our consent process.

g. As a related point, I suggest also to record if and how many patients in the control group will attend any post-ICU/psychological follow-up visit by themselves, independently from the study protocol.

Thank you for this suggestion. We have added this as a data collection point for our follow-up visits, and have outlined this in Table 1: Schedule of assessments: "Rehabilitation services/psychological therapy".

h. Minor comment: on page 12, last two lines, the abbreviation KHSC should be expanded.

Thank you for this observation, we have expanded the abbreviation KHSC to "Kingston Health Sciences Centre".

Once again, we would like to thank the reviewers for their thoughtful comments and the opportunity to improve our manuscript. We hope our revisions address all concerns satisfactorily.