

**ECRIN-ON-BOARD – STUDY SYNOPSIS**

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Czech Republic: Lenka Souckova | Lenka.souckova@fnusa.cz

France: Amélie Michon | amelie.michon@ecrin.org

Germany: Anke Strenge-Hesse | anke.strenge-hesse@uk-koeln.de

Hungary: Timea Molnar | molnar.timea@pte.hu

Italy: Lucia Palmisano | l.palmisano@iss.it

Portugal: Catarina Maderia | catarina.madeira@fcm.unl.pt

Spain: Joaquín Sáez-Peñataro and Mohammed Ezzeldin Sharaf | jsaez@clinic.ub.es and mezzeld@clinic.ub.es

Turkey: Burc Aydin | burcaydin@gmail.com

**General Information**

Principal Investigator name and institution:

Anders Perner, MD, PhD, Professor in Intensive Care, Copenhagen University Hospital, Rigshospitalet, Denmark

Sponsor:

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

Participating countries:

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

Planned number of clinical sites: 60

Planned number of trial patients: 6,512

**Study**

What is the trial’s working title?

Fluid in Intensive Therapy in the Intensive Care Unit (FIT-ICU)

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

There seems to be a possibility to reduce all-cause mortality with 15-20% relative risk reduction (RRR) in ICU patients using restrictive fluid administration compared with standard of care fluid regimens in a systematic review (20) and feasibility trial (19), both under review (personal communication).

How will the result of the trial change medical practice?

Fluid administration will be evidence based and possibly individualized according to known risk factors including genetic risk profiles.

Describe the subject population:

All adult patients, acutely admitted to intensive care not fulfilling the exclusion criteria

List the inclusion and exclusion criteria:

We will screen patients for inclusion who:

• Are aged 18 years or above

• Are acutely admitted to the ICU

• Can be randomised within 6 hrs of ICU admission AND

• Have received at least 2 litres of intravenous fluids in the last 24 hours

The aim is to enrol patients who have received initial fluid therapy as soon as possible after ICU admission. The 2 litre criterion is based on the observed median fluid volume given prior to randomisation in a large resuscitation trial in sepsis (Promise NEJM 2014)(29). Children will not be screened because their outcomes are so much better than those observed in adults.

We will exclude patients who fulfil one or more of the following criteria:

• Severe hypernatremia, p-Na > 155 mmol/l

• Severe hyponatremia, p-Na < 125 mmol/l

• Diabetic ketoacidosis

• Hyperosmolar, non-ketotic hyperglycaemia

• Out of hospital cardiac arrest

• Organ transplant during current hospital admission

• Acute burn injury of more than 15% of the body surface area

• Withdraw of life support (mech. ventilation, vasopressor/inotrope or RRT) deemed imminent

• Consent not obtainable

• Previously enrolled in the FIT-ICU trial

**Statistics**

What is the trial design?

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 acutely admitted to intensive care units (ICU) in Europe. All patients participate in the observational study no 1. (the SICS-pack study) as well and will be randomized to a restrictive fluid therapy (experimental) or a standard care fluid therapy (control) during the ICU stay. At the same time sites (ICU’s) will be cluster randomized to a ‘compliance encouragement strategy’ or to a ‘usual conduct of trial strategy’. The restrictive vs. standard fluid therapy part of the trial will be stratified for site, presence of septic shock and (genetic) risk factors for death. The cluster randomized compliance part of the trial will be stratified within national boundaries and for sites being university hospitals or not.

Description of the interventions in the individualized part of the trial, the fluid part:

Duration for both interventions

The intervention period is the entire ICU stay

Restrictive fluid therapy regimen:

The experimental intervention is the restrictive fluid therapy.

No intravenous fluids should be given except if one of the below extenuating circumstances occurs; in these cases, intravenous may be given:

• In case of severe hypoperfusion or severe circulatory impairment defined by either lactate >4 mM, MAP <50 mmHg (with or without vasopressor/inotrope), mottling beyond the kneecap (mottling score ≥ 3) OR urinary output <0.1 ml/hr/IBW for more than 2 consecutive hrs unless the patients has established kidney failure. An intravenous bolus of 250-500 ml of crystalloid solution may be given followed by re-evaluation. These criteria identify patients at increased risk of death (Boyd CCM 2011 (30), Ait-Oufella ICM 2013 (3), Varpula ICM 2005 (31) and were tested the CLASSIC feasibility trial assessing restrictive vs. standard care fluid therapy in patients with septic shock (Hjortrup 2016, in review) (19).

• In case of overt fluid losses (e.g. diarrhoea, bleeding or ascites drainage) fluid may be given to correct for the loss.

• In case the oral/enteral route for water or electrolyte solutions is contraindicated or has failed as judged by the clinical team intravenous fluids may be given to correct dehydration or electrolyte deficiencies or to ensure a total input of 1 litre per 24 h including medications and nutrition

• In case the oral/enteral route for nutrition is contraindicated or has failed as judged by the clinical team intravenous nutrition may be given if the patient has been admitted to the ICU for more than a week (ASPEN guideline 2016) (33) or to patients severely malnourished.

• Intravenous fluids may be given as carrier for medication, but the volume should be reduced to the lowest possible volume for the given medication

Standard care fluid regimen:

The control intervention is standard care.

There will be no upper limit for the use of either intravenous or oral/enteral fluids. In particular

•Intravenous fluids should be given in the case of hypoperfusion or circulatory impairment and should be continued as long as hemodynamic variables improve including static or dynamic variable(s) as chosen by the clinicians. These criteria are based on the SSC guideline (Dellinger ICM 2014) (1)

•Intravenous fluids should be given as maintenance if the ICU has a protocol recommending maintenance fluid

•Intravenous fluids should be given to substitute expected or observed loss, dehydration or electrolyte derangements

•Intravenous nutrition may be given if the patient does not tolerate the oral/enteral route and has been admitted to the ICU for more than a week (ASPEN guideline 2016) (33) or to patients severely malnourished.

Types of fluid to be used in both intervention groups

•Fluids given for circulatory impairment: Only isotonic crystalloids are to be given (as per the Scandinavian Guideline for Fluid resuscitation, Perner AAS 2014) (32) without the use of a pressure bag.

•Fluids given to substitute overt loss: Isotonic crystalloids are to be given. If large amounts of ascites are lost than human albumin 5% may be given (ref).

•Fluids given for dehydration: Water or isotonic glucose should be given.

•Fluids given for electrolyte deficiencies: Fluids should be chosen to substitute the specific deficiency.

•Fluids given as maintenance: Fluids should be chosen according to the ICU’s protocol

Blood products are only to be given on specific indications including severe bleeding, severe anaemia and prophylactic in case of severe coagulopathy.

For the cluster randomized part of the trial:

Compliance encouragement strategy:

A) On sites randomized to compliance encouragement strategy the Good Clinical Practice monitoring and site visits will be performed according to the monitoring and source data verification plan. Reports on the results from the monitoring sessions will be distributed to the site investigators.

B) To the sites randomized to the compliance encouragement strategy monthly reports of the compliance with the protocol for both fluid regimens registered within the eCRF will be made and send from the data manager to the site investigators encouraging them to improve compliance if not above 90% or maintain their rate and completeness of compliance if it is above 90%. Fluid balances will be reported.

C) At the sites randomized to the compliance encouragement strategy there will be monthly meetings among site investigators discussing how to advance compliance with the assigned fluid regimens based on A. Alternatively discussions will focus upon possible problems with compliance to the protocol and how to overcome them.

D) An overall compliance count of patients without major protocol violations in percent of all randomized patients will be displayed and highlighted on the eCRF interface when investigators log in to the website.

E) Adherence to pre-trial practice, registered before trial start in study 1, in the patients randomized to the ‘Standard fluid regimen’ will be monitored and monthly reports send to the sites randomized to the ‘Compliance encouragement strategy’.

Usual conduct strategy:

A) On sites randomized to usual conduct strategy the Good Clinical Practice monitoring and site visits will be performed according to the monitoring and source data verification plan. Reports on the results from the monitoring sessions will be distributed to the site investigators.

What are the trial endpoints/outcome measures?

A) Primary outcome is all-cause mortality secondary outcomes: B) Overall compliance with the protocol for assigned fluid regimens, compliance defined as number of patients without major protocol violations divided by the number of all randomized patients. C) Mortality within the follow-up period of one year from randomization of the last patient (mortality within the total follow-up period). D) Health related quality of life (HRQoL) after one year of follow-up for all patients. Dead patients will be assigned the lowest possible HRQoL score. E) Days alive at 90 days without life support (ventilator therapy, renal replacement therapy (RRT), inotropic or vasopressor drug infusion). F) Serious adverse events (SAE) defined as :

A) Death

B) Ischaemic events as stroke, myocardial infarction, splanchnic ischaemia.

C) Acute kidney injury

D)The need for life support during ICU stay (RRT, respirator, and inotropic drugs)

E) New episodes of shock

 Reporting of SAE's will take place through the eCRF and to the authorities from all sites as defined in the national legislation. As all patients in the ICU are prone to develop SAE’s, according to the ICH-GCP criteria, with high frequency, making it virtually impossible to report all SAE’s, we will focus on the above listed SAE’s hypothesized to be associated with restrictive or standard care fluid therapy and report to the ethical committee and the EuDract database.

What is the power calculation of the sample size?

In order to detect or reject a 20% relative risk reduction19, 20, achieving a maximal type 1 error of 1% for the primary outcome and the 6 possible comparisons in a trial with 4 groups and a type 2 error of 20%, we aim for randomization of 6,512 patients admitted to the ICU’s listed in the trial. The type 1 error is adjusted for multiplicity due to 6 possible comparisons (12, 13, 14) as we cannot rule out, and actually hypothesize that there is a possible interaction between fluid restrictive strategy and a compliance encouragement strategy. In fact we anticipate that the compliance encouragement will augment the intervention effect of fluid restriction. The sample size estimation is based on a mortality within 90 days for the patients included in the control group (liberal resuscitation fluid administration) of 25% (19, 20) and randomization 1:1:1:1 to the 4 groups, defined by individual and cluster randomization, and will be able to detect or refute an absolute risk reduction of 5% or more, corresponding to a number needed to treat of 20 or less.

Assuming no interaction between the fluid intervention and the compliance encouragement strategy and a strict 2 x 2 factorial design the trial will have 90% power to detect or reject a RRR of 14% in mortality of the restrictive regimen compared with the standard of care fluid therapy.

If we assume no interaction between the fluid intervention and the compliance encouragement strategy and a strict 2 x 2 factorial design, considering only the comparison between ‘the compliance encouragement’ group of sites and ‘the usual conduct of trial’ group of sites in the cluster part of the trial, we will be able to detect a 5% absolute risk reduction of non-compliance between the compliance encouragement group of 25 sites compared with the usual performance group of 25 sites. The assumed percentage of protocol violations in the usual performance group is 25%. The sample size is adjusted for an assumed intra cluster correlation coefficient (15, 26) of 0.015 (a design effect of 2.94) and maximal type 1 and 2 errors of 5% and 20% respectively. In an individualized randomized trial with equal group sizes 2,214 patients would be needed to detect or reject an absolute 5% reduction of non-compliance with the chosen type 1 and 2 errors of 5% and 20% respectively.

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. We will perform per protocol analyses as well excluding patients with one or more major protocol violation.

To obtain adequate power in the statistical analyses we will adjust the primary analyses for stratification variables listed in, and present the intervention effect with 95% confidence intervals in the overall population as well as in the planned subpopulations listed. We will also present analyses adjusting for age and SOFA score in addition to the stratification variables. Mortality within the maximal follow-up period of one year from randomization of the last patient will be analyzed using Cox regression primarily adjusted for the stratification variables as listed above and secondarily for further design variables of age and SOFA score.

We will use an electronic case report form (eCRF) with a pragmatic design and incentive strategies to maximize complete registration in order to minimize the occurrence of missing data. However, if missingness exceeds 5% and Little’s test is statistically significant, missing data will be handled using multiple imputation (MI) in at least 10 imputed dataset using chained imputation. Results using MI, if necessary, will be considered the primary result of the trial. 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.

A data safety and monitoring committee (DSMC) will oversee the trial, having immediate and full access to all data in the trial database during the entire trial period. At least one interim-analysis will be performed after 50% of the planned sample size has been randomized (3,256 patients), but, the DSMC may conduct interim-analyses whenever they want. However, the level of statistical significance for interim-analyses should be adjusted according to the LanDemets group sequential monitoring boundaries using the achieved fraction of the acquired samples size relative to the required sample size. The confidence intervals for the interim calculated intervention effects will be adjusted according to the achieved information fraction as well.

Are there any particular ethical considerations?

Fluid is an important part of all therapeutic strategies in ICU patients. Patients admitted to the ICU are often haemodynamically unstable and fail to meet normal values of blood pressure or cardiac output. Therefore, it’s been practice for decades to administer resuscitation fluid with the aim to restore or at least increase hemodynamic variables. Evidence questions whether liberal fluid administration has sufficiently positive effects to outweigh possible serious adverse effects including acute kidney injury and even excess mortality (19, 20). Nevertheless, there is profound diversity in the practice of administrating resuscitation fluid in ICU’s in Europe and the true effects of different strategies for fluid administration on mortality, SAE, kidney injury, HRQoL, and use of life support in the ICU is unknown. Based on the knowledge acquired so far a restrictive and a liberal strategy would not a priori be considered unsafe, however, which of the strategies that perform best, or whether they perform equally good, on the outcomes of mortality, SAE, kidney injury, HRQoL, and use of life support in the ICU has to be investigated in a large, pragmatic, randomized trial with minimized risk of bias.

**Measures to ensure trial completion**

Describe the recruitment strategy, schedule and timelines:

Schedule for study conduct including timelines for key study milestones:

• First Patient (or study subject), First Visit (FPFV): First of June 2019

• Last Patient (or study subject), First Visit: 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

Description of recruitment strategy

Having several years of experience with recruitment of patients into randomized trials (8, 10, 19, 23) we will use this experience to enhance allocation to this trial within the network of ICU’s participating in the Horizon 2020 project. We will screen all patients admitted to the ICU’s fulfilling the inclusion criteria. This includes incentive strategies of case money paid for the extra work of randomization, registration, and follow-up of patients in the trial, a pragmatic eCRF, registrating only what is absolutely needed to know, with a user friendly interface and use of public databases to retrieve outcomes. We will encourage investigators during meetings and with newsletters as well as visits to the sites helping them sorting out any difficulties with recruitment, registration, and data retrieval within the trial period.

The compliance part of the trial will test whether systematically gathered, supplemental material on protocol violations, and weekly or monthly meetings and discussions within the sites randomized to the compliance encouragement strategy can improve compliance further. 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 will allocate 110 (range: 50 to 250) patients during the 2 years of inclusion.

Assignment of intervention for controlled trial

All screened patients also participating in the observational study 1. (SICS-pack), registered in the eCRF, not fulfilling any exclusion criteria, also registered in the eCRF, will be randomized on a central website produced by the Copenhagen Trial Unit. A resuscitation fluid regimen will be assigned via the website to each patient after registration of the baseline characteristics. The site investigator will implement the assignment for each patient and oversee that the adequate amount of resuscitation fluid is delivered to the patient based on assigned criteria for fluid administration during the ICU stay. The compliance with the protocol to the criteria required by the assignment will be controlled in weekly samples of patients in the ICU and communicated to the doctors and nurses within the ICU’s randomized to the ‘encouragement of compliance strategy’.

The allocation group will not be blinded for the investigators and the treating personnel because this is practically impossible as the randomized allocation will and should be common knowledge in the ICU in order to comply with the allocated fluid intervention regimen.

The retrieval of life status, SAE’s, HRQoL, and periods of life support through public registries will be blinded for the outcome assessors as well as the statisticians involved in the analyses during interim- and final statistical analyses. The allocation group, that each patient belonged to (x or y), will only be known for the data manager and will first be demasked when relevant abstracts, summarizing the trial results for different possibilities of x and y, are approved by the trial investigators.

Study management, study monitoring, data and sample management

Planned strategy for study/trial management: The trial will be protocolised according to the SPIRIT21 statement and reported according to the CONSORT statement (22). A steering committee consisting of national investigators from Denmark, Finland, France, Germany, Netherlands, United Kingdom, Sweden and Switzerland will lead the trial and organize information on trial progression to all investigators in newsletters and meetings. An independent DSMC will oversee the quality of trial data and perform interim-analyses to avoid foreseeable harm to trial patients.

Study monitoring plan (monitoring visits, level of source data verification, etc.): The fluid part of the trial will be monitored according to GCP rules within the national legislations and the EU Directive for clinical trials. We will conduct GCP monitoring including central monitoring based on the frequency of SAE reporting and on patients at risk for being unduly excluded (screened patients) or included (randomized patients) as well as on the main outcomes. The source data verification (SDV) will be performed on 10% of patients chosen at random as well as patients at risk for having a flawed registration in the eCRF. The SDV will be performed preferably during the initial phase of the trial at each site in order to improve the overall quality of data registration further on.

Data collection and management: all trial data will be registered in the eCRF produced by Copenhagen Trial Unit and the Centre for Research in Intensive Care, previously used in the CLASSIC (19) and the SUP-ICU (25) trials. The eCRF have a user friendly interface with several administrative facilities to strengthen the overview of the trial progression, data completeness, and compliance with the protocol, centrally as well as locally.

Sample management: the primary sample in this trial is the intention-to-treat population, however, we will also analyze a per protocol population excluding patients with major protocol violations. We will judge the following events as major protocol violations:

A) Patients assigned to restrictive fluid administration receiving fluid when not fulfilling criteria for restrictive fluid administration.

B) Patients assigned to liberal fluid administration exclusively receiving fluid fulfilling criteria for restrictive fluid administration.

C) Patients assigned to liberal fluid administration not receiving fluid fulfilling criteria for liberal fluid administration.

D) Patients transferred to another ICU, during period necessitating ICU treatment, not participating in the trial thereby not complying with the protocol during the total ICU stay.

Sponsor, coordinating centre(s) and committees

The trials will be lead by the Steering Committee (SC) making all important advices to the sponsor and responsible for the scientific and practically conduct of the trial.

An independent DSMC will oversee the trial, having immediate and full access to all data in the trial database, during the entire trial period. The DMSC will advise the SC to stop or to continue the trial after interim-analyses as well as requesting data quality improvement when and if necessary.

Study medication

Trial fluids comprising of unbalanced and balanced crystalloids. Blood, and colloids, except Hetastarch (7, 8), will only be allowed as described in Types of fluid to be used in both intervention groups. The investigational trial fluids are registered medicinal products (IMP).

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