**Author’s response to reviews**

**Title:** Enteral Nutrition Tolerance And REspiratory Support (ENTARES Study) in preterm infants: study protocol for a randomized controlled trial

**Authors:**

Francesco Cresi (francesco.cresi@unito.it)

Elena Maggiora (elena.maggiora@gmail.com)

Silvia Borgione (silvia.borgione@unito.it)

Elena Spada (elenaspada.bios@gmail.com)

Alessandra Coscia (alessandra.coscia@unito.it)

Enrico Bertino (enrico.bertino@unito.it)

Fabio Meneghin (fabio.meneghin@asst-fbf-sacco.it)

Luigi Corvaglia (luigi.corvaglia@unibo.it)

Maria Luisa Ventura (mlois.ventura@gmail.com)

Gianluca Lista (gianluca.lista@asst-fbf-sacco.it)

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Reviewers’ report:

Reviewer #1: It is an interesting and well-done protocol about enteral feeding and respiratory support in preterm infants. I would like to ask just for some minor points that require clarification.

1) It is not clear why just preterm infants with a gestational age of 25-29 weeks will be included.

We have included preterm infants with a gestational age of 25-29 weeks as this population has recently become the more investigated population in the study of non-invasive respiratory
supports (e.g. SLI, CURPAP, COIN studies etc.). However, their effects on nutrition have never been evaluated. Aim of the present study is to evaluate the correlation between two very popular issues in this population: non-invasive respiratory management (NCPAP and HHFNC) and feeding tolerance.

2) The allocation concealment mechanism is not clear. Please describe the steps that will be used to conceal the sequence.

The randomization sequence is automatically generated by a software hosted in the online database of the study. Users are blind to the sequence and the software assigns each patient to one of the two arms at the time of enrollment. The database is available on www.entares.hostinggratis.it/homepage.php with the following temporary credentials (username: entares; password: entares)

The text has been modified accordingly. (Page 9, rows 1-3)

3) The sample size is based on "a difference of 30% between the 2 arms". Why was this parameter used?

Our hypothesis is that a difference of 30% between the groups (that is about 6 days) is considered the minimum need to observe a clinically relevant effect. We added this information in the “Discussion” section. (Page 16, rows 22-24)

4) The information about "Age ≤ 5 days?" that appears in the picture 1 is not mentioned in the text.

We thank the reviewer for the important notice. The missing information has been added to the text in the “Methods” section. (Page 8, row 7)
Finally, I encourage you to complete the SPIRIT checklist.

We thank the reviewer for the suggestion; the SPIRIT checklist has been added here attached.

Reviewer #2: The authors have clearly written up a well designed study on an important topic of respiratory management in newborns and its effects on time to enteral feeding, an important outcome related to the possible development of NEC in these babies. Balancing the risks and benefits of improved respiration with improved nutritional support is difficult and the results of this trials will be of high interest to those the neonatology field. Overall, the manuscript is well written and I have only a few comments/suggestions:

- Patients who die or are transferred out of the hospital will be excluded from the analysis. Please consider adding these as outcomes or as important SAEs to report. Otherwise, the current ITT analysis plan is appropriate.

The primary endpoint will be analyzed according to the ITT principle. In this way subjects dead or transferred out to other hospitals will be considered as drop-out in the survival analysis. There is no reason to think that the different respiratory support implies differently the possibility to be transferred and we are confident that with a stratified randomization the numbers of deaths and transfers will be comparable between the two arms. However, we will take care to describe the percentage of this subjects in each arm. This outcome has been added to the secondary outcomes list in the “Methods” section, table 4. (Page 13, row 2)

- Perhaps consider adding a couple limitations to the study in the discussion. (1) The exclusion of more sick babies (neuro/surg, sepsis, major malformation, etc) makes results less generalizable to all NICU patients and (2) inability to double-blind may influence outcome if practitioners already have preconceived ideas for or against types of respiratory support relating to nutritional delivery systems. However, the second limitations seems to be minimized by the standardization of how much to increase feeds and when to interrupt enteral feeds (Table 1 and 2).
(1) In our study we planned to exclude the sickest babies since they are most likely not eligible as they are generally intubated and mechanically ventilated and because their underlying conditions could influence the time to reach full enteral feeding. Using their data we could not understand the hypothetical exclusive impact of non-invasive respiratory support on feeding tolerance.

(2) We agree, but it is not possible to make the clinician blind to the type of respiratory support used. Undoubtedly, this limit will be minimized by the standardizing the management of enteral feeding between the research centers.

- Table 3 shows what data will be records but I recommend adding the timeframe of each of these recordings. For example, ventilation/respiration parameters recorded when there is a change in respiratory support, feeding parameters recorded daily, etc

We agree with the reviewer. All this information is described in the legend of Table 3 in the “Methods” section. (Page 12, rows 1-10)

- The primary outcome will be analyzed by "survival analysis with a non parametric distribution." Please correct the typo from "not" to "non". Also, I am assuming you mean Kaplan-Meier. I would also suggest employing a Cox regression model or other multivariate model where the stratification factors (GA<=28 weeks and site) could be incorporated into the model to ensure no Type 1 or 2 error bias has resulted by not accounting for these factors (see Kahan and Morris BMC Medical Research Methodology 2013, 13:99).

We rewrote the paragraph “Statistical analysis and sample size” adding more information. We hope the paragraph is clearer now. (Page15, rows 2-8)

- What is meant by "by proper" on line 41 page 3?
We changed the phrase in “appropriate generalized linear models”. We will evaluate the appropriate analysis method while analyzing data. For example, the opportunity to transform a variable to normalize it and the better type of transformation for that variable. (Page 15, row 8)

- What is meant by the delta: 5.7 on line 48 page 3? Is this the difference in time to enteral feeds between the JCPAP and HHHFNC from the observation pilot data? If so please state so more clearly.

Delta 5.7 (number of days) corresponds to the 30% difference in the time to reach full enteral feeding that the authors expect to observe evaluating a sample size of 141 patients per arm. This was calculated basing on data collected from January to June 2017 in all the NICUs participating to the study. No pilot study has been performed.

The text has been modified. (Page 15, rows 11-13)

Reviewer #3:

Best regard,

Interesting research protocol. Important knowledge generated, since the problem of feeding in the premature infant with non-invasive respiratory support is problematic and difficult to achieve full nutrition in a timely manner via enteral.

the methodological design is well planned, and is adequate to achieve the objectives planned in the protocol. The analysis plan would seem to be fine. However, it should be reviewed by an expert in biostatistics.