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Effect of fluid balance control in critically ill patients: Design of the stepped wedge trial POINCARE-2

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A B S T R A C T

A high number of recent studies have shown that a positive fluid balance is independently associated with impaired prognosis in specific populations of patients hospitalized in intensive care unit (ICU): acute kidney injury, acute respiratory distress syndrome (ARDS), sepsis, high risk surgery. However, to date, there is no evidence that control of fluid overload reduces mortality in critically ill patients. The main objective is to assess the efficacy of a strategy limiting fluid overload on mortality in unselected critically ill patients hospitalized in ICU. We hypothesized that a strategy based on a weight-driven recommendation of restricted fluid intake, diuretics, and ultrafiltration initiated from 48 h up to 14 days after admission in critically ill patients would reduce all-cause mortality as compared to usual care. We use a stepped wedge cluster randomized controlled trial combined with a quasi-experimental (before-and-after) study. Patients under mechanical ventilation, admitted since > 48 h and < 72 h in ICU, and with no discharge planned for the next 24 h are eligible. A total of 1440 patients are expected to be enrolled in 12 ICUs. Sociodemographic and clinical data are collected at inclusion, and outcomes are collected during the follow-up. Primary outcome is all-cause mortality at 60 days after admission. Secondary outcomes are patients weight differences between admission and day7 (or day 14), 28-day, in-hospital, and 1-year mortality, end-organ damages, and unintended harmful events. Analyses will be held in intention-to-treat. If POINCARE-2 strategy proves effective, then guidelines on fluid balance control might be extended to all critically ill patients.

Trial registration: ClinicalTrials.govNCT02765009

1. Introduction

Most critically ill patients develop a positive fluid balance, mainly during the first two weeks of their hospital stay. Causes of positive fluid balance are multifactorial: a reduced urine output subsequent to shock state, positive pressure mechanical ventilation, acute kidney injury, major surgical procedures, and simultaneous fluid loading to maintain blood volume and acceptable arterial pressure. Additionally, the efficacy of fluid loading is frequently suboptimal, in relation to severe hypoalbuminemia and inflammatory capillary leakage. Usually, this results in a substantial cumulated positive fluid balance of about 4–10 l [1–3] at the end of the first week of stay. Several studies have shown that such a positive fluid balance was associated with impaired prognosis in specific populations of Intensive Care Units (ICU) patients admitted for acute kidney injury [2,4–7], acute respiratory distress syndrome (ARDS) [8,9], sepsis [8–10], serious trauma [11], or high risk

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	Months 1-2	Months 3-4	Months 5-6	Months 7-8	Months 9-10	Months 11-12	Months 13-14	Months 15-16	Months 17-18	Months 19-20	Months 21-22	Months 23-24	Months 25-26	Months 27-28	Months 29-30	Months 31-32	Months 33-34	Months 35-36
ICU 1	CONTROL	CONTROL	CONTROL	Training	*STRATEGY*	*STRATEGY*	*STRATEGY*	strategy	strategy	strategy	strategy	strategy	strategy	strategy	strategy	strategy	strategy	strategy
ICU 2	control	CONTROL	CONTROL	CONTROL	Training	*STRATEGY*	*STRATEGY*	*STRATEGY*	strategy	strategy	strategy	strategy	strategy	strategy	strategy	strategy	strategy	strategy
ICU 3	control	control	CONTROL	CONTROL	CONTROL	Training	*STRATEGY*	*STRATEGY*	*STRATEGY*	strategy	strategy	strategy	strategy	strategy	strategy	strategy	strategy	strategy
ICU 4	control	control	control	CONTROL	CONTROL	CONTROL	Training	*STRATEGY*	*STRATEGY*	*STRATEGY*	strategy	strategy	strategy	strategy	strategy	strategy	strategy	strategy
ICU 5	control	control	control	control	*CONTROL*	*CONTROL*	*CONTROL*	Training	*STRATEGY*	*STRATEGY*	*STRATEGY*	strategy	strategy	strategy	strategy	strategy	strategy	strategy
ICU 6	control	control	control	control	control	*CONTROL*	*CONTROL*	*CONTROL*	Training	*STRATEGY*	*STRATEGY*	*STRATEGY*	strategy	strategy	strategy	strategy	strategy	strategy
ICU 7	control	control	control	control	control	control	*CONTROL*	*CONTROL*	*CONTROL*	Training	*STRATEGY*	*STRATEGY*	*STRATEGY*	strategy	strategy	strategy	strategy	strategy
ICU 8	control	control	control	control	control	control	control	*CONTROL*	*CONTROL*	*CONTROL*	Training	*STRATEGY*	*STRATEGY*	*STRATEGY*	strategy	strategy	strategy	strategy
ICU 9	control	control	control	control	control	control	control	control	*CONTROL*	*CONTROL*	*CONTROL*	Training	STRATEGY	STRATEGY	STRATEGY	strategy	strategy	strategy
ICU 10	control	control	control	control	control	control	control	control	control	*CONTROL*	*CONTROL*	*CONTROL*	Training	STRATEGY	STRATEGY	STRATEGY	strategy	strategy
ICU 11	control	control	control	control	control	control	control	control	control	control	*CONTROL*	*CONTROL*	*CONTROL*	Training	STRATEGY	STRATEGY	STRATEGY	strategy
ICU 12	control	control	control	control	control	control	control	control	control	control	control	*CONTROL*	*CONTROL*	*CONTROL*	Training	STRATEGY	STRATEGY	STRATEGY

Fig. 1. POINCARE 2 stepped-wedge cluster randomized trial design.
Notes: Underlined cells contribute to randomized stepped-wedge analyses, Capitals cells contribute to before and after analyses, ICU Intensive Care Unit.

surgery [12]. However, little is known about the putative role of positive fluid balance by itself on outcome. It has been suggested that positive fluid balance worsened pulmonary edema in ARDS patients [13]. Extravascular lung water, which is associated with impaired survival in critically ill patients [14,15], and high intra-abdominal pressure might be a partial clinical expression of the ubiquitous tissue and organ edema [16]. Such edema might itself impair prognosis through multiple organ failure due to capillary leak related to inflammation and hypoalbuminemia. In fact, hypoalbuminemia can cause positive fluid balance by inducing negative oncotic pressure. Albumin administration to critically ill patients yet controversial proved to be efficient on organ functions and fluid balance [17]. However, evidence of the association between a positive fluid balance and mortality in critically ill patients does not prove that interventions controlling fluid balance improve prognosis. Two randomized controlled trials in patients with ARDS showed that a strategy of fluid balance control, consisting of water input restriction and diuretic administration, reduced time under mechanical ventilation and ICU length of stay with no noticeable adverse effects [1,13]. Interestingly, adjunction of albumin administration to the aforementioned strategy proved to be efficient in patients with hypoproteinemia [18]. Yet fluid restriction, mainly if applied early, could be deleterious in reducing both tissue oxygen delivery and organ perfusion pressure, especially in case of septic shock since early-goal therapy based on early fluid resuscitation proved to be effective on survival in patients with septic shock [19]. However, a recent trial in patients with septic shock demonstrated that fluid restriction was feasible and well-tolerated, at least with respect to circulatory efficacy [20]. Although avoiding fluid overload is now recommended in ARDS management, there is no evidence that this approach, when delayed after the acute phase, would be beneficial on survival in a broader population of critically ill patients (i.e. with sepsis, acute kidney injury, or mechanical ventilation). A recent trial proved the efficacy of a natriuretic peptide-driven fluid management strategy in a broader sample of 304 critically ill patients on both time to successful end of mechanical ventilation and fluid balance, but failed to prove effective on survival [21].

We hypothesized that a strategy based on fluid balance control initiated 48 h after admission in critically ill patients would reduce all-cause mortality.

We conducted a stepped wedge cluster randomized trial to assess the efficacy of such a strategy on 60-day all-cause mortality in a broad population of critically ill patients.

2. Methods

2.1. Objectives and hypotheses

The main objective was to assess the efficacy of a fluid balance control strategy on 60-day all-cause mortality in critically ill patients.

Secondary objectives were:

- To assess the effectiveness of a fluid balance control strategy in critically ill patients on fluid balance control at day 7 and at day 14, on 28-day, in-hospital, and one-year all-cause mortality, on in-ICU number and seriousness of end-organ damages, on time to end of mechanical ventilation, time to vasopressor weaning, and time to end of renal replacement therapy
- To assess the therapeutic efficacy and the effectiveness of a fluid balance control strategy on 60-day all-cause mortality in critically ill patients globally and according to SOFA and reasons for admission in the ICU
- To assess the efficacy, therapeutic efficacy and effectiveness of a fluid balance control strategy on 60-day renal recovery in critically ill patients
- To describe the frequency of unintended harmful events associated with the strategy during its administration in critically ill patients

The hypothesis is that the strategy of fluid balance control is superior to standard care on all the aforementioned outcomes.

2.2. Design and setting

The (*POids INtensive CARE 2*) POINCARE 2 stepped-wedge cluster randomized trial involved 12 ICU of 9 hospitals spread over 10 French cities: Paris (Academic hospital), Poissy (Community hospital), Lyon (Academic hospital), Strasbourg (Academic hospital), Nancy (Academic hospital), Dijon (Academic hospital), Belfort (Community hospital), Metz-Thionville (Community hospital), and Verdun (Community hospital). The list of the centers involved and related investigators is available on Clinicaltrial.gov Internet site, where POINCARE-2 trial is registered as NCT02765009.

In addition to the stepped-wedge trial involving the 12 centers over 36 months, a before and after quasi-experimental study was conducted over all the centers involved (Fig. 1).

2.3. Population and sampling

Eligible ICUs were ICUs with mixed and balanced activities of post-surgical and medical critical care.

All patients under mechanical ventilation (through endotracheal intubation) admitted in one of the 12 recruiting ICU for > 48 h and ≤ 72 h and with an expected length of stay after inclusion > 24 h were eligible.

Exclusion criteria were: age < 18 years, clinical condition or unavailability of bedside scale impeding weight assessment, multiple trauma, ICU stay > 24 h immediately preceding the index ICU admission, pregnancy, expected withdrawal of life-sustaining therapy < 7 days after admission, patient refusal to personal data collection and use, history of ICU stay in one of the 12 recruiting ICUs during the study period, and under guardianship.

All the participants of one study time-period contributed to either the control or the strategy group, depending on the date of inclusion and the ICU of admission (Fig. 1). The time schedule of enrolment, intervention, and assessment is presented in Table 1.

Table 1
Time schedule of enrolment, interventions, and assessments.

		Admission Day0	Day1–14 (daily)	Day28	ICU discharge	Hospital discharge	Day 60	Day 365
	Eligibility screen	X						
Clinical	Socio-demographics (Sex, Age)	X						
	Comorbidities (Cirrhosis, cancer, immunodeficiency, heart failure, diabetes mellitus, chronic kidney disease)							
	Reason for ICU[1] admission (Post-surgery, ARDS [2], Acute kidney injury [RIFLE], Sepsis, Other)	X						
	IGS2, McCabe score	X						
	SOFA	X						
	Diuresis	X	X					
Therapy	Crystalloids Colloids	X	X					
Monitoring	Body weight	X	X					
	Biological assays (Albuminemia, serum sodium, potassium and urea)		X					
	Furosemide use		X					
	Albumin use		X					
Outcomes	Vital status		X	X	X	X	X	X
	Body weight			X	X			
	SOFA		X (only Days 1, 3, 7, 14)	X				
	Mechanical ventilation		X	X	X			
	Vasoactive drug administration		X	X	X			
	Renal replacement therapy		X	X	X	X	X	
	Adverse events (systolic blood pressure < 90 mmHg, Na > 155 mmol/L once a day, K < 2.8 mmol/L once a day, RIFLE > Risk)		X	X				

[1] Intensive Care Unit
[2] Acute Respiratory Distress Syndrome

2.4. Strategy

The POINCARE-2 strategy assessed was based on a protocol aiming at fluid balance control. Once the strategy was implemented in the ICU (Fig. 1), all the patients admitted in the ICU including those who were not enrolled in the trial underwent the trial protocol from 48 h to day 14 after admission. The POINCARE-2 strategy protocol (Fig. 2) relied mainly on daily weighing and subsequent decision of water and salt restriction and administration of diuretics and albumin in case of excessive weight gain. Body weight gain was considered as a marker of fluid retention because the alternative method to assess fluid balance, i.e. subtracting recorded fluid output from input, yet simple in theory, is actually prone to large errors due to multiple sources of input and output, among which some are differentially omitted, and unstandardized methods of assessment [22,23]. Daily body weight assessment was done by trained nurses, using intensive care beds with integrated weighing scales when available, ceiling hoist scales, or bed scales. Diuretics and albumin were prescribed by ICU senior MD specialized in critical care, or by ICU residents under the supervision of ICU senior MD specialized in critical care.

The POINCARE-2 strategy will be compared to standard care, as delivered by each ICU staff in usual practice.

Clinical trials often rely on rules based on patient clinical status to modify the allocated strategy. As every patient admitted to the participating ICU received the POINCARE-2 strategy (Fig. 2) as part of standard care once the strategy was implemented in the concerned ICU (Fig. 1), no criterion was used to modify the allocated strategy. However, once the POINCARE-2 strategy was implemented, contraindication to water and salt restriction, such as arterial hypotension with a systolic arterial pressure < 90 mmHg, or contraindication to diuretic administration, such as serum potassium < 2.8 mmol/L, or serum sodium > 155 mmol/L, or a new deterioration of renal function with an « injury » level of the RIFLE classification, led to discontinue the POINCARE-2 strategy in the relevant patients. Correction of hypotension was immediately started according to usual procedures of the concerned center if needed.

All the ICUs' staff received training sessions and complete documentation aiming at improving POINCARE-2 strategy protocol adherence during the training phase (Fig. 1). Full information was delivered about the rationale and ways to deliver the protocol to all the patients admitted in the ICU. Independent research nurses monitored trial participants' adherence to the strategy protocol by collecting daily body weight, biological assays, and treatment prescriptions from admission to day 14 from medical records once the strategy was implemented (Fig. 1). To assess potential contamination bias during the control period (Fig. 1), i.e. whether the POINCARE-2 strategy was already partially implemented before the planned implementation, data concerning the components of the POINCARE-2 strategy, i.e. daily body weight, biological assays, and treatment prescriptions, were also collected by independent research nurses in patients included during the control period.

No component of the POINCARE-2 strategy protocol prohibited the use of relevant concomitant care and interventions in participants.

The assignment of the POINCARE-2 strategy protocol was held at a cluster level, each ICU representing one cluster. The time of assignment for each cluster is described in Fig. 1. The time of inclusion of each ICU in the trial was randomly determined by affecting computer-generated random numbers to each ICU and then ranking them by these random numbers (JMV, NA). Once the time of inclusion of an ICU was determined, the research team, i.e. the coordinating research nurse, the project manager, and the principal investigator (PEB) met with the whole ICU staff and the dedicated onsite research nurse to inform them about the trial procedures for the control period and launch the trial during the month before the time of inclusion. The control period started at this time at a cluster level. When the control period was over and during the training period (Fig. 1), the research team planned a meeting with the ICU staff to deliver information, posters, and brochures about the strategy to implement (Fig. 2). The strategy period started at the end of the training period at a cluster level.

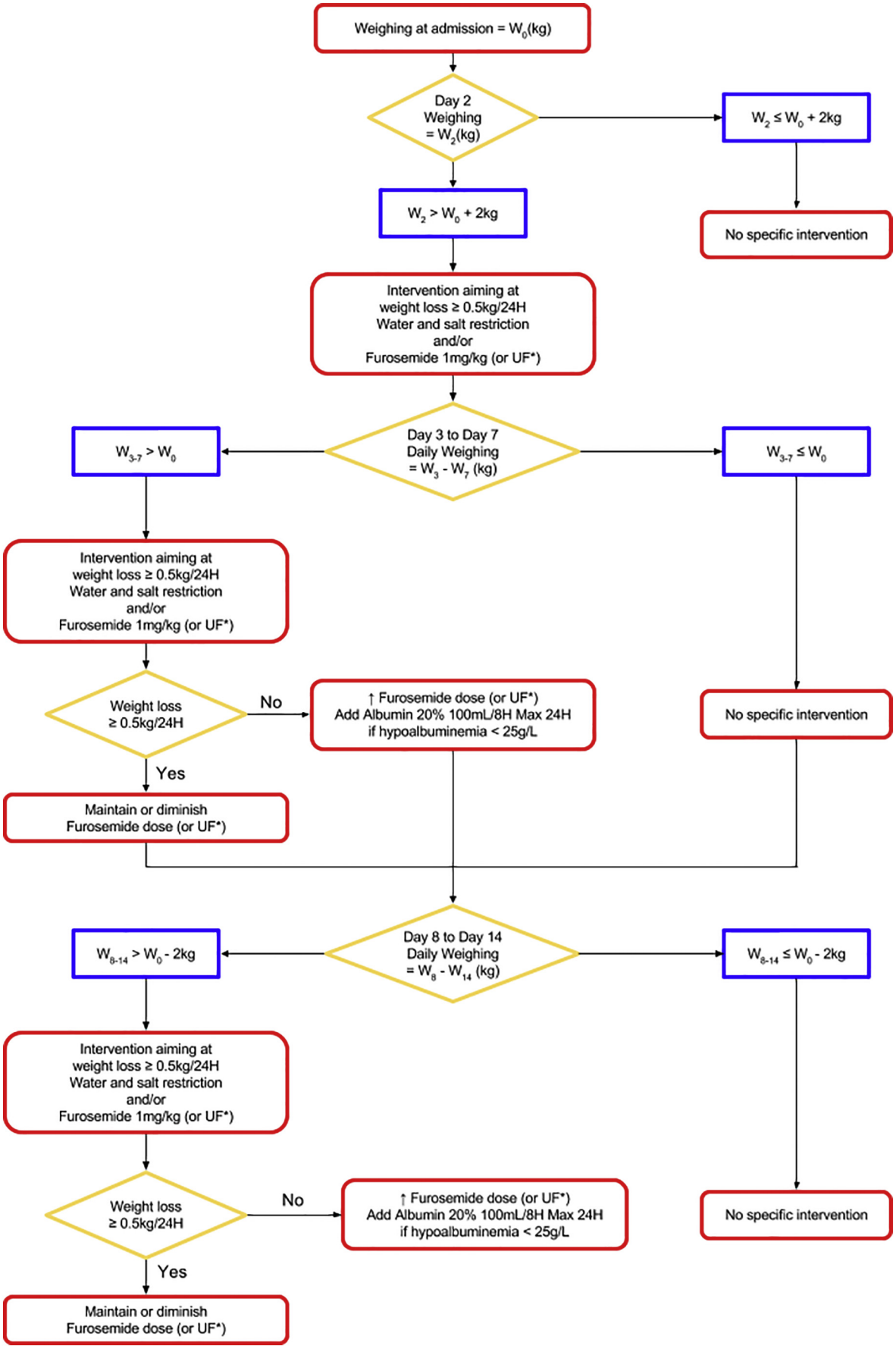

Fig. 2. POINCARE 2 strategy: a protocol aiming at fluid balance control.
Note: * Ultrafiltration in case of renal replacement therapy.

2.5. Outcomes

The primary outcome was 60-day all-cause mortality. Vital status was collected 60 days after admission. If the participant was dead at the time of assessment, date of death was collected.

Secondary outcomes were:

- Fluid balance control at day 7 and at day 14, assessed by body weight difference between day 7 and admission, and between day 14 and admission
- 28-day, in-hospital and one-year all-cause mortality, assessed by vital status collected at day 60 and at one year after admission
- Survival time period at day 60 and one year
- End-organ damage, assessed by time-related SOFA changes until day 28, cumulated number of ventilator-free days alive from day 0 to day 28, cumulated number of vasopressor-free days alive from day 0 to day 28, cumulated number of renal replacement therapy-free days alive from day 0 to day 60
- Unintended harmful events, assessed by the 14-day frequency of arterial hypotension, serum sodium > 155 mmol/L at least once a day, serum potassium < 2.8 mmol/L at least once a day, and renal damage as assessed by the "injury" level of the RIFLE criteria [24], acute ischemic events (myocardial infarction, patent mesenteric ischemia)

The time schedule of outcome assessment is presented in Table 1.

2.6. Data collection

Characteristics collected at admission consisted of socio-demographics, i.e. sex, date of birth, comorbidities, i.e. cirrhosis, cancer, immunodeficiency, heart failure, diabetes mellitus, chronic respiratory insufficiency and chronic kidney disease, reason for ICU admission, i.e. post-surgery, ARDS, acute heart failure, acute kidney injury, sepsis, or other, clinical characteristics, i.e. SAPSII [25], McCabe score [26], SOFA [27], RIFLE [24], body weight (kg), systolic blood pressure (mmHg), urine output (mL/24H), biological assays, i.e. serum sodium (mmol/L), serum potassium (mmol/L), serum albumin (g/L), and serum urea (mmol/L), and therapeutics, i.e. crystalloids or colloids (mL/24H), furosemide (mg/kg/24H), albumin (concentration, mL/24H), vasoactive drugs (type and duration of administration), time under mechanical ventilation, and renal replacement therapy.

Some of the characteristics at admission were also collected daily from day 2 to day 14, at day28/60, or at ICU/hospital discharge (Table 1).

Material used to assess body weight at admission was the same as the one described in the intervention section. Arterial pressure was assessed using noninvasive or invasive devices. Urine output was assessed as part of routine care. Biological assays were performed in each ICU hospital in a dedicated department, as part of routine care.

The time schedule of participants' characteristic assessment is presented in Table 1.

2.7. Data management and monitoring

ICU dedicated research nurses extracted all the data onsite from medical records, and collected them using a standardized electronic case report form (eCRF) developed with CSOnline 7.5 (2016 Ennov Clinical, Paris, FRANCE) (Appendix). Range checks were applied to all numerical variables of the eCRF. Data consistency was monitored in real-time for dates, delays, and conditional variables. Notifications were sent to the dedicated research nurses in case of incomplete eCRF or data inconsistency. Access to the database was controlled by personal login and password. Investigators and research nurses accessed only to their own ICU's patients. The research team, the coordinating nurse, the monitoring nurse, the project manager, the data manager had full access to the data collected for coordination, recruitment, follow-up, and data monitoring purposes. The data monitoring committee was composed of NA, PEB, the coordinating nurse, the project manager, the monitoring nurse, and the data manager. NA and PEB defined consistency checks for clinical variables. The data manager was in charge of generating automatic consistency checks when possible. The coordinating nurse, the monitoring nurse, and the project manager were in charge of data monitoring coordination with the help of research nurses. The full database will be stored on the Nancy CHRU server for 15 years after the end of the trial.

An audit could be conducted at any time by independent experts on the CHRU research director demand.

2.8. Ethics approval

Eligible patients were informed about the trial's objectives, the possibility to have access to and to modify their personal data, and to indicate that they did not want their personal data used for research purpose. If an eligible patient was unable to receive the trial information at the time of admission, the information was delayed and delivered before ICU discharge. If the patient died before receiving the trial information, he/she was considered as a non-refusal participant as long as his/her kin did not communicate his/her refusal to participate in the trial as stated by the French law (n°2004–806 du 9 août 2004). The French ethic law does not require any written consent for research studies focusing on authorized medications, such as diuretics or albumin that have proved to be effective in the indication under study, i.e. fluid overload or hypoalbuminemia, or nursing procedures that are part of usual care such as weighing patients, so that the standard of care encompasses both usual care and strategy. Nevertheless, the non-refusal to participate in the trial after delivery of oral and written information was notified in the medical record by the investigator in charge of the patient recruitment and information. Accordingly, the *Comité de protection des personnes* (CPP), i.e. French equivalent for institutional review board, has reviewed the trial protocol under the number ID-RCB: 2015-A00662–47, approved it, and granted waivers for written informed consent authorization on June 8th 2015.

Once assessed as eligible by the medical staff of the recruiting ICU, each patient was registered in the eCRF, and then identified by the recruiting ICU by the use of the first letter of his/her name and surname, his/her date of birth (month and year), and a computer-generated identifying number indicating his/her rank in the inclusion process. The *Commission Nationale Informatique et Liberté* (CNIL) granted the trial data processing authorization on February 18th 2016 (n°915,734).

Patients presenting unintended effects due to weighing, or furosemide or albumin use were due to receive standard care indicated in such conditions. They were invited to follow the recruiting hospital procedures used in standard care unintended effect situations to receive possible compensation.

Trial results will be communicated to the participants on demand.

Authorship for publications derived from the trial data will conform to the *International Committee of Medical Journal Editors* (ICMJE) authorship guidelines. The principal investigator, clinical investigators, and MD monitoring or contributing to the trial will be part of the main result publication authors.

2.9. Statistical analyses and sample size

For each outcome, analyses will be conducted using the whole database, the stepped wedge randomized design (randomized analyses) dataset, and confirmed by analyses conducted using the before and after quasi experimental design (before and after analyses) dataset. Each ICU contributes to the randomized analyses for three or six periods of 2 months as control, strategy, or both (reported in underlined capital letters in Fig. 1). The dataset for randomized analyses will be

restricted to those blocks. Although these data include fewer patients, they have the advantage to exclude potential bias due to time trends, as each outreach 2 month-ICU cell in the strategy group is balanced by another randomly chosen 2 month-ICU cell of the same period in the control group. Each ICU contributes to the before and after analyses for six periods of 2 months with a first 6-month-period in the control group and a second 6-month-period in the strategy group (reported in capital letters in Fig. 1). The dataset for before and after analyses did not rely on randomization but each outreach 2-month-ICU cell in the control period was balanced by a 2 month-ICU cell of the same ICU in the strategy period. This improves the ICU characteristics balance in the two groups (strategy vs. control). All analyses will be held in intention to-treat for efficacy assessment, per protocol for therapeutic efficacy assessment, and as treated for effectiveness assessment.

For per protocol and as treated analyses, a dose of intervention delivered will be calculated, by summing the daily deviations to the strategy protocol divided by the length of stay in the ICU in days for participants staying in the recruiting ICU < 14 days and by 14 for the others. This dose of intervention delivered will be calculated from data collected on the eCRF (daily deviance from weight at admission, oral and parenteral inputs, diuretic administration, albumin administration, and renal replacement therapy use) for each patient included in the trial whatever his group (strategy or control) to assess both the adherence to the strategy protocol during the ICU strategy period and the contamination during the control period. To be included in the per protocol or as-treated analyses, intervention dose of participants from the control group will have to be less than the first decile of the total intervention dose delivered and the intervention dose of participants from the strategy group will have to be greater than the ninth decile of the total intervention dose delivered.

No intermediate analysis was planned.

First, a flow chart of the patients from eligibility to inclusion in the analyses will be drawn.

Second, patients' characteristics at admission will be described in the strategy group vs. the control group using numbers and percentages for categorical variables and means and standard deviations (or medians and interquartile ranges in case of non-normal distribution) for continuous variables.

These characteristics will be compared using standardized differences, chi square or Fisher tests for categorical variables, or Student's or Wilcoxon tests for continuous variables according to condition of application.

Each outcome will be described using basic statistics overall and in the two groups (strategy vs. control).

To assess the effect of the strategy on each binary (continuous) outcome logistic (linear) regression models will be used, and Cox models will be used for survival time. Two-level models, in which 2-month-ICU cell will be entered as a random effect with baseline characteristics and strategy entered as fixed effects, will be used to take into account clustering of the data. For before and after analyses, study 2-month-period will be entered in the models as a covariate. For the whole sample analyses, a GLIMMIX procedure for binary and continuous outcomes will be used with the ICU and the period as random effects and with the strategy group and eventually unbalanced baseline characteristics also associated with the outcome as fixed effects. Missing data will be held by multiple imputations, except in case of intention-to-treat analyses, where maximal bias hypothesis will be assumed. All the analyses will be conducted with SAS© 9.4 (SAS Institute, Inc., Cary, NC, USA).

2.10. Sample size

For the main randomized analysis, among the 12 recruiting ICU, four will contribute to the control group only for 6 months, four will contribute to the strategy group for 6 months, and four will contribute to a 6-month period in the control group and to a 6-month period in the strategy group, which is equivalent to eight 6-month-ICU control and eight 6-month-ICU strategy, i.e. 8 clusters. Based on previous estimates of in-hospital mortality rates in ICU patients receiving mechanical ventilation varying between 34 and 44% [28–30], and on a previously reported 90-day mortality rate of 40% in this population [31], we hypothesized a 60-day mortality rate of 40–45 (42.5)%. However, we had to consider patients who would die between ICU admission and inclusion. Previous ICU survival estimates suggested that this early mortality varied between 4% and 8% [32–34]. We hypothesized a 5% value for early mortality, resulting in a hypothesized 60-day mortality of 35–40 (37.5) % in the control group.

With an expected 60-day mortality at 37.5% in the control group, a coefficient of variation k set at 0.26, a number of 8 clusters available, alpha set at 0.05, a power set at 0.8, and a minimal 15% reduction in mortality [33–35] expected in the strategy group (i.e. determined as clinically relevant), a total of 917 participants was required. Accordingly, it is necessary to enroll 10 patients per month in each concerned ICU (Fig. 1).

For the confirmatory before and after analysis, with an expected 60-day mortality at 37.5% in the control group, a coefficient of variation k set at 0.26, a number of 12 recruiting ICU 10 patients per months during 2 six-month periods, i.e. control then strategy (Fig. 1), resulting in a total of 1440 patients included, alpha set at 0.05, the resulting power to detect a minimal 15% reduction in mortality will be 95%.

3. Discussion

3.1. Current status of the trial

The trial was funded by the *French Direction Générale de l'Organisation des Soins* (DGOS) as part of the national *Programme Hospitalier de Recherche Clinique* (PHRC) 2014. The mandatory French ethic committees (CPP and CNIL) granted authorization for the trial. The eCRF is achieved and the related dataset is partially completed. The trial recruitment has been launched in June 1st 2016 and will end on May 31st 2019. The twelve ICUs have entered the trial and included 1321 patients so far. The control period for the last ICU included is over, allowing us to publish the study protocol without compromising the study design by motivating the application of the published strategy protocol in patients recruited during a control period. The trial protocol addressed recommended SPIRIT practices when applicable [36].

3.2. Implications

POINCARE-2 trial is expected to add evidence of the negative impact of a positive fluid balance on mortality by showing an association of a fluid balance control strategy with improved survival in a broad sample of critically ill patients, i.e. with a fair external validity, and using a controlled randomized trial design, i.e. with a fair internal validity. Accordingly, guidelines focused on fluid balance control currently applied in ARDS patients might eventually apply to a broader extent of critically ill patients.

In addition, the POINCARE-2 strategy is based on the assumption that basic clinical procedures such as weighing patients might actually be the cornerstone of fluid balance assessment. This technique, simpler and more reproducible than 24-h fluid input and output assessment, if effective, should be of great help in critically ill patient care.

Whatever the results, the trial should help to better understand fluid balance and fluid balance control in critically ill patients, and their prognostic impact on mortality, end-organ damage, and unintended events.

3.3. Limitations

Despite its innovative and original aspects, the POINCARE-2 trial has some limitations.

First, we opted for a late timing inclusion window and broad inclusion criteria. These options will result in a sample of patients with several subtypes of underlying disorders (shock states, ARDS, acute kidney injury, post-operative heart failure). Fluid loading is usually recommended for the 24–48 first hours in septic or hypovolemic patients, and most of them are stabilized in a few days. Although very different with respect to the early phase of their illness, stable patients with fluid overload might benefit from a strategy of fluid control, irrespective of their illness. However, if the pathophysiology of fluid inflation critically depends on the nature of the underlying disorder, which is unlikely, an unselected sampling will result in a heterogeneous sample of patients that might lead to inconclusive results. On the other hand, results derived from an unselected sample of ICU patients, corresponding to usual practice, will have a better external validity.

Second, due to the stepped-wedge design, the recruitment period and follow-up last 38 months. The publication of the trial results will occur later than the one expected with a classical individual randomized trial design. However, the nature of the assessed strategy, involving multiple providers, i.e. MDs, nurses and patients, multiple components, i.e. weighing, input restriction and medication administration, and delivered over a 14-day period, makes it a complex intervention as defined by Campbell et al. and Craig et al. [37,38]. Complex intervention evaluation requires appropriate methods to comprehensively assess their effect, i.e. understand the whole range of their effects and how the intervention works. When evidence is already available for some of the components of the intervention assessed, stepped-wedge design is an interesting option for ethical consideration [38]. In fact, they allow every cluster included to eventually implement the assessed intervention.

Third, the sample size calculation was based on cluster randomized trial assumptions and parameters [39] without considering time effect factor in the equations. Simple equations for sample size calculation in stepped-wedge trials were first published in August 2015 [40], i.e. a year after the trial was funded and granted for ethical authorization. However, as recommended by the available literature on the subject at the time of the protocol elaboration for funding purpose [41], we suppressed the time effect in the randomized analyses design, as suggested in Priestley et al.'s work [42]. Accordingly, our sample size estimation should prevent us from power overestimation associated with lack of time effect consideration [40].

4. Conclusion

While the association between positive fluid balance and pejorative outcome is established, the hypothesis that there is a causative link between fluid restriction and better outcome has never been demonstrated in a general population of ICU patients. Positive results may change our clinical practice for a broad population of ICU patients, at reasonable costs. Weighing patient daily as an index of fluid status, a simple and inexpensive procedure available in almost all ICUs is rarely used to manage fluid. Whatever the results, the study should help to improve the understanding of pathophysiology of fluids in severely ill patients.

Declaration of interests

NA declares no conflict of interest.

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Authors' contribution

NA conceived the study design, sampling, and statistical analyses. PEB conceived and coordinated the study. PEB and NA conceived the protocol for ethical approvals and funding purposes, and drafted the manuscript. JMV conceived data management and process evaluation of data collection, and helped draft the manuscript. CA conceived the statistical analysis plan. LA, MB, CC, GL, BrMa, FM, BeMi, HO, JPQ, JB, FS, DB, and PEB enrolled patients. They revised the manuscript critically for important intellectual content. All authors read and approved the final manuscript.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cct.2019.06.020.

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