|  |
| --- |
| **SCIENTIFIC ASSESSMENT REPORT** |

|  |  |
| --- | --- |
| ***Scientific Board Secretariat*** | ***Day 1******(first Monday of each month)*** |

**PROJECT ID CODE: 2016-08-EOB 01/08/2016**

|  |  |
| --- | --- |
| ***Coordinating EuCo*** | ***Day 0******(within the end of each month)*** |

**STUDY PROTOCOL SUBMISSION SUBMITTED ON 08/07/2016**

 **PROJECT FULL TITLE: Fluid in Intensive Therapy in the Intensive Care Unit (FIT-ICU)**

**PROJECT ACRONYM:** **FIT-ICU**

**PRINCIPAL INVESTIGATOR:**

 Name **Anders Perner**

 Affiliation: **Center for Research in Intensive Care (CRIC),**

 **Copenhagen University Hospital,**

 **Rigshospitalet, Denamark**

 e-mail: **Anders.Perner@regionh.dk**

 phone : xxxxxxxxxxxxx

**SPONSOR:** Name: **Center for Research in Intensive Care (CRIC)**

Affiliation: **Copenhagen University Hospital,**

 **Rigshospitalet, Denamark**

 e-mail: xxxxxxxxxxxxx

 phone: xxxxxxxxxxxxx

**COORDINATING EuCo:** Name . **Christine Kubiak**

 Affiliation xxxxxxxxxxx

 e-mail: **Christine.KUBIAK@ecrin.org**

 phone: xxxxxxxxxxxxx

**SCIENTIFIC BOARD PRELIMINARY CHECK**

 **Week 1**

|  |  |
| --- | --- |
| ***Scientific Board Secretariat*** | ***Day 7*** |

**SCIENTIFIC BOARD PRELIMINARY CHECK EXPECTED ON 07/08/2016**

**CirculateD on 08/07/2016**

|  |  |
| --- | --- |
| ***Scientific Board Secretariat*** | ***Day 7*** |

**Referee(S) agreed. Protocol circulated on****13/07/2016**

**Protocol circulated to the SCIENTIFIC BOARD on** **21/07/2016**

**Referees’ comments and recommendations**

 **Weeks 2-3**

|  |  |
| --- | --- |
| ***Methodological reviewer***  | ***Day 21*** |

**Assessment report EXPECTED ON 22/08/2016 CirculateD on 28/07/2016**

**Deleted**

**ScIENTIFIC BOARD’s comments and recommendations**

**Weeks 2-3**

|  |  |
| --- | --- |
| ***Scientific Board members*** | ***Day 21*** |

**Comments EXPECTED ON 22/08/2016 CirculateD on 29/07/2016**

**Deleted**

**Scientific Board recommendations**

 **Week 4**

|  |  |
| --- | --- |
| ***Scientific Board Secretariat*** | ***Day 28*** |

**SCIENTIFIC BOARD advice EXPECTED ON 29/08/2016 Released on 02/08/2016**

Background

General design

This is a modified 2 x 2 factorial, centrally randomized, using computer generated allocation sequences, 4 parallel groups, stratified, outcome assessor and statistician blinded, multicentre, multinational trial of adult patients, who are admitted to intensive care units (ICU) in Europe.

The first factor will be the fluid therapy regimen (standard vs restrictive fluid) and the second factor the compliance strategy regarding the protocol (standard vs encouraged). Notably, the first factor will be stratified by site presence of septic shock and (genetic) risk factors for death, and second factor is randomised in clusters and stratified by university hospitals or not.

The 2 fluid regimens and the 2 compliance strategies are clearly detailed and appear reasonable.

The primary outcome is all-cause mortality which is complemented with a series of secondary outcomes; (a) overall compliance with the protocol for assigned fluid regimens, (b) mortality within the follow-up period of one year from randomization of the last patient, (c) health related quality of life (HRQoL) after one year of follow-up, (d) days alive at 90 days without life support, (e) serious adverse events (SAE).

Sample size

The sample size (6,512 patients) has been driven by the primary outcome and the aim is to assess a 20% relative risk reduction (absolute risk reduction of 5%), assuming that the control rate is expected to around 25%, for a two-sided 1% alpha level and 80% statistical power. The type 1 error is adjusted for 6 possible comparisons. Assuming no interaction between the fluid interventions and the compliance the trial would have 90% for a 14% for fluid therapies comparison. In an individualized randomized trial with equal group sizes of 2,214 patients, the study would have 80% statistical power to detect a 5% reduction of non-compliance (25 encouraged sites vs 25 sites with usual performance) assuming an expected control rate of about 25%, and intra cluster correlation coefficient of 0.015.

Primary analysis

The primary analyses will all be on the intention-to-treat population, being all randomized patients that do not withdraw their informed consent to use acquired data during their participation. Per protocol analyses will be conducted as secondary analysis. The analyses will be adjusted by the stratification variables and age and SOFA. The main outcome will be analysed using the Cox regression method primarily adjusted by the variables described.

Handling of missing data

There is a plan to handle missing data using procedures relying in the Missing At Random (MAR) assumption, conditioned to the rate of missingness (>5%) and the Little’s test.

Handling of multiplicity

P-values<0.01 for comparisons between the 4 intervention groups will be considered statistically significant in the final analysis when the planned sample size has been achieved. The effect on compliance in the cluster part of the trial will be considered statistically significant if P<0.05.

Interim analyses-DSMC

A data safety and monitoring committee (DSMC) will oversee the trial. At least one interim-analysis will be performed after 50% of the planned sample size has been randomized (3,256 patients). No details are given on the concrete method, and it is stated that the DSMC may conduct interim-analyses whenever they want.

**Comments on the proposal**

Overall, the summarized synopsis it is sufficiently detailed to address a complete methodological evaluation. However, the following issues and recommendations are raised:

Rationale

Both the two experimental as well as the two control interventions should be based on updated systematic reviews. Reference 20 regarding fluid administration refers to a personal communication only. The two trial hypotheses should be supported by better evidence that they really are still open and clinically important questions.

Sample size

The sample size description is quite comprehensive in the synopsis and appears sufficiently justified and reasonable. However, it is not fully understood why the 1% alpha level is selected. It should be described the potential impact of the number of comparisons (the number of 6 for the main analysis is stated but not described) and the interim analysis strategy (which is not specified).

Primary analysis

The trial design consists of 2 factors with different strategies for the randomisation. There is no information on the role of the cluster randomisation in the analysis. This should be mentioned.

Handling of missing data

The final plan should take into account also other methods in addition to those relying on the MAR assumption. Those methods assume that missingness can be predicted given the observed data and this is not always a good assumption. A conservative approach penalising treatment related missingness (i.e. because of potential lack of efficacy or safety issues) appears to be more reasonable and the shrinkage in variability might be handled by MI methods.

Taking into account that even a very little amount of missingness may bias the results and that the use of tests for missing data are quite controversial, it is recommended that a plan for handling is extensively planned (although not needed at this stage).

Handling of multiplicity, Interim analyses-DSMC

As stated in the above sample size subsection, with the information available in the synopsis, the selection of 1% to adjust for 6 comparisons is not fully understood. In addition, the impact of the final concrete method for the interim analysis/es is not clear.

It is acknowledged that the DSMC may ask for any analysis at any time for safety issues. However, the problem is that inferential efficacy analyses may trigger the premature finalisation of the trial for overwhelming efficacy and then increase the Type 1 error. Therefore, any analysis intended to assess inferential efficacy should be planned upfront and never be triggered based on data results. Maybe this was not the intention of the plan but the current wording may be interpreted this way.

Others

Minor comments that the CIs may wish to take into account for future versions: while the mention to the consensus documents leaded by the scientific journals (CONSORT, SPIRIT) are fully endorsed, there is no reference to regulatory documents that might be helpful for general concepts (ICHE9) and for some critical issues mentioned above, such as handling of missing data, multiplicity, interim analyses and the DMC/DSMB .

For the preparation of their final protocol the CIs are also advised to:

* adopt the ECRIN transparency rules (<http://www.ecrin.org/images/pdf/Check_List_for_submission_to_the_ECRIN_Scientific_board_SOP_03_ECRIN_V2_2015_10_15.pdf> ), and
* describe plans for sharing data after the trial and in what format and where they will be placed

Conclusion

The rationale for the study should be substantiated by systematic reviews of the literature.

The following issues should also be addressed at this stage: selection/justification of 1% alpha level, description and pre-specification of strategy and number of interim analysis/es, role of the DSMC regarding triggering potential un-planned interim analysis, handling of missing data.

**rEFERENCES**

 The European Medicines Agency’s scientific guidelines on biostatistics help medicine developers prepare marketing authorisation applications for human medicines. URL: <http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000602.jsp&mid=WC0b01ac05807d91a4>

 CPMP/ICH/363/96. ICH E9 Statistical Principles for Clinical Trials. URL: <http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_001228.jsp&mid=WC0b01ac05807d91a4>

 CPMP/EWP/1776/99 Rev1. Guideline on Missing Data in confirmatory trials. URL: <http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_001221.jsp&mid=WC0b01ac05807d91a4>

 CPMP/EWP/908/99. Points to Consider on Multiplicity issues in Clinical Trials. URL: <http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_001220.jsp&mid=WC0b01ac05807d91a4>

 CHMP/EWP/2459/02. Methodological issues in confirmatory clinical trials planned with an adaptive design: <http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_001223.jsp&mid=WC0b01ac05807d91a4>

 CHMP/EWP/5872/03 .Data monitoring committees: <http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_001225.jsp&mid=WC0b01ac05807d91a4>