

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Protocol for a multicentre longitudinal mixed methods study: Feeding and survivorship outcomes in previously healthy young Paediatric Intensive Care Survivors – The PIES study
AUTHORS	Morton, Kathryn; Darlington, Anne-Sophie; Marino, LV

VERSION 1 – REVIEW

REVIEWER	Andrew Kiragu Children's Minnesota and Hennepin Healthcare
REVIEW RETURNED	20-Jul-2020

GENERAL COMMENTS	<p>The authors propose an interesting and important study that has the potential to add to the body of knowledge regarding post-ICU nutrition in children. The recognition that Post-Intensive Care Syndrome (PICS) affects children and the impact of PICS on nutrition is an area in which additional research is needed. A few questions/concerns:</p> <ol style="list-style-type: none"> 1. The authors have not indicated why they are only choosing to study children up to age 4 and not across the whole pediatric age group up to age 17. Clarification regarding this should be given 2. Clarification should also be given about whether additional ICU data is being collected on patients- for example, severity of illness scores, ICD9/ ICD10(diagnosis codes), etc. as well as their clinical status at the time of discharge. I believe that this data will be useful in helping to interpret the results of their study 3. Are the authors collecting any additional data on feeding interventions in the ICU and post ICU, including Speech therapy assessments/treatments and consultations with a dietician? 4. The authors have indicated there will be caution and interventions for parents potentially having PTSD from having their child in the ICU. What interventions are in place for children with behavior/PTSD concerns? 5. How are data on patients' psychological and rehabilitation needs and their impact on nutrition being addressed? 6. While it is understandable that a lack of funding means that parents of families who can not read English are excluded, this is a weakness of this study that should be stated since it has the potential to exclude an important and diverse group of patients decreasing the generalizability of their results.
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REVIEWER	Carley Riley Cincinnati Children's Hospital, USA
REVIEW RETURNED	18-Aug-2020

GENERAL COMMENTS	In their paper "Protocol for a multicentre longitudinal mixed methods study: Feeding and survivorship outcomes in previously
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	<p>healthy young Paediatric Intensive Care Survivors – The PIES study,” the authors describe the design for their qualitative-quantitative study to explore the impact of feeding difficulties and identify any clinical risk factors during the first 6 months of PICU-discharge in previously healthy young children.</p> <p>Though the study seeks to examine interesting questions, I am not entirely clear of the value of publishing these methods separate from the individual papers that will result as they complete their study.</p> <p>With regards to what the authors present, here are my major concerns:</p> <p>Introduction</p> <ul style="list-style-type: none"> o The Introduction would benefit from better organization. I find the Introduction to be more wandering than focused and sharp. For greatest impact, I suggest that the authors communicate a clear frame for their study. o I suspect that the study frame would benefit from inclusion of a practicing pediatric critical care physician or clinician on the study team, as it appears to me that there was none on the study team. <p>Quantitative methods</p> <ul style="list-style-type: none"> o The authors have not included data on clinical diagnoses, including GI illness at admission or experienced during ICU/hospital course, and/or need for surgery in their analyses, yet nutritional practices may be informed or influenced by diagnosis and/or surgery. o The authors describe their intended sample size for the quantitative phase of their study as follows: “Assuming a potentially low prevalence of just 20% (which is less than the NICU and CHD population owing to their underlying baseline disease,(16-20), a sample size of 204 child participants would be sufficient to estimate prevalence to within +/- 5.5%. Anticipating a 40% drop-out as often seen with online surveys, (41, 42), this requires an initial recruitment of 340 participants. We anticipate enrolling these 340 participants from at least eight PICUS in equal proportions (42 participants per site) over a 12-month recruitment phase” (lines 206-212). I would encourage the authors to explain their reasoning for accepting +/- 5.5%. I would encourage the authors to explain their rationale for sampling equally across units of varying size. I also encourage the authors to publish the percentage of the total patient population the sample represents. <p>Qualitative methods</p> <ul style="list-style-type: none"> o It is unclear to me why the authors have chosen to sample a number of participants that they already anticipate will fail to meet saturation. I would encourage the authors to present this rationale or limitation. o When initially presenting their reasoning for including both father and mothers in the qualitative phase of their study, the authors states: “Both fathers and mothers will be asked to complete the parental questionnaires where possible, to increase our understanding of the experiences that fathers have after their child has survived intensive care” (lines 228-230). I would encourage the authors to rephrase this rationale to state “to increase understanding of the experiences that both fathers and mothers have after their child has survived intensive care.” The authors
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	<p>provide this less biased frame when they provide their reasoning behind including both parents later in the paper.</p> <p>Mixed methods o Though the authors state that “The qualitative data will strengthen the survey findings by adding the human perspective, exploring behaviour, feelings and experiences of the parents/caregivers told by them, (49). The information gained from the interviews will assist interpretation and analysis of the survey results, drawing conclusions to the clinical significance of the results with implications for clinical practice, (50)” (lines 347-351), it is not clear to me how this study benefits from its mixed methods design. It reads as quantitative and qualitative studies completed in parallel, with the participants of the qualitative study selected from within those of the quantitative study. How the authors will leverage their mixed methods design remains unclear.</p> <p>Other o I was wondering about other family variables that may influence recovery from critical illness, feeding behaviours, or parental/caregiver stress, such as pre-existing family or parent stressors/mental health, pre-existing or emergent unmet social needs or social determinants of health, and number of children in family and/or birth order of patient. o The language reads a bit clunky at times, something I imagine could be readily improved in working with an editor.</p>
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VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

The authors propose an interesting and important study that has the potential to add to the body of knowledge regarding post-ICU nutrition in children. The recognition that Post-Intensive Care Syndrome (PICS) affects children and the impact of PICS on nutrition is an area in which additional research is needed. A few questions/concerns:

1. The authors have not indicated why they are only choosing to study children up to age 4 and not across the whole pediatric age group up to age 17. Clarification regarding this should be given

During an admission to PICU, children are exposed to multiple physical and environmental stressors, often involving many traumatic and painful oral experiences which have been linked to swallowing and eating problems in adult survivors of intensive care. However, there is a lack of information regarding the impact of these experiences on the feeding behaviour and feeding skill acquisition in children. Most children admitted to PICU are under school age, with 46% aged less than 1 year and a further 23% aged between 1 and 3 years. Younger children spend longer in PICU, with an average length of stay of almost 4 days for children under 1 year-of-age, compared to less than 2 days admission for children aged 5 years and older (PICANet 2018). The majority of these children spend the entire PICU admission unable to eat or drink orally resulting from an endotracheal tube (ETT) in situ or as a result of being unable to consume enough nutrients due to their clinical condition. Although the reviewers make a good point in questioning the reason behind only studying children aged 4 years and under, it is the skills and behaviours learnt during those first 1000 days of life that are seen as imperative for future eating skills, attitudes and behaviours needed for healthy adult life, as well as being the patient population admitted to PICU.

2. Clarification should also be given about whether additional ICU data is being collected on patients- for example, severity of illness scores, ICD9/ ICD10 (diagnosis codes), etc. as well as their clinical status at the time of discharge. I believe that this data will be useful in helping to interpret the results of their study

Data about the participants PICU admission and status at discharge will be collected to identify any clinical predictors for the development of feeding difficulties. Linear and multiple regression analysis will be used to predict and compare clinical variables (PICU clinical data) on feeding difficulty scores. ICD9/ICD10 diagnosis codes will not be used, but reason for admission and other severity of illness indicators will be collected, including length of intubation and mechanical ventilation (in hours), length of PICU days (in hours), number of extubations and re-intubations, type of ETT (nasal and/or oral), length of non-invasive mechanical ventilation(i.e. BIPAP), length of non-invasive respiratory support (i.e. AIRVO), length of inotrope requirement, length of intravenous sedation , length and model of enteral nutrition (bolus, continuous, NBM periods, location of feeding tube), use of parental nutrition, any oral diet, any evidence of gastric intolerances (i.e documented vomiting, diarrhea, abdominal distention), use of motility agents, use of constipation medication and acid suppressions (yes/no). We have added further text within the manuscript describing the PICU clinical data that is being collected:

“Routinely collected PICU clinical data:

For all recruited patients, data already routinely recorded during the child’s PICU admission will be captured on a paper or electronic Case Report Form completed by the RC research nurse, a clinical team member delegated by the local PI or by the Chief Investigator at a later date. The variables of interest have been identified as:

- Length of PICU stay (in hours)
- Length of intubation (in hours)
- Length of mechanical invasive ventilation (in hours)
- Number of (re) intubations
- Type of ETT (oral or nasal)
- Length and type of non-invasive ventilation (in hours and mode)
- Inotrope requirement (yes/no)
- Mode of feeding during PICU admission (enteral, bolus or continuous, parental nutrition, oral diet, location of feeding tube)
- Time from extubation to commence oral feeding (in hours)
- Mode of feeding at PICU discharge
- Documented evidence of gastric intolerance (vomiting, diarrhea, abdominal distention).”

3. Are the authors collecting any additional data on feeding interventions in the ICU and post ICU, including Speech therapy assessments/treatments and consultations with a dietician?

We are collecting data on feeding interventions during the PICU admission, at discharge and throughout the follow-up period. Data collected about the PICU admission includes all the routine clinical data collected as described in your previous question, plus any episodes of Nil By Mouth, any type of oral feeding; mode of feeding at PICU discharge, use of motility agents(yes/no), use of acid suppressors (yes/no) and constipation medication (yes/no).We are also recording if the participant was reviewed by a dietitian during admission (yes/no) and seen by a SLT (yes/no).

We will also be asking families if they have had accessed any dietitian and/or SLT support since discharge, as an indicator of ongoing health burden related to nutrition and feeding. Parents/caregivers will be completing a feeding assessment questionnaire at 1, 3- and 6-months post PICU discharge in the follow-up survey. This information will be used to identify any clinical predictors for the development of feeding difficulties, such as associations between length of NGT feeding and

time from extubation to commencement of oral feeding, on feeding difficulty score. All this information has been further described within the manuscript as described above (point 3).

4. The authors have indicated there will be caution and interventions for parents potentially having PTSD from having their child in the ICU. What interventions are in place for children with behavior/PTSD concerns?

We agree with the reviewer that there is a need for widely available support for any identified or suspected PTSD or behavioural concerns for parents and children throughout the study. We have clearly stated within the full protocol and within the Participation Information Sheet that talking about feeding problems or the intensive care admission may bring up upsetting emotions and/or memories. Initial instances of distress will be dealt by the researcher and supported by the PICU psychology team at the researchers host institution. The researcher will also signpost the participants to the Patient Advice and Liaison Services (PALS), clinical psychology team based at Southampton Children's Hospital and other local healthcare teams.

5. How are data on patients' psychological and rehabilitation needs and their impact on nutrition being addressed?

Information about the patients psychological and rehabilitation needs, and their impact on nutrition and feeding, will be asked at the follow-up interviews at 3- and 6-months post PICU discharge, including asking questions about which follow-up support services they have accessed (if any).

6. While it is understandable that a lack of funding means that parents of families who can not read English are excluded, this is a weakness of this study that should be stated since it has the potential to exclude an important and diverse group of patients decreasing the generalizability of their results.

We agree with the reviewer that a major limitation to this study is the fact that an important and diverse group of non-English speaking families will be excluded from this study. This has now been clearly stated within the manuscript:

"The exclusion on non-English speaking families in The PIES study is a limitation of the study design in terms of selection bias and may affect the generalisability of the results. This will be investigated in the interpretations of the study results and implications for clinical practice."

Reviewer: 2

In their paper "Protocol for a multicentre longitudinal mixed methods study: Feeding and survivorship outcomes in previously healthy young Paediatric Intensive Care Survivors – The PIES study," the authors describe the design for their qualitative-quantitative study to explore the impact of feeding difficulties and identify any clinical risk factors during the first 6 months of PICU-discharge in previously healthy young children.

Though the study seeks to examine interesting questions, I am not entirely clear of the value of publishing these methods separate from the individual papers that will result as they complete their study.

With regards to what the authors present, here are my major concerns:

Introduction

o The Introduction would benefit from better organization. I find the Introduction to be more wandering than focused and sharp. For greatest impact, I suggest that the authors communicate a clear frame for their study.

We agree with the reviewer and have extensively revised this section.

o I suspect that the study frame would benefit from inclusion of a practicing pediatric critical care physician or clinician on the study team, as it appears to me that there was none on the study team.

We have a PICU Consultant Intensivist and Associate Professor at the University of Southampton involved in this study, who has been part of the ethics peer review process and was a co-author on the Scoping Review paper for this project.

Quantitative methods

o The authors have not included data on clinical diagnoses, including GI illness at admission or experienced during ICU/hospital course, and/or need for surgery in their analyses, yet nutritional practices may be informed or influenced by diagnosis and/or surgery.

Data about the participants clinical diagnoses at admission and throughout the PICU admission including discharge will be collected to identify any clinical predictors for the development of feeding difficulties. Linear and multiple regression analysis will be used to predict and compare clinical variables (PICU clinical data) on feeding difficulty scores. Data collection includes; length of intubation and mechanical ventilation (hours), length of PICU days (hours), number of extubations and re-intubations, type of ETT (nasal and/or oral), length of non-invasive mechanical ventilation (i.e. BIPAP), length of non-invasive respiratory support (i.e. AIRVO), length of inotrope requirement, length of intravenous sedation, length and model of enteral nutrition (bolus, continuous, NBM periods, location of feeding tube), use of parental nutrition (yes/no), any oral diet (yes/no), any evidence of gastric intolerances (i.e. documented vomiting, diarrhea, abdominal distention), use of motility agents, use of constipation medication and acid suppressions (yes/no). We have included this information within the manuscript.

o The authors describe their intended sample size for the quantitative phase of their study as follows: "Assuming a potentially low prevalence of just 20% (which is less than the NICU and CHD population owing to their underlying baseline disease, (16-20), a sample size of 204 child participants would be sufficient to estimate prevalence to within +/- 5.5%. Anticipating a 40% drop-out as often seen with online surveys, (41, 42), this requires an initial recruitment of 340 participants. We anticipate enrolling these 340 participants from at least eight PICUs in equal proportions (42 participants per site) over a 12-month recruitment phase" (lines 206-212).

I would encourage the authors to explain their reasoning for accepting +/- 5.5%. I would encourage the authors to explain their rationale for sampling equally across units of varying size. I also encourage the authors to publish the percentage of the total patient population the sample represents.

We anticipate enrolling 340 children (and their families) from 10 PICUs (was originally 8 PICUs) over a 12-month period. We agree with the reviewer that it makes sense for larger PICUs to recruit more participants than smaller units and have acknowledged this within the manuscript as a recruitment strategy for maximizing recruitment:

"We anticipate enrolling those participants from 10 PICUs over a 12-month period. It is expected that recruitment numbers will vary across the sites and across the recruitment period, accounting for seasonal admissions involving healthy children being admitted for bronchiolitis and other respiratory and/or septic illness in the winter months. Recruitment targets will be discussed at each site set up, with the allowance of over-recruiting in larger sites where possible."

Qualitative methods

o It is unclear to me why the authors have chosen to sample a number of participants that they already anticipate will fail to meet saturation. I would encourage the authors to present this rationale or limitation.

"A realistic and pragmatic sample size of 15 to 20 parents/caregivers will be interviewed at 3 and 6 months after PICU discharge with the aim of increasing research knowledge in this unknown field. We recognize that we may not achieve data saturation with this sample size, as there are many different influences and variables surrounding the child's PICU admission and parent/caregivers feeding experiences and survivorship journeys. However, this limitation will be acknowledged, investigated and discussed in the data analysis and future reporting of any study results, including the impact this may have on the study's credibility and generalisability."

o When initially presenting their reasoning for including both father and mothers in the qualitative phase of their study, the authors states: "Both fathers and mothers will be asked to complete the parental questionnaires where possible, to increase our understanding of the experiences that fathers have after their child has survived intensive care" (lines 228-230). I would encourage the authors to rephrase this rationale to state "to increase understanding of the experiences that both fathers and mothers have after their child has survived intensive care." The authors provide this less biased frame when they provide their reasoning behind including both parents later in the paper.

Thank you for the suggested text which we have added to the manuscript:

"To increase our understanding of the experiences that both fathers and mothers have after their child has survived intensive care, we are encouraging both fathers and mothers to complete the parental questionnaires where possible."

Mixed methods

o Though the authors state that "The qualitative data will strengthen the survey findings by adding the human perspective, exploring behaviour, feelings and experiences of the parents/caregivers told by them, (49). The information gained from the interviews will assist interpretation and analysis of the survey results, drawing conclusions to the clinical significance of the results with implications for clinical practice, (50)" (lines 347-351), it is not clear to me how this study benefits from its mixed methods design. It reads as quantitative and qualitative studies completed in parallel, with the participants of the qualitative study selected from within those of the quantitative study. How the authors will leverage their mixed methods design remains unclear.

We believe that the study design adheres to the core principles of mixed method design as it combines quantitative and qualitative approaches to generate a deeper and broader understanding of the prevalence and impact of feeding difficulties for children and families who survive critical illness. The data from the quantitative survey and the qualitative interviews will be integrated at both data collection and data analysis stages to identify, compare and contrast emerging themes. This an essential component of mixed methods, and one in which differentiates it from other methodologies. This has been clarified within the manuscript, using the following text:

"Based on the research question and objectives, a prospective, longitudinal mixed methods design will be used. Quantitative and qualitative data will be collected simultaneously over several times points, analysed separated and then integrated giving equal emphasis to each strand (Cresswell and Plano- Clark 2011)."

Other

o I was wondering about other family variables that may influence recovery from critical illness, feeding behaviours, or parental/caregiver stress, such as pre-existing family or parent stressors/mental health, pre-existing or emergent unmet social needs or social determinants of health, and number of children in family and/or birth order of patient.

Pre-existing parental/caregiver stress and social determinants of health information is being collected in The PIES study data collection and follow-up surveys. This information will be used to identify any relationships or associations between family variables and the development of feeding difficulties. For

example, data analysis will include looking for associations between parental stress score and feeding difficulty score, and level of maternal education on feeding difficulty score. We have added additional text within the manuscript to reflect this data collection:

“Demographic Information:

At each survey, parental factors, family variables and socio-economic data will be collected to identify any relationship between family background and the development of feeding difficulties for young survivors of critical illness. This includes parental/caregiver:

- Stress using the Parental Stress Score
- Ethnic origin
- Age
- Gender
- Highest level of education
- Living situation
- Employment status
- Siblings in household.”

o The language reads a bit clunky at times, something I imagine could be readily improved in working with an editor.

We have extensively revised the manuscript and thank you for your further consideration.

VERSION 2 – REVIEW

REVIEWER	Andrew Kiragu Children's Minnesota and Hennepin Healthcare United States
REVIEW RETURNED	12-Nov-2020

GENERAL COMMENTS	I have reviewed the edited manuscript and am satisfied that the authors have responded to the questions raised, made the suggested edits where possible, and clarified the data elements that they will be collecting in the study.
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REVIEWER	Carley Riley Cincinnati Children's Hospital
REVIEW RETURNED	16-Nov-2020

GENERAL COMMENTS	The authors have responded thoroughly and well to the concerns that I raised in my earlier review of this paper. The added details that they have provided have strengthened the methods paper considerably. I also applaud their reworking of the introduction as it now reads more clearly and presents their rationale well.
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