PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	The FeBRILe3 Project: protocol for a prospective pragmatic, multi-site observational study and safety evaluation assessing Fever, Blood cultures and Readiness for discharge in Infants Less than 3 months' old
AUTHORS	Mace, Ariel Olivia; Martin, Andrew C.; Ramsay, Jessica; Totterdell, James; Marsh, Julie A.; Snelling, Tom

VERSION 1 – REVIEW

REVIEWER	Paul Aronson Yale School of Medicine, USA
REVIEW RETURNED	08-Dec-2019

GENERAL COMMENTS	Implementation of a CPG to facilitate earlier discharge of febrile infants <3 months old has potential for significant impact by reducing unnecessarily long hospital stays and antimicrobial use, which have associated risks. Overall, the authors describe the protocol well, including the safety monitoring plan. Though I am not familiar with the sequential Bayesian safety monitoring framework, the authors describe this methodology in detail. I do have several questions/suggestions: 1) Can the authors describe how the CPG will be implemented? The success of implementation will likely vary based on the method of implementation (posted guideline, availability on the hospital intranet, clinical decision support, etc) as well as any associated educational initiatives towards providers about the CPG? Details about method of implementation would be important. 2) While the authors will be recording hospital length of stay during the study period, will they be assessing CPG adherence? For example, tracking whether "low risk" infants were actually discharged at 24 hours? Adherence to the CPG will likely affect outcomes, and tracking adherence is necessary to understand the impact of the CPG. 3) Do the authors need to adjust their results for clustering by hospital as this is a two-site trial? 4) This is a less of a protocol question, and more of a question about the CPG. The CPG recommends to discharge "low risk" infants at 24 hours but keep "standard risk" infants in the hospital for 48 hours (or more). Looking at the "low risk" criteria in the CPG, these criteria are often used (at least in the U.S.) to identify infants who may be discharged from the emergency department without need for hospitalization. For the purposes of the CPG, why are these infants being hospitalized instead of being discharged from the ED? In my opinion, the impact of the CPG would be greater if the CPG recommended instead that the "standard risk"

	infants be discharged at 24 hours (or even at 36 hours), given that the literature shows that >90% of blood pathogens (and similarly, CSF pathogens) are identified within 24 hours by culture.

REVIEWER	Russell J. McCulloh Children's Hospital and Medical Center, United States of America
REVIEW RETURNED	28-Dec-2019

GENERAL COMMENTS	Thank you for the opportunity to review this protocol on a common and vexing topic in pediatrics. The authors present the study protocol for a prospective, single-arm pragmatic intervention trial to test the impact of implementing a clinical practice guideline (CPG) for managing young infants with fever. General comments: Overall the rationale for the protocol is sound and the outcome measures are relevant. I have some questions regarding the rationale for including children 61-90 days of age as some guidelines exist to manage these children differently from children 60 days old and younger and the epidemiology differs significantly, including the risk of meningitis. Additionally, it would be good to know what the baseline time to discharge for infants in the participating sites is currently. The rationale for the primary outcome is that the length of hospital stay is going to get shorter, but what if the baseline length of stay for low-risk infants is already near the target? Finally, it is uncertain to me what specific procedures will be performed on children as these are alluded to in the protocol but the specific documents that would outline these procedures are not included in the supplementary materials or the protocol itself. As this is an area where I and colleagues have done a lot of work I've included some references to our prior work that may be helpful to consider in this protocol, if for no other reason than as background to help justify the proposed targets and to help inform the sample size calculations for the primary outcome. Introduction: 1. The overall background and cited literature is appropriate. I would also consider the following systematic review and meta-analysis on the epidemiology of bacteremia and meningitis, which incorporates data from some of the other articles cited in the protocol: Biondi EA, Lee B, Ralston SL, et al. Prevalence of Bacteremia and Bacterial Meningitis in Febrile Neonates and Infants in the Second Month of Life: A Systematic Review and Meta-analysis. JAMA Netw Open. 2019;2(3):e190874. doi:https://doi.org/10.1001/jamanetworkopen.2019.0874 2. Need to account for the following multi-site QI collaborative that included discharge of low-risk infants <60 days within 30 hours as a core metric: Biondi EA, McCulloh R, Staggs VS, et al. Reducing Variability in the Infant Sepsis Evaluation (REVISE): A National Quality Initiative. Pediatrics. 2019;144(3):e20182201. doi:10.1542/peds.2018-2201 3. Why additionally focus on children 61-90 days of age? There are guidelines that address this population differently, including the American Academy of Pediatrics guidelines for diagnosis and management of UTI in children 2-24 months old and evidence that the risk of meningitis in the third month of life is likely much lower (see Aronson, et. al., 2014, cited in this protocol already). Methods:

	1. How will you assess fidelity to the intervention? 2. Reasonable secondary outcomes 3. Very appropriate primary outcome. The fact that you are obtaining information on readmissions through a combination of electronic health records review AND directly contacting parents of discharged patients will help ensure that you do not miss infants who were readmitted to a different facility. 4. How are you addressing non-SBI infections? Many multi-plex molecular tests exist to identify a host of viral pathogens from blood, CSF, and respiratory secretions. Are you obtaining these results systematically or opportunistically/as performed? Are they obtained routinely on all infants? If so, what age ranges? 5. The sequential Bayesian safety monitoring framework is a great choice for this single-arm study. A suggestion for a reference for this section: Thall PF, Simon RM, Estey EH. Bayesian sequential monitoring designs for single-arm clinical trials with multiple outcomes. Stat Med. 1995;14(4):357–379. doi:10.1002/sim.4780140404 or Thall PF, Simon RM, Estey EH. New statistical strategy for monitoring safety and efficacy in single-arm clinical trials. J Clin Oncol. 1996;14(1):296–303. doi:10.1200/JCO.1996.14.1.296 6. Assuming standard of care medical interventions, some of which incur a risk of adverse events, what are your adverse events for which you are monitoring (aside from readmission) and how do you account for them in your safety monitoring? Discussion: 1. Page 14, last sentence: This sentence implies that all infants <3 months old with fever get all invasive testing. Please specify what procedures infants will experience during the intervention. Supplementary materials: 1. The ED lumbar puncture and FWS guidelines are referenced multiple times but not included in the protocol, making it unclear to me what procedures actually are likely to be performed on infants >28 days of age. Please include these supplementary materials. 2. The survey does not include any items related to the family's perception of the health of their infant post-discharge. Would consider including a question or two in this area. 3. Have you validated or piloted the survey? An example of how one group did validation with a fever survey among parents of young children (not all of them infants): de Bont EG, Francis NA, Dinant GJ, Cals JW. Parents' knowledge, attitudes, and practice in childhood fever: an internet-based survey. Br J Gen Pract. 2014;64(618):e10–e16. doi:10.3399/bjgp14X676401

REVIEWER	SHUO FENG University of Oxford United Kingdom
REVIEW RETURNED	08-Feb-2020

GENERAL COMMENTS	The authors proposed a study on examining the safety, as measured by readmission rate, and impact of the updating of guideline for infants who are admitted with fever without source and with a pre-defined low risk of serious bacterial infection. The rationales are well justified and methods are comprehensively described. I include a few comments below that I think would be helpful for further improvement. Introduction

	1. Page 4, paragraph 1 & 2. “Fever without source (FWS) is one of the most common reasons young infants less than 3 months old present to hospital.” Could the authors provide more details on the proportion of FWS among total consultations/hospitalisations, the proportion of high/standard/low risk children, as well as the numbers of unnecessary treatment and hospitalisation? These stats could be helpful in understanding the potential burden to the healthcare system. Outcomes 2. Page 6-7, secondary outcomes. The authors might consider further investigating the differences in hospital bed days and difference in hospitalisation cost, calculated by considering both first admission the readmission, before and after the implementing of the new guideline. Sample size 3. Page 10, line 24-25. Could the authors give the justification on the maximum number of infants is 500? 4. Page 11, Description of sequential Bayesian analysis. Regard to the complete Bayesian model, it would be helpful to describe the rationale on choices of distributions and parameters, for example, beta distribution and parameter alpha and beta. Safety monitoring 5. Page 12, line 38-40. “evidence of unsafe practice (inferiority) is defined as a >95% probability that the rate of readmission is >0.08.” Do the authors mean “>=0.08” according to the hypothesis?

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Paul Aronson

1) Can the authors describe how the CPG will be implemented? The success of implementation will likely vary based on the method of implementation (posted guideline, availability on the hospital intranet, clinical decision support, etc) as well as any associated educational initiatives towards providers about the CPG? Details about method of implementation would be important.

Additional information regarding the implementation process has been added to the *Study Procedures section* (page 8) of this manuscript for further clarity: *“Implementation of this CPG was through a consultative process including: i) general paediatric and emergency department staff input into CPG creation (including junior medical officers, consultant paediatricians and nursing staff), ii) approval by the hospital Clinical Practice Advisory Committee, iii) dedicated education sessions with general paediatric medical staff prior to and after introduction of the CPG, iv) easy accessibility to the CPG via quick-links on the departmental intranet homepage, v) regular departmental email reminders with links to the CPG, and vi) poster reminders to use the CPG within clinical workrooms on the general paediatric wards.”*

2) While the authors will be recording hospital length of stay during the study period, will they be assessing CPG adherence? For example, tracking whether "low risk" infants were actually discharged at 24 hours? Adherence to the CPG will likely affect outcomes, and tracking adherence is necessary to understand the impact of the CPG.

This study will assess adherence to the CPG by comparing anticipated length of stay per risk group to patient's actual length of stay. This calculation has been built into the electronic database. Documented use of the CPG and reasons for non-adherence to the CPG will be captured when available.

The following additional information has been added to the *Secondary Outcomes* (page 7) to reflect this: *"Length of stay will also be utilised to assess adherence to CPG recommendations for "low risk" patient management (anticipated discharge at 24 hours). Documented use of the CPG and reasons for non-adherence will be captured when available."*

3) Do the authors need to adjust their results for clustering by hospital as this is a two-site trial?

Hospital study site is captured within the dataset to allow for site-specific reporting with respect to the outcomes and assessment of differences between sites. However, the primary evaluation of safety will combine data across both sites. The authors do not intend to adjust results for clustering as, given that there are only two sites, any estimate of the amount of variance across sites will be unreliable. The degree of clustering is determined by the relative magnitude of the variation across individuals and the variation across sites. When using only two sites, it's likely that the across site variance is mis-estimated (and potentially estimated as 0 if the readmission rates are similar between sites). In addition, the two sites were not selected at random from all possible sites, and so may not reflect usual variability between sites.

In this case, the authors feel it is of more interest to investigate 7-day readmission rate within each site independently, or completely pool the data from both sites.

4) This is a less of a protocol question, and more of a question about the CPG. The CPG recommends to discharge "low risk" infants at 24 hours but keep "standard risk" infants in the hospital for 48 hours (or more). Looking at the "low risk" criteria in the CPG, these criteria are often used (at least in the U.S.) to identify infants who may be discharged from the emergency department without need for hospitalization. For the purposes of the CPG, why are these infants being hospitalized instead of being discharged from the ED? In my opinion, the impact of the CPG would be greater if the CPG recommended instead that the "standard risk" infants be discharged at 24 hours (or even at 36 hours), given that the literature shows that >90% of blood pathogens (and similarly, CSF pathogens) are identified within 24 hours by culture.
The management recommendations for "low risk" and "standard risk" infants was extensively considered during the consultative process for creation of this CPG, with the knowledge that some international guidelines identify the low risk group as eligible for discharge from the ED and standard risk group within 24 – 36 hours of admission. These practices are a marked shift from the routine local practice of hospitalisation and minimum 48-hour admission for all febrile infants, with no prior formal risk stratification process in place. During the consultation process to create this guideline within the general paediatric teams at both sites, it was acknowledged that implementing substantial change to clinical practice, such as direct discharge home from ED (in comparison to hospitalisation and 48-hour admission) would be challenging without local evidence to demonstrate the safety of earlier discharge in the local population.

The FeBRILe3 project is anticipated to be the first phase in changing local practice for infants with fever without source. By implementing this change within an active safety monitoring framework, we hope this will facilitate a more prompt and complete adoption of the practice, and that the baseline information collected for all infants in the study cohort will provide supportive local evidence for future

recommendation changes, such as earlier discharge for standard risk infants, in line with US practices.

Reviewer: 2
Reviewer Name: Russell J. McCulloh

General comments: Overall the rationale for the protocol is sound and the outcome measures are relevant. I have some questions regarding the rationale for including children 61-90 days of age as some guidelines exist to manage these children differently from children 60 days old and younger and the epidemiology differs significantly, including the risk of meningitis.

The CPG for inpatient management of FWS implemented at the two study sites is intended to follow on from the local tertiary centre guidelines for the emergency management of FWS, in which management is based on the age groups of <1 month, 1-3 months and >3 months of age. The CPG specifies management for infants <3 months old to enable continuity with this emergency department guideline (which has been added as a supplementary file 2 to this manuscript revision).

The authors recognise that the older cohort >60 days has different risk profiles to younger infants. During the consultation process within the general paediatric teams to create the CPG, it was felt that changing the age ranges for FWS investigation would be challenging until there was local data to demonstrate safety in this cohort. Through the inclusion and collection of baseline data for all infants up to 3 months old, the authors intend to describe the local epidemiology for pathogens causing FWS within each age group (<1 month, 1-2 months and 2-3 months) to support future changes in practice that may rationalise investigation and management in the older age groups.

Additionally, it would be good to know what the baseline time to discharge for infants in the participating sites is currently. The rationale for the primary outcome is that the length of hospital stay is going to get shorter, but what if the baseline length of stay for low-risk infants is already near the target?

Authors AOM, ACM and TLS have performed a retrospective analysis (unpublished) of all infants less than 3 months old admitted to any Perth metropolitan hospital over a 5 year period (n = 11,669, years 2008 – 2012) and identified infants with discharge codes likely to correlate with “low risk” presentations, including “viral infection” and “fever, unspecified”. This was performed given the limitations of retrospectively identifying “low risk” infants in the absence of any prior risk stratification process at either hospital site for infants with FWS. This retrospective cohort had a mean length of stay of 2.4 days (SD 2.3), which will be used for comparison of length of stay for “low risk” infants after implementation of the study guideline. This baseline length of stay information has been added to the manuscript text *Study setting* (page 6): *“A large local retrospective birth cohort analysis has identified… a mean length of stay of 2.4 days (SD 2.3) for infants with a discharge diagnosis of “viral infection” or “fever, unspecified””.*

Finally, it is uncertain to me what specific procedures will be performed on children as these are alluded to in the protocol but the specific documents that would outline these procedures are not included in the supplementary materials or the protocol itself.

The following additional information regarding the local ED management guideline has been included within the *Safety cohort exposure* section (page 8) and as an additional supplementary file (file 2) to provide clarification around the recommended investigations and procedures for all infants presenting with FWS: *"This CPG is intended to follow on from the tertiary Emergency Department guidelines for the initial investigation of infants presenting with FWS (supplementary file 2); investigations may include but are not limited to full blood count, C-reactive protein, urine, blood and/or cerebrospinal fluid microscopy and culture, and viral studies based on clinical presentation, patient age and clinician discretion."*

Introduction:

1. The overall background and cited literature is appropriate. I would also consider the following systematic review and meta-analysis on the epidemiology of bacteremia and meningitis, which incorporates data from some of the other articles cited in the protocol: Biondi EA, Lee B, Ralston SL, et al. Prevalence of Bacteremia and Bacterial Meningitis in Febrile Neonates and Infants in the Second Month of Life: A Systematic Review and Meta-analysis. JAMA Netw Open. 2019;2(3):e190874. doi:https://protect-au.mimecast.com/s/f2HGC81Zj6t6Z14RQunX95t?domain=doi.org

2. Need to account for the following multi-site QI collaborative that included discharge of low-risk infants <60 days within 30 hours as a core metric: Biondi EA, McCulloh R, Staggs VS, et al. Reducing Variability in the Infant Sepsis Evaluation (REVISE): A National Quality Initiative. Pediatrics. 2019;144(3):e20182201. doi:10.1542/peds.2018-2201

3. Why additionally focus on children 61-90 days of age? There are guidelines that address this population differently, including the American Academy of Pediatrics guidelines for diagnosis and management of UTI in children 2-24 months old and evidence that the risk of meningitis in the third month of life is likely much lower (see Aronson, et. al., 2014, cited in this protocol already).

The recommended references have been incorporate into the manuscript *Introduction* (page 4-5): *"A growing body of primary literature suggests that some infants who warrant hospitalisation can be safely discharged at 24 – 36 hours,[1,2,7-13] and that older infants, with different risk profiles for SBI compared to the younger cohort, may warrant less conservative management.[14-16]"* and *"Internationally, quality improvement projects have been implemented to reduce variability in infant sepsis care.[13]"*

Methods:

1. How will you assess fidelity to the intervention?

As noted above (response to Reviewer 1, comment 2) this study will assess adherence to the CPG by comparing anticipated length of stay per risk group to patient's actual length of stay. This calculation has been built into the electronic database. The following additional information has been added to *Secondary Outcomes* (page 7) to demonstrate this: *"Length of stay will also be utilised to assess adherence to CPG recommendations for "low risk" patient management (anticipated discharge at 24 hours). Documented use of the CPG and reasons for non-adherence will be captured when available."*

4. How are you addressing non-SBI infections? Many multi-plex molecular tests exist to identify a host of viral pathogens from blood, CSF, and respiratory secretions. Are you obtaining these results systematically or opportunistically/as performed? Are they obtained routinely on all infants? If so, what age ranges?

Describing the epidemiology of both SBI and non-SB infections is a secondary objective for this study. Results for all investigations performed on infants presenting with FWS will be captured within the study dataset. As investigations are performed at the discretion of the treating clinician, not all tests will be available for each infant. However all available investigation results (including microscopy, culture, viral and bacterial PCR and other molecular tests) are captured within a single pathology database and can be extracted systematically for all enrolled patients.

Additional text has been added to clarify that SBI and non-SBI results from clinician-directed investigations will be captured for the study cohort:

Secondary Objectives (page 6): *"The secondary research objectives address gaps in local evidence regarding infections in these infants. These include: (i) describing the epidemiology of local pathogens, both SBI and non-SBI, causing FWS, …. (iii) describing the clinical and laboratory characteristics of infants with FWS in our cohort and relationship to SBI and non-SBI diagnoses"*

Data collection (page 9):*"The collection and testing of laboratory specimens will be per routine hospital procedures for FWS investigation (i.e., standard of care and clinician discretion). Information for all tests performed, including molecular tests and other investigations for SBI and viral pathogens, will be collected."*

5. The sequential Bayesian safety monitoring framework is a great choice for this single-arm study. A suggestion for a reference for this section: Thall PF, Simon RM, Estey EH. Bayesian sequential monitoring designs for single-arm clinical trials with multiple outcomes. Stat Med. 1995;14(4):357–379. doi:10.1002/sim.4780140404 or Thall PF, Simon RM, Estey EH. New statistical strategy for monitoring safety and efficacy in single-arm clinical trials. J Clin Oncol. 1996;14(1):296–303. doi:10.1200/JCO.1996.14.1.296 6.

The recommended reference has been incorporated into the manuscript (*Data analysis plan,* page 11).

Assuming standard of care medical interventions, some of which incur a risk of adverse events, what are your adverse events for which you are monitoring (aside from readmission) and how do you account for them in your safety monitoring?

In addition to readmission information, safety events occurring during the patient's admission, defined as a clinical incident that has or could have caused moderate harm, serious harm or death, will be identified and documented by the project nurses during case-note review. This can include adverse events relating to hospitalisation or antimicrobial administration. The Safety Review Group will be made aware of any clinical incident for reporting purposes. Clinical incidents not pertaining to the primary endpoint will be managed as per hospital policy and reported in the study findings on completion of the study.

The following information has been added to *Safety Monitoring* (page 13) to clarify the adverse event and safety review processes of this study: *"Other safety events occurring during the patient's admission, defined as a clinical incident that has or could have caused moderate harm, serious harm or death, will be identified and documented by the project nurses during case-note review and will be reported to the SRG. Clinical incidents not pertaining to the primary endpoint will be managed as per hospital policy and will be reported in the study findings on completion of the study."*

Discussion:

1. Page 14, last sentence: This sentence implies that all infants <3 months old with fever get all invasive testing. Please specify what procedures infants will experience during the intervention.

As noted above, specific procedures that the infant may experience during the intervention have been added to the manuscript to provide clarity in *Safety cohort exposure* section (page 8):
"…investigations may include but are not limited to full blood count, C-reactive protein, urine, blood and/or cerebrospinal fluid microscopy and culture, and viral studies based on clinical presentation, patient age and clinician discretion"
The above sentence identified by the Reviewer has been reworded to demonstrate that the authors hope that this dataset may help identify which infants within our cohort may be managed in the future without specific investigations which were previously standard practice, such as lumbar punctures: *Discussion* (page 15) *"Future questions include identifying which infants may be safely managed without specific investigations (including lumbar punctures), without antibiotics, or without admission at all."*

Supplementary materials:

1. The ED lumbar puncture and FWS guidelines are referenced multiple times but not included in the protocol, making it unclear to me what procedures actually are likely to be performed on infants >28 days of age. Please include these supplementary materials.

The Emergency Department guidelines for the initial investigation and management of FWS has been added as Supplementary file 2 to this revision.

2. The survey does not include any items related to the family's perception of the health of their infant post-discharge. Would consider including a question or two in this area.

The authors have intended the survey question *"I felt [firstname] was ready to be discharged home from the hospital at the time we were sent home"* to capture the family's perception of their child's health at the time of discharge. As the CPG allows low-risk infants to be discharged home earlier than previous practice, the authors felt it important to capture parental readiness for discharge as a key outcome and reflection of the perceived health of the infant.

3. Have you validated or piloted the survey? An example of how one group did validation with a fever survey among parents of young children (not all of them infants): de Bont EG, Francis NA, Dinant GJ, Cals JW. Parents' knowledge, attitudes, and practice in childhood fever: an internet-based survey. Br J Gen Pract. 2014;64(618):e10–e16. doi:10.3399/bjgp14X676401

The study survey was reviewed by the Wesfarmers Infectious Disease Community Reference Group at the Telethon Kids Institute (Perth, Western Australia), which includes parents and grandparents of young children. This group provided assistance with appropriate wording and suggestions of further

questions they would like to be asked, and endorsed the final survey tool and administration method for the study.

Reviewer: 3
Reviewer Name: SHUO FENG

Introduction

1. Page 4, paragraph 1 & 2. "Fever without source (FWS) is one of the most common reasons young infants less than 3 months old present to hospital." Could the authors provide more details on the proportion of FWS among total consultations/hospitalisations, the proportion of high/standard/low risk children, as well as the numbers of unnecessary treatment and hospitalisation? These stats could be helpful in understanding the potential burden to the healthcare system.

As "fever without source" describes an infant's status on presentation to hospital, infants presenting with FWS may subsequently receive a principal diagnosis on discharge of viral infection, SBI or have no identifiable cause of fever. Authors AOM, ACM and TLS have performed a retrospective analysis (unpublished) of all infants less than 3 months old admitted to any Perth metropolitan hospital over a 5 year period (2008 – 2012). Approximately 30% of infants in this age group had an infection-related primary discharge diagnosis for their index admission, however the true number presenting with FWS was not able to be captured. As both study sites did not previously risk stratify infants presenting with FWS, the proportion of infants who were low/standard/high risk of SBI were not available. The following additional text regarding previous infection-related presentation rates within this cohort has been added to *Study Setting* (page 6) to provide further background information: *"A large local retrospective birth cohort analysis identified that approximately 30% of hospitalisations within the first 3 months of life are for infection-related diagnoses".*

Outcomes

2. Page 6-7, secondary outcomes. The authors might consider further investigating the differences in hospital bed days and difference in hospitalisation cost, calculated by considering both first admission the readmission, before and after the implementing of the new guideline.

Full cost analyses will be performed by a health economist on completion of this study. Length of stay for any readmissions will be incorporated into the length of stay hospitalisation cost analyses, with comparison to previously available length of stay data. The following additional text has been added to *Outcomes* (page 7) to reflect this*: "Length of stay for readmissions will also be incorporated into the analyses".*

Sample size

3. Page 10, line 24-25. Could the authors give the justification on the maximum number of infants is 500?

The following details have been added to *Sample size* (page 10) to clarify the selected maximum sample size: *"The study uses sequential Bayesian analyses for monitoring where the trial continues unless pre-specified stopping criteria are met (safe/unsafe) based on the accumulating data. A sample size of 500 infants was deemed feasible based on experience at the two sites and the study timeline, anticipating an average of 5 infants per week. Simulation of the design assuming a maximum*

sample size of 500 infants estimated 83% power to declare safety assuming a 7-day readmission rate equal to the historical rate of 0.05."

4. Page 11, Description of sequential Bayesian analysis. Regard to the complete Bayesian model, it would be helpful to describe the rationale on choices of distributions and parameters, for example, beta distribution and parameter alpha and beta.

The section *Description of sequential Bayesian analysis* (page 12) has been expanded with additional details describing the rationale for the choices regarding distributions and the prior hyperparameters: *"We assume analyses are conducted at interims* $k = 1, \ldots, K-1$ *with sample sizes* N_k *and the terminal analysis at* $k = K$ *at the maximum assumed sample size. We model the number of 7-day readmissions at interim analysis* k*, denoted* y_k*, as a binomial random variable governed by the probability of 7-day readmission,* θ*. For simplicity, we specify a conjugate Beta prior on parameter* θ*"* and *"The hyperparameters* α *and* β *will be set to 1 for a non-informative prior distribution on the 7-day readmission parameter".*

Safety monitoring

5. Page 12, line 38-40. "evidence of unsafe practice (inferiority) is defined as a >95% probability that the rate of readmission is >0.08." Do the authors mean ">=0.08" according to the hypothesis?

This has been corrected to >=0.08 to align with the hypotheses as stated.