

**ECRIN-ON-BOARD – STUDY SYNOPSIS**

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**General Information**

Principal Investigator name and institution:

Iwan van der Horst, MD, PhD, Associate Professor, Department of Critical Care, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

Sponsor:

Center for Research in Intensive Care (CRIC), Copenhagen University Hospital, Rigshospitalet, Denmark

Participating countries:

The Netherlands, Denmark, France, Sweden, Finland, United Kingdom, and Switzerland

Planned number of clinical sites: 60

Planned number of trial patients: 25000

**Study**

What is the trial’s working title?

Simple Intensive Care Unit Study (SICS) pack

What is the rationale for trial   
(with details of existing evidence   
e.g., metaanalysis, systematic review)?

Debate is ongoing within the community of critical care medicine whether a randomised clinical trial (RCT) or an observational study (OS) is the optimal design for research in critical care. Arguments are the inevitable heterogeneity between patients included and patents not included in RCT and in patient populations with heterogeneous average intervention effects, selection of outcomes not important for decision, all leading to results that are difficult to interpret and apply. Proponents of the RCT stress the methodological arguments including unobserved confounding while opponents emphasize that potentially important differences between included and not included patients and that on average intervention effects are lost due to multiple heterogeneous intervention effects in subgroups. Unlike this debate our research proposal involves an integrated approach of an observational study with a randomised trial to combine the strengths of both designs.

How will the result of the trial change medical practice?

The observational study is designed as an ongoing multinational multicenter infrastructure, build of different modules, each focusing on a specific research question. All variables to be collected for both the observational study and the trial, including all outcomes, will be included in the modules of the observational study. Further, this observational study may serve as infrastructure not only for the randomised trial part of The SICS-pack FIT-project (Fluid Intensive Therapy, FIT; see randomised trial, study no2), but also for future randomized trials.

This combined approach of an observation study with a randomised trial on top will provide opportunities for evaluating the outcomes of both the participants included in the randomised trial and the participants excluded from the trial but included in the observational study. Thereby, the generalizability of the observed effect of the trial can solidly be investigated.

Another major advantage of the module structure of the observational study is that there are opportunities for sophisticated measurements and highly specialised academic research questions to be answered, but above all that community hospitals are able to participate at the level they see fit. As such generalisable results for the entire critically ill population may be formulated rather than subgroup answers only. This will also facilitate the generalizability of the results of the studies, and stimulates opportunities for lasting cooperation as well.

Finally, a major advantage of the module structure of the observational study is that by constructing the simplest possible core module while having the possibility to extend to specific research questions in additional modules there is a guaranteed lowest probability for failure. Sites can sign up for modules according to their local available resources and facilities.

We would strongly argue that in contrast to the current debate within critical care, opponents of the two study designs (randomised versus observational) should seek for positive interactions, amplification, and integration, just like national borders within Europe should not in any way obstruct multicenter research cooperation. Rather, participation from countries outside the group of core applicants of this call will be expected.

Describe the subject population:

All patients acutely admitted to the Intensive Care unit will be eligible for inclusion in the observation cohort study. In principle, all patients are eligible for each module of the study. One of the main goals is to be as inclusive as possible.

List the inclusion and exclusion criteria:

Inclusion criteria are:

• Are aged 18 years or above

• Are acutely admitted to the ICU

Exclusion criteria:

• All patients who are planned admitted (e.g., after planned surgery or for any other reasons)

• Consent not obtainable

• Previously enrolled in the FIT-ICU trial

**Statistics**

What is the trial design?

The study will be a prospective observational cohort study of patients acutely admitted to the Intensive Care Unit. The cohort study will be composed of modules, with each module addressing a specific research question.

The first module, the core module, will provide the basic characteristics and the primary outcomes: all-cause 90 day mortality and severe adverse events (SAE). A secondary module will provide all secondary outcomes, including health related quality of life (HRQoL). A third module will collect one blood sample to be stored for genetic analyses. A fourth module will collect all data of prognostic variables. New mortality prediction models could be build on established models enhanced with additional phenotyping and genotyping risk factors A fifth module evaluates cardiovascular mechanisms including advanced imaging, such as ultrasound of heart and lungs. A sixth module evaluates long term kidney function. A seventh module focusses on patient and relatives satisfaction and interaction.

Module 1: the core module

Research question:

The research question is how baseline characteristics of patients and sites are associated with all-cause 90-day mortality.

Variables

Only standard baseline demographic and clinical characteristics together with all-cause 90 day mortality will be collected within module 1. Also the variables based on which the participants will be screened and selected for the randomised trial need to be collected in the core module. Module 1 is the basis and provides elementary data only. Contributing to module 1 is the minimum requirement for each site in order to participate. The leanest content of module 1 guarantees low thresholds for sites to participate so that generalizability of results can be maximised.

Module 2: Secondary outcomes

Introduction

The Core Outcome Measures in Effectiveness Trials (COMET) Initiative pursues the development and application of agreed standardised sets of outcomes, known as ‘core outcome sets’ (COS). These sets represent the minimum that should be measured and reported in all clinical trials of a specific condition. Common core study endpoints facilitate pooling of data in meta-analyses and interpreting results of studies whose entry criteria and study populations might be very diverse. Investigators would not be limited to using the COS outcomes, however they would be encouraged to ensure that at the least this information was collected and reported; while researchers may continue to explore other outcomes as well.

The International Forum for Acute Care Trialists (InFACT) was launched in 2008 as a network of investigator-led clinical research groups and academic institutions whose focus is the optimal care of critically ill children and adults (www.infactglobal.org). For critical care core outcome sets are currently in initial phases of development in the following areas (in close collaboration with COMET): Mechanical ventilation, Long term outcomes for acute respiratory failure (www.improvelto.com), Closed head injury, Sepsis, Subarachnoid hemorrhage, Delirium, Physical Rehabilitation, Cardiac Arrest.

Unfortunately, currently no core outcome sets have yet been finished for areas of critically ill patients. We therefore defined our standard set of patient important outcomes according to GRADE.

Research question

The research question is how the interventions of the randomised trial are associated with patient important outcomes and how the outcomes of the patients included in the randomized trials relate to the outcomes of the patients not included in the trial but included in the observational study, i.e., can the results of the trial be generalized to the acute critically ill population.

Variables

The importance of outcomes according to the patients perspective following GRADE.(4)

References

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Module 3: genetics and epigenetics

Introduction

In 2000 the Human Genome draft was completed which resulted in an explosion of studies examining genetic determinants of disease (1,2). Understanding genetic determinants of critical illness may improve current risk stratification models, provide individualized therapies, and improve our current understanding of disease mechanisms. Consequently, physicians have tried to understand if and how genetic variation affects susceptibility and outcome of critical illnesses, and how detrimental side effects and expense of adjuvant therapy could be avoided in patients who, by genotype, are predicted not to benefit.

Some diseases have one single gene as determinant (i.e., Mendelian traits; e.g., cystic fibrosis) while most critical illnesses are multifactorial diseases with ‘complex traits’ (e.g., sepsis with multiple genetic variations within inflammatory mediators involved in the sepsis pathway) (3-8). However, environmental factors such as type of organism, antibiotic susceptibility, site of infection, how soon the infection is detected, and whether it is treated appropriately may greatly modify genetic effects. Multiple contributing confounders make searching for genetic determinants challenging. While environmental factors and effect modifiers contribute to complexity also heterogeneity in patient populations add to the difficulties (e.g., multiple different diseases may evolve to sepsis).

Single nucleotide polymorphisms (SNPs) are the most commonly occurring type of variant in the genome, and they are the most frequently studied in genetic association studies. The development and mapping of haplotypes of all SNPs (HapMap) has contributed to understanding the patterns of diversity across the human genome (9). Tools such as HapMap have allowed researchers to move away from a candidate gene approach to genome-wide association studies. Genome-wide association studies (GWAS) do not require a prior hypothesis of candidate genes to test for association with disease. However, haplotype analysis has produced a lot of non-reproducible results, so that today results are required to have been reproduced in a separate cohort before being accepted for publication. Genetic association studies specifically require sufficient numbers of events and numbers of participants for reliable conclusions.

Epigenetics refers to the regulatory processes that control gene expression without altering the DNA sequence, with the most studied epigenetic process being DNA methylation. Because epigenetic variation reflects both genetic and environmental exposures, there is potential to identify novel disease associated genes and pathways that might not be discovered through genetic studies alone. Methylome-wide association studies (MWASs) have already begun to identify genomic CpG sites whose methylation levels are associated with BMI [10]. DNA-methylation levels at specific CpG sites have already shown to be accurate predictors of age and smoking status [11-13], and such phenotypic prediction could extend to other complex traits and diseases and potentially improve prediction over genetic information.

Research question

Primary: Which SNPs can be identified in the critically ill population to be associated with mortality or adverse outcome?

Secondary: Can genetic factors improve mortality prediction models and ultimately contribute to selection in randomised trials based on risk stratification.

Variables

Genetic and epigenetic analyses from one blood sample of each patient at ICU entry

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Module 4: prognostication

Introduction

A personalized and evidence based approach to future interventions necessitates a detailed knowledge of phenotypic as well as genotypic risk factors. Patients with various diseases are admitted to the Intensive Care Unit and each disease is defined by a multitude of complex interactions of risk-factors, effect-modifiers, and time-dependent effects, i.e., the underlying genetic constitution (Stolk). Current randomized clinical trials select patients based on their symptoms or disease at ICU entry. This concept of selection for inclusion in RCTs ignores the underlying genetic constitution of patients, which may be an important determinant of the outcome. Further, randomised trials in critical care are criticized for including heterogeneous populations leading to neutral average treatment effects (Burke, Ioannidis, Vincent).

Adaptive enrichment trial design pre-specifies the inclusion of important subgroups of patients and the evaluation of each subgroup at each interim-analysis. Heterogeneity of treatment effects are evaluated in each interim analysis (using trial sequential methods) so that decisions to terminate or continue inclusion can be taken on a timely basis. Simulation data have shown that the adaptive enrichment design is associated with increased power, lower required sample sizes, shorter duration, and lower costs (Simon 2013). One other major advantage is that fewer patients are unnecessarily harmed as subgroups reaching the boundary for harm or futility may be identified at an earlier time point and not exclusively after the final analysis.

Inclusion of patients in RCT’s based on a multivariable risk prediction model could address heterogeneity in treatment effects when subgroups of patients are identified a priori based on expected amount of benefit (Iwashyna 2015). Several mortality risk prediction models (e.g., APACHE IV, MPM, and SAPS) have been validated for critically ill patients and are widely used (Zimmerman, Higgins, Metnitz). A personalized selection procedure for RCT’s based on an elaborated risk profile for mortality, preferably including genetic or epigenetic variables (identified in module 3), combined with an adaptive enrichment trial design (adaptation of subgroups and sample sizes) seems the future direction to address the heterogeneity in treatment effects across different critical care populations in an evidence based manner.

Research question

Is it possible to predict mortality risk including genetic variables on top of other (known) risk factors ?

Variables

Combination of prognostic variables at ICU entry using different prognostic models and enhanced with genetic risk factors.

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Module 5: cardiovascular pathophysiology including advanced imaging

Introduction

Ultrasound is increasingly applied in critical care today. However, validation of techniques have been poor or insufficient, while based on either selected or low numbers of patients. All hemodynamic variables will be obtained through additional physical examination combined with echography of the heart and lung, and will be defined and measured uniformly.

Research question

Can cardiovascular variables contribute to improved understanding of critically ill patient?

Variables

Variables obtained by ultrasound of heart (e.g., cardiac output) and lung (e.g., pleural fluid, B-lines).

Module 6: Chronic long-term kidney function

Introduction

Acute kidney injury (AKI) is a frequent complication of life-threatening disorders seen in patients in ICUs, and occurs in 15-33% of all critically ill patients. AKI is defined as an increase in waste products in the blood (reflected e.g. by increased serum creatinine) and/or a reduction in urine output, and is associated with a higher mortality and with the development of chronic kidney disease (CKD) [1]. Patients acquiring AKI in the ICU and requiring renal replacement therapy have a 50% chance of not surviving their hospital stay [2,3]. Patients who survive their episode of AKI, 25% will develop CKD/ESRD end stage renal disease in their lifetime 4 with as an ultimate outcome lifelong dialysis or kidney transplantation. To date, there is a limited understanding of the risk factors for developing AKI and chronic kidney disease after AKI, especially in critically ill patients. This limited understanding is further hampered by the extreme variation in patient age, co-morbidity, medication, and severity of the insult/injury of ICU patients. Patients that develop AKI in the ICU in which kidney function normalizes are not actively followed up in regular care, while preventive measures in selected high risk patients might reduce CKD and end stage renal disease.

Research question

How is critical illness associated with long-term kidney function?

Variables

Kidney function in AKI patients one year after ICU discharge

References

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Module 7: Patient and relatives satisfaction

Quality of care is increasingly recognised as being important as an outcome, from the perspective of the patients, but also from the perspective of relatives.

Research question

How is critical illness associated with satisfaction of relatives?

Variables

Satisfaction of relatives

What are the trial endpoints/outcome measures?

Module 1: all-cause mortality and SAE

Module 2: All outcomes are graded according to the patient’s perspective following GRADE. For large trials in critically ill patients these outcomes are “standard” standard set of core outcomes which will be more or less the same for a future next trial.

Module 3: genetics and epigenetics

Module 4: prognostic variables

Module 5: cardiovascular pathophysiology including advanced imaging

Module 6: Chronic long-term kidney function

Module 7: Patient and relatives satisfaction

What is the power calculation of the sample size? The sample size for the observational study is driven by the numbers of patients needed for genetic association studies, since these specifically require sufficient numbers of events and numbers of participants for reliable conclusions. With an anticipated of 25000 patients we expect to meet these criteria. As there are currently no large datasets available there is uncertainty whether these estimate will appear sufficient.

Are there any particular ethical considerations? For the observational study there are no specific ethical considerations apart from usual ethical aspects such as informing patients and families and obtaining informed consent.

**Measures to ensure trial completion**

Describe the recruitment strategy, schedule and timelines:

The observational study (study no. 1) will start enrolment before the start of the randomised trial (study no. 2.). This allows all participating sites to include patients of study no. 2 during the continuation of study 1. Moreover, the prospective cohort studies aims to answer research questions beyond the end of study no. 2, the randomised trial.

•First Patient (or study subject), First Visit (FPFV): First of June 2018

•Last Patient (or study subject), First Visit will be 1 year after the 90 days follow-up of the last randomized patient in study 2: 31th of May 2021

•Last Patient (or study subject), Last Visit: 31th of August 2021

•End of Study (including follow-up and data analysis): 31th of May 2022

We will screen all patients admitted to the ICU’s fulfilling the inclusion criteria.

We expect 60 sites of ICU’s in Europe to participate, 5 in the The Netherlands, 20 in Denmark, 10 in France, 5 in Sweden, 5 in Finland, 10 in United Kingdom, and 5 in Switzerland. On average each site is expected to include at least 400 patients in this observational study during three years.