PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	The FLUID Trial: A Protocol for a Hospital – Wide Open - Label Cluster Cross-Over Pragmatic Comparative Effectiveness Randomized Pilot Trial
AUTHORS	McIntyre, Lauralyn; Taljaard, Monica; McArdle, Tracy; Fox-Robichaud, Alison; English, Shane; Martin, Claudio; Marshall, John; Menon, Kusum; Muscedere, John; Cook, Deborah; Weijer, Charles; Saginur, Raphael; Maybee, Alies; Iyengar, Akshai; Forster, Alan; Graham, Ian; Hawken, Steven; McCartney, Colin; Seely, Andrew; Stiell, Ian; Thavorn, Kednapa; Fergusson, Dean

VERSION 1 – REVIEW

REVIEWER	Carmen Pfortmueller Department of Intensive Care Inselspital, Bern University Hospital, Switzerland
REVIEW RETURNED	16-Mar-2018

GENERAL COMMENTS	The FLUID Trial: A Protocol for a Hospital – Wide Cluster Cross-Over Pragmatic Comparative Effectiveness Randomized Pilot Trial I thank the editor for giving me the opportunity to review this very interesting study protocol. This is a very interesting study investigating an important clinical problem. Abstract: - Please change “2” for two. - “No large multi-centre randomized trials have been conducted to evaluate the effect of these two fluids on clinically important outcomes”. I do not agree with this statement. Several large scale clinical trials on fluids and clinical outcomes have been conducted over the past years, however results have not been conclusive so far. What you probably wanted to say is that no trial assessed death and hospital readmissions. - I this supposed to be a feasibility study for further large trials? There already were such trials, why perform a feasibility study? I think you need to be more specific that will assess death and readmissions as other outcomes have been extensively studied. Not knowing this, the reader is confused when reading your abstract. Introduction: - The first paragraph is poorly referenced. - “until recently”, the safety of 0.9%NaCl has been questioned for years, please rephrase - “Ringer’s lactate is considered a balanced crystalloid[3,4] because it does not induce acidosis.” I do not agree. Please properly explain the “buffer concept” of buffered infusates. - “None of the individual trials included in these reviews were powered for clinically important outcomes such as death”. This sentence is not correct. While there were no trials that were powered

	to assess death, many trials assessed acute kidney failure. Methods: - Elegibility: Why do you include all patients, regardless of fluid exposure? What is the percentage of patients that do not receive fluid? Did you perform a sample size analysis? - Trial conduct: How will you assess study fluid compliance in detail? Will you simple count the bottles still in storage? - There will be no blinding of the study fluids?

REVIEWER	Robert Hahn Södertälje Hospital and Karolinska Institutet Stockholm, Sweden
REVIEW RETURNED	21-Mar-2018

GENERAL COMMENTS	The use of saline as an infusion fluid instead of Ringer´s lactate has been questioned many times, the reasons being the development of acidosis and a higher incidence of postoperative complications, mostly nausea. Renal failure from saline as compared to Ringer´s has only been demonstrated with historical controls, and no prospective randomised study has ever demonstrated a higher mortality. Therefore, the purpose of the present, very ambitious, study is well motivated. The entire project seems to be carefully planned. My criticism mainly consists in uncertainty of whether the project plan deserves to be published when the project has already been running for 2 years.

REVIEWER	Sumeet Reddy Waikato Hospital, New Zealand
REVIEW RETURNED	21-Mar-2018

GENERAL COMMENTS	Overall, this is a clear protocol for a valuable study. I have a few suggestions and questions regarding the study protocol: - Please put open-label in the title of the paper. - Normal saline should be changed to 0.9% saline. - Page 6, Lines 21-22: The 95% CI for the odds ratio stated for mortality and renal replacement therapy include 1.0. This would imply there is no difference between arms of the study. - Will patients at participating hospitals be aware that there is a clinical trial happening ? - Although it may not be possible to record the individual volume of fluid giving to each patient is it possible to calculate the total volume of fluid administered during each cluster. - For the primary outcome will both out-of-hospital and in-hospital mortality be collected?

REVIEWER	Shirley Cheung Accident & Emergency Department, Tuen Mun Hospital, Hong Kong
REVIEW RETURNED	24-Mar-2018

GENERAL COMMENTS	This is a study to evaluate the feasibility of a trial in large scale population and to study the efficacy of Ringer's Lactate vs Normal saline in different patients. The part regarding evaluation of feasibility of a study protocol was well described. However, refinement may be needed regarding the study of clinical outcomes. The PICO question for the study of efficacy of fluid seemed not clear enough. As the protocol is targeted at a large group of subjects, studying clinical outcomes in aggregate may not be appropriate. Authors may

	consider dividing subjects into different groups for comparisons. Four hospital were selected to be the participating hospitals, how and why did the authors pick these four? Details for the subsequent processing of data collected or statistical methods used can be discussed.

REVIEWER	NOR AZIM MOHD YUNOS Jeffrey Cheah School of Medicine and Health Sciences, Monash University Malaysia
REVIEW RETURNED	04-Apr-2018

GENERAL COMMENTS	This is a clearly written protocol on a hospital-wide cluster randomized cross-over pilot trial comparing 0.9% saline with Ringer's lactate. The authors have excellently explained the details of this innovative design of a large multi-centre fluid trial with an advantageous use of the well-established and validated ICES health administrative data. The outcomes for the pilot trial are appropriately chosen to inform the larger FLUID trial, which in turn will address important patient-centred outcomes. Despite the currently ongoing other large fluid trials that individually recruit patients and blind the fluids, the results of this trial when it goes beyond the pilot phase, will still contribute to the much-needed health system and patient-centred evidence on the choice of crystalloids. It will also be another example of well-designed pragmatic large trial that includes a waiver of consents, an approach that will facilitate future clinical trials. I have a couple of minor suggestions or comments. While the authors have planned for a priori subgroup analysis of different age groups, it will still be important to explain why they have decided to enrol both adult and paediatric patients together. The other minor comment is on the reference number 25, which should ideally refer to the specific paper on the critically ill patients (or refer to both the paper and the editorial).

VERSION 1 – AUTHOR RESPONSE

Reviewers' Comments to Author:

Reviewer: 1

Comment 1: Please change "2" for two.

Response to Comment 1: All single numbers are now written out in the manuscript.

Comment 2: "No large multi-centre randomized trials have been conducted to evaluate the effect of these two fluids on clinically important outcomes". I do not agree with this statement. Several large scale clinical trials on fluids and clinical outcomes have been conducted over the past years, however results have not been conclusive so far. What you probably wanted to say is that no trial assessed death and hospital readmissions.

Response Comment 2: Thank you for this comment. In light of the recent SMART and SALT-ED trial publications (Self et al, Semler et al, NEJM, 2018 references # 2 and 29) that are now both correctly referenced in the manuscript, we have added the word "few" to that introduction sentence in the abstract.

Comment 3: I this supposed to be a feasibility study for further large trials? There already were such trials, why perform a feasibility study? I think you need to be more specific that will assess death and readmissions as other outcomes have been extensively studied. Not knowing this, the reader is confused when reading your abstract.

Introduction:

Response to Comment 3: Our FLUID executive team and Canadian Critical Care Trials Group agreed that prior to conducting the future large FLUID trial that is powered for the composite outcome of death or re-admission to hospital within the first 90 days of the index admission it would be critical to prove that we can in fact be successful at implementing a hospital wide intervention in academic and community hospitals and to use the learning that we obtain from the FLUID pilot in the future large FLUID trial. To enhance clarity for the reader, we now refer to the large FLUID trial as the future large FLUID trial in the abstract and throughout the manuscript.

Comment 4: The first paragraph is poorly referenced.

Response Comment 4: References are now added to the first paragraph.

Comment 5: "until recently", the safety of 0.9%NaCl has been questioned for years, please rephrase

Response Comment 5: We have modified the sentence to now state that "varying levels of evidence have led to question the safety of normal saline…." and added an additional reference from a recent systematic review of crystalloid fluids in the peri-operative and critically ill patient populations that was published in 2018 by Kawano -Dourado and colleagues on page 15 of the manuscript.

Comment 6: "Ringer's lactate is considered a balanced crystalloid [3,4] because it does not induce acidosis." I do not agree. Please properly explain the "buffer concept" of buffered infusates.

Response to Comment 6: We have now briefly also explained the buffer in Ringer's Lactate and how the buffer may also help prevent acidosis on page 15 of the manuscript.

Comment 7: “None of the individual trials included in these reviews were powered for clinically important outcomes such as death”. This sentence is not correct. While there were no trials that were powered to assess death, many trials assessed acute kidney failure.

Response Comment 7: We agree with the reviewer that there have been other trials assessing acute kidney failure; however, the largest trial from these two systematic reviews was 120 patients and as such, too small to detect small but clinically relevant differences in renal outcomes such as the requirement for renal replacement therapy or dialysis. We have now included in the introduction section (on page 15) an additional summary of a systematic review that was published by Kawano – Dourado and colleagues in 2018 and conducted in the peri-operative and critically ill patient populations which rated the quality of evidence as low but also imprecise and with insufficient power to detect small but clinically important differences between the fluids.

Comment 8: Eligibility: Why do you include all patients, regardless of fluid exposure? What is the percentage of patients that do not receive fluid? Did you perform a sample size analysis?

Response to Comment 8: We necessarily need to include all patients as fluid exposure data are not routinely tracked with the routinely collected hospital data. The access to routinely collected data at the hospital level is one of the main reasons for the use of a cluster randomized design, which allows us to conduct the trial at substantially reduced cost compared to a trial using individual randomization with individual patient follow-up within hospitals. All patients in the hospital during each study period will be exposed to the allocated fluid. Moreover, the vast majority of acutely ill (or those who require surgery) patients receive fluids during their hospitalization. Implementing the intervention at the level of the hospital means that patients will receive that same fluid as they move from different geographical locations in the hospital (ex: emergency room to ward, emergency room to ICU, pre-op area to OR to PACU to ward etc,). Due to the sheer number of patients that will be enrolled in FLUID, there will be no individual patient level fluid data collection. We will not know the proportion of patients who don’t receive fluid.

As noted on page 19, no formal sample size calculation was conducted for the FLUID pilot trial because the pilot is focussed on demonstrating feasibility of the future large FLUID trial.

However, in the sample size section, our calculations for the future large trial will account for a proportion of patients who don’t receive the allocated fluid during their hospitalization. In the future large FLUID trial, a sensitivity analysis will include exclusion of patients who do not receive fluids upon admission to hospital (direct admissions to psychiatry) summarized on page 21 of the manuscript.

These calculations will be refined following the successful completion of the pilot, and will need to be inflated to account for non-adherence, an approximate small sample correction, and the use of the normal approximation to the binomial distribution, cluster size variation and any potential cluster attrition.

Comment 9: Trial conduct: How will you assess study fluid compliance in detail? Will you simple count the bottles still in storage?

Response to Comment 9: In the manuscript on pages 15 and 16, we summarize how our approach to monitoring compliance and our targets for study fluid compliance (adherence).

*Adherence to the FLUID protocol**:** In the FLUID trial adherence will be measured not at the individual patient-level, but according to the aggregate use of the study fluid throughout the hospitals (all hospital wards, monitored units, and departments) using the hospital inventory system; monitoring adherence according to individual patients will not be feasible due to the sheer number of hospital admissions.*

To calculate adherence, the total use of the allocated study fluid will be divided by the total combined use of 0.9% saline and Ringer's lactate. Adherence will be monitored at 2 week intervals over the 14-week study periods. At the conclusion of the FLUID pilot trial, these adherence rates will be described according to each study group across all 4 participating hospitals, for individual hospitals, and for different wards across all and individual participating hospitals.

Logistical reasons (e.g., stocking issues on the hospital wards, lack of study fluid availability in the hospital, lack of signage where fluids are stored indicating automatic substitution) for non-adherence will be documented at the participating hospitals to evaluate if non-adherence is modifiable from the logistical perspective.

Successful adherence to the FLUID protocol is defined as a total of at least 80% of the prescribed study fluid for each study group being administered across all 4 participating hospitals over the 3-month study periods.

Comment 10: There will be no blinding of the study fluids?

Response to Comment 10: Study fluids will not be blinded in the trial. In the manuscript on page 9, we address blinding (masking) in the following paragraph.

FLUID will be an open-label clinical trial since the cost of blinding the fluids throughout each hospital is logistically and financially prohibitive. However, the risk of reporting bias is minimal as our clinical outcomes for the pilot trial and future large trial are objective and will be obtained using provincial health administrative data (housed at Institute for Clinical Evaluative Sciences) in Ontario.

Reviewer: 2

Comment 11: The use of saline as an infusion fluid instead of Ringer´s lactate has been questioned many times, the reasons being the development of acidosis and a higher incidence of postoperative

complications, mostly nausea. Renal failure from saline as compared to Ringer´s has only been demonstrated with historical controls, and no prospective randomised study has ever demonstrated a higher mortality. Therefore, the purpose of the present, very ambitious, study is well motivated. The entire project seems to be carefully planned.

My criticism mainly consists in uncertainty of whether the project plan deserves to be published when the project has already been running for 2 years.

Response to Comment 11: We thank the reviewer for this review and comment. Although the project has been running for 2 years, the descriptive analysis that will be conducted with the use of the Ontario health administrative database through the Institute for Clinical Evaluative Sciences has not begun because the data for the primary outcome will only be available in June 2018.

Reviewer: 3

Comment 12: Please put open-label in the title of the paper.

Response to Comment 12: We have added the words 'open label' to the title of the protocol

Comment 13: Normal saline should be changed to 0.9% saline.

Response to Comment 13: Normal saline has been changed to 0.9% saline in the manuscript.

Comment 14: Page 6, Lines 21-22: The 95% CI for the odds ratio stated for mortality and renal replacement therapy include 1.0. This would imply there is no difference between arms of the study.

Response to Comment 14: We agree and have changed this sentence to indicate the authors found 'non – significant' reductions in death and requirement for renal replacement therapy.

Comment 15: Will patients at participating hospitals be aware that there is a clinical trial happening?

Response to Comment 15: Throughout the hospital on patient wards, step down and intensive care units, there will be signs/posters to indicate the trial is currently running. Information related to the FLUID trial will also be posted on the Institution research websites (ex: Ottawa Hospital Research Institute) for patients/families to learn more about the clinical trial. At conclusion of the pilot trial at each site, we are planning a separate survey of the bedside nurses and treating physicians in part to

obtain an estimate of the number of patients/families that approached them for more information about FLUID during its conduct.

Comment 16: Although it may not be possible to record the individual volume of fluid giving to each patient is it possible to calculate the total volume of fluid administered during each cluster.

Response to Comment 16: Yes, it will be possible to calculate the total volume of both0.9% saline and Ringer's lactate used for each cluster (hospital) during each study period. All FLUID pilot participating hospitals have confirmed that they can provide this study fluid volume information through use of the hospital inventory systems which track inventory of these fluids on every fluid cart throughout the entire hospital.

Comment 17: For the primary outcome will both out-of-hospital and in-hospital mortality be collected?

Response to Comment 17: Yes, 90-day mortality will include deaths that occur both out of and in hospital over that time period.

Reviewer: 4

Comment 18: This is a study to evaluate the feasibility of a trial in large scale population and to study the efficacy of Ringer's Lactate vs Normal saline in different patients.

The part regarding evaluation of feasibility of a study protocol was well described. However, refinement may be needed regarding the study of clinical outcomes.

Response to Comment 18: The outcomes for the FLUID pilot trial are described on pages 15-17 of the manuscript. The clinical outcomes (primary and secondary) for our future large FLUID trial are described on page 17 of the manuscript. We have modified the paragraph on Secondary Clinical Outcomes on page 17 to more clearly state that in the pilot trial the clinical outcomes for these sub groups will be described in aggregate (not by study group).

Comment 19: The PICO question for the study of efficacy of fluid seemed not clear enough.

Response to Comment 19: In the Introduction Section on page 6 of the manuscript we summarize the PICO question as follows:

The future large FLUID trial will examine whether Ringer's lactate reduces the incidence of death and hospital re-admissions compared to 0.9% saline in all patients admitted to hospital. Prior to embarking on our large-scale trial, we will undertake the FLUID pilot trial to examine feasibility related to study

fluid protocol adherence, time to research ethics board (REB) approvals, and time to readiness to initiate the trial.

We believe the PICO question is clear but can the reviewer please clarify what is unclear.

Comment 20: As the protocol is targeted at a large group of subjects, studying clinical outcomes in aggregate may not be appropriate. Authors may consider dividing subjects into different groups for comparisons.

Response to Comment 20: The aggregate analysis is planned only for the feasibility trial because we are not adequately powered to examine clinical outcomes. For the future large FLUID trial we agree that an examination of sub groups will be important to understand if the magnitude of the treatment effect differs for patients who are more likely to receive higher exposure to fluids, with greater risk profiles, or higher severity of illness. On page 21 of the manuscript, we summarize a number of sub groups that we plan to examine in the future large FLUID trial. For further clarity, we have added a sentence to state that for the FLUID pilot trial, clinical outcomes according to these sub groups will only be described in aggregate (not according to study groups).

Comment 21: Four hospital were selected to be the participating hospitals, how and why did the authors pick these four?

Response to Comment 21: We aimed to select both academic and community hospitals for the pilot trial because we anticipate that trial implementation issues may differ at these hospitals. Since the Institute for Clinical Evaluative Sciences database is located in the province of Ontario we have limited our selection of sites to Ontario. We have inserted the following statement in the body of the manuscript on page 7 to explain how pilot sites have been selected: For pilot site selection, we have recruited a convenience sample of hospitals where the Principal Author practices, and through the Canadian Critical Care Trials Group (because FLUID is part of this network) and the direct contact of a critical care physician at a community centre located in the same city as the FLUID co-ordinating centre in Ottawa, Ontario.

Comment 22: Details for the subsequent processing of data collected or statistical methods used can be discussed.

Response to Comment 22 Our statistical analyses for the pilot trial are described in detail on page 20. The data and the sources for each data variable that will be collected through the Institute of Clinical Evaluative Sciences are summarized in Supplementary File 2. We reiterate that this is a feasibility study in which analyses will primarily involve descriptive analyses of feasibility outcomes. Because we are underpowered to assess differences in clinical outcomes, we have not provided a statistical analysis plan for evaluating between-arm differences in clinical outcomes. Should the pilot trial be successful and we proceed with the future large FLUID trial, a full statistical analysis plan for analyzing effectiveness outcomes will be developed.

Reviewer: 5

Comment 23: I have a couple of minor suggestions or comments. While the authors have planned for a priori subgroup analysis of different age groups, it will still be important to explain why they have decided to enrol both adult and paediatric patients together.

Response to Comment 323: We thank the reviewer for this comment. Although pediatric patients are not excluded from FLUID, only pediatric patients who are admitted through the same emergency room as adults in our participating hospitals (more common for community hospitals) will be included as we are not recruiting pediatric specialty hospitals to participate in FLUID (we have inserted this latter sentence into the manuscript on page 9). Although the pediatric population will represent a great minority of the patients included in FLUID, a sub group analysis according to this patient group that will be conducted in the future large FLUID trial may shed important light on the design of future pediatric crystalloid trials.

Comment 24: The other minor comment is on the reference number 25, which should ideally refer to the specific paper on the critically ill patients (or refer to both the paper and the editorial).

Response to Comment 24: We have modified the last paragraph of the Introduction Section on page 6 and have specifically linked the comments made on the SMART trial to the editorial written by Dr. Myburgh; the SMART trial is also now correctly referenced in the Introduction Section. We also suggest that longer term outcomes and economic evaluations should be performed on not only the critically ill, but at the level of the hospital since these fluid interventions are so widely administered.

FORMATTING AMENDMENTS (if any)

Required amendments will be listed here; please include these changes in your revised version:

1. Please convert and upload the Supplementary Files/Appendices into PDF file format.

Response to 1: Done

2. Please remove all figures from the body of the manuscript and re-upload your figure files separately.

Response to 2: Done

3. Please note that we do not accept figures in Word document, PowerPoint or PDF format.

Response to 3: Figure 1 format has been revised

All figures and images should be supplied as high-quality image files, we recommend TIFF or JPG/JPEG. Please ensure images are a minimum of 300dpi and a maximum of 600dpi (resolution). Figure Resolution requirements apply (90mm x 90mm).

During submission, ensure that the figure files are labelled with the correct File Designation of “Mono Image” for black and white figures and “Colour Image” for colour figures.

4. Patient and Public Involvement statement:

Response to 4: We have included a patient/public involvement statement summarized below in the Methods Section on page 22.

In the early planning phases of the FLUID pilot trial, we recruited a Patient Partner (AM) who is an active member of our FLUID executive committee. Our patient partner participates on FLUID executive conference calls and contributes to all decisions about the study. Our patient partner participated in and contributed to discussions about the FLUID pilot trial study design, outcome measures, and ethical argumentation, and the communication strategies related to the trial. In the early planning phases of the pilot trial, our team also consulted with The Ottawa Hospital’s Patient Advocacy Committee to guide our communication approach to hospitalized patients and their family members about this waived consent study.

VERSION 2 – REVIEW

REVIEWER	Cheung Wing Yan Shirley Accident & Emergency Department, Tuen Mun Hospital, Hong Kong
REVIEW RETURNED	11-Jun-2018

GENERAL COMMENTS	Large scale trial protocol with well-explained plan and outcome measures

REVIEWER	NOR'AZIM MOHD YUNOS Jeffrey Cheah School of Medicine & Health Sciences, Monash University Malaysia
REVIEW RETURNED	12-Jun-2018

GENERAL COMMENTS	The authors have responded to my earlier minor suggestions. Overall, the revised manuscript of the protocol is now more clear and concise.