The Fluid Translation of Research into Practice Study

(Fluid-TRIPS)

The Fluid Translation of Research into Practice Study (Fluid-TRIPS): An International Cross-Sectional Survey of Fluid Resuscitation Practice

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STATEMENT OF COMPLIANCE

This document is a protocol for a clinical research study. The study will be conducted in compliance with all stipulations of this protocol, the conditions of ethics committee approval, the NHMRC National Statement on Ethical Conduct in Human Research (2007) and the Note for Guidance on Good Clinical Practice (CPMP/ICH-135/95) annotated with Therapeutic goods Administration comments. The New Zealand Interim Good Clinical Research Practice Guidelines (Volume 2 1998 and Volume 3 2000)

THE GEORGE INSTITUTE
for Global Health

The University of Sydney

1 Synopsis

Background: Treatment in Intensive Care Units (ICU) is costly[1] and with an ageing population, by 2020 the demand for intensive care services is expected to increase by 50%.[2] One of the most common therapeutic interventions prescribed in intensive care is fluid resuscitation (using crystalloid or colloid solutions), with at least one third of patients managed in ICUs receiving this intervention on any given day.[3] Several large-scale clinical trials[4-9] and meta-analyses[10-14] have provided evidence of how fluid resuscitation can impact on important patient outcomes such as need for dialysis and mortality.

Objective: The primary objective of this project is to describe international trends in the prescription of intravenous fluids for fluid resuscitation in adult intensive care patients and compare this to the same data collected in 2007 from SAFE-TRIPS.

Method: An international cross-sectional survey will be undertaken which audits fluid resuscitation practice in participating ICUs on a single day.

Sampling: Convenience sampling will be used, leveraging from the SAFE-TRIPS project.

Data collection: Total number of patients in the ICU on the study day; Availability and unit cost of resuscitation fluid; General patient demographic information; ICU admission diagnostic categories; APACHE II Score; Volume and name of crystalloid or colloid; Indication for resuscitation; Characteristics of fluid prescriber; Organ support (at time of fluid resuscitation episode); Physiology (at time of fluid resuscitation episode); and Total fluid volumes administered.

Outcome: The findings from this project will provide important insights into the process of translating evidence from clinical trials on fluid resuscitation into clinical practice.

2 General Information

2.1 Title

The Fluid Translation of Research into Practice Study (Fluid-TRIPS): An International Cross-Sectional Survey of Fluid Resuscitation Practice

2.2 Study management committee

Naomi Hammond (Co-Chair), Colman Taylor (Co-Chair), Manoj Saxena, Simon Finfer, John Myburgh, Anders Perner, Nicola Watts, Laurent Billot, Parisa Glass, Bette Liu, Maryam Correa (Project Manager)

2.3 International liaison committee

An international liaison committee will be set up to coordinate the communication and conduct of the study within each country or region (see section 11.3 and 12.2).

2.4 Coordinating centre

The George Institute for Global Health will be the coordinating centre and data custodians for this international study. All data management and analysis will be conducted at the George Institute.

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3 Background and Rationale for Project

3.1 Current fluid resuscitation research

The SAFE study

In 1998, the Cochrane Injury Group Albumin Reviewers (CIGAR) published a systematic review and meta-analysis comparing the effects of albumin to a range of crystalloid solutions and concluded that the administration of albumin was associated with a significant increase in death (relative risk [RR] 1.68, 95% confidence intervals [CI] 1.26 to 2.23, $p<0.01$).[15] Despite methodological limitations of this meta-analysis, this study caused substantial alarm, particularly in Australia where albumin was widely used.

As a result, our group at the George Institute, in collaboration with the Australian and New Zealand Intensive Care Society Clinical Trials Group (ANZICS-CTG), conducted the NHMRC funded Saline vs Albumin Fluid Evaluation (SAFE) study to examine the effect of resuscitation with 4% albumin to its carrier solution, saline, on death at 28 days in a population of adult ICU patients.[16] The results published in the New England Journal of Medicine demonstrated no difference in death between albumin and saline (RR 0.99, 95%CI 0.91 to 1.09, p=0.87). This landmark study addressed a fundamental question about the safety of albumin for fluid resuscitation.[15]

The SAFE-TRIPS study

As published evidence of fluid prescribing patterns was only available from surveys and questionnaires of clinician preferences conducted in a small number of ICUs in single countries,[17-19] the SAFE-Translation of Research into Practice Study (TRIPS) study was established[3]. The SAFE-TRIPS study was an international cross-sectional observational study conducted in 25 countries and 391 ICUs during 2007. The study aimed to assess which fluids were being used for resuscitation in critically ill patients. Fluid resuscitation was defined as the administration of either a bolus of crystalloid, colloid or blood product that was delivered within the time frame of an hour.

There were two key findings from the SAFE-TRIPS study: firstly, despite the absence of evidence of superiority and the associated increased costs, colloids were more frequently administered to resuscitate critically ill patients than crystalloids, with Hydroxyethyl starch (HES) the most commonly prescribed synthetic colloid. Secondly, the choice of fluid varied substantially and geographic location, rather than patient factors, appeared to be a strong determinant of practice variation.

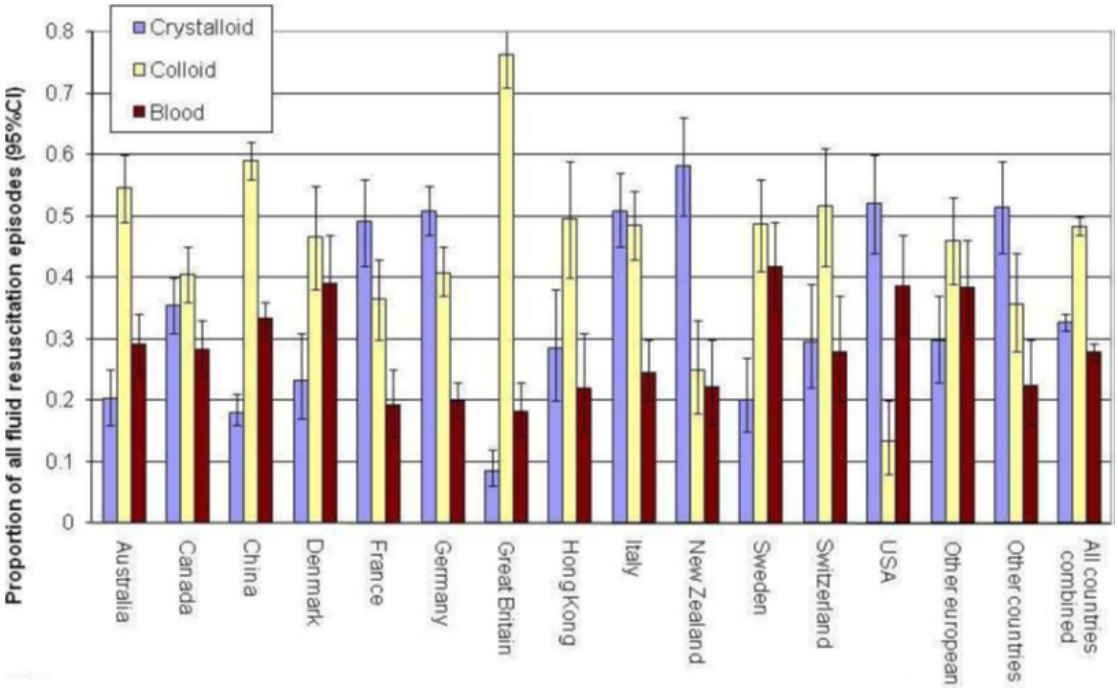

Figure 1: Proportion of fluid resuscitation episodes in SAFE-TRIPS given as crystalloid, colloid and blood product according to country

The CHEST study

The findings from SAFE-TRIPS and the implications of Therapeutic Goods Administration (TGA) licensing of 6% HES 130 in Australia in 2006, provided the impetus to conduct a large-scale, high-quality RCT, modelled on the SAFE study. The Crystalloid vs. Hydroxyethyl Starch Trial (CHEST) compared resuscitation with the most commonly used colloid globally, 6% HES (130/0.4), to the most commonly used crystalloid globally, 0.9% saline, in ICU patients. This trial was conducted by our group at the George Institute and through the ANZICS-CTG.[5] CHEST randomized 7000 intensive care patients who required fluid resuscitation, to either 6% HES (130/0.4) or 0.9% saline (the carrier fluid for 6% HES). This study demonstrated no difference on the primary outcome of 90 day mortality between the two groups (RR 1.06; 95% CI 0.96 to 1.18; P=0.26), nor any difference in mortality in predefined subgroups. However, the study did demonstrate that patients resuscitated with HES were significantly more likely to receive renal replacement therapy (RRT) compared to patients resuscitated with saline (RR 1.21; 95% CI 1.00 to 1.45; P=0.04). Importantly CHEST had a pre-published analysis plan,[20] in which there was an *a priori* specification that the study design incorporated 90% power at an alpha of 0.5 to detect a relative increase in the risk of renal

failure by 1.5. There were also significant increases in the number of adverse events (predominantly cutaneous manifestations and increased need for blood product transfusion) in the HES group compared to the saline group.

The 6S Study

At the time CHEST was in the final stages of recruitment, the Scandinavian Starch for Severe Sepsis/Septic Shock study (6S) was published.[4] This study assessed the effects of 6% HES (130/0.42) compared with a balanced crystalloid solution (Ringers acetate, which was the carrier solution for the HES preparation being evaluated in this study) on mortality and kidney failure in 798 patients with severe sepsis. The 6S investigators reported an increased risk of death at 90 days in those patients resuscitated with 6% HES (130/0.42) (RR 1.17; 95% CI 1.01 to 1.36; P=0.03). HES patients were also more likely to need renal replacement therapy (RR 1.35; 95% CI 1.01 to 1.80; P=0.04) compared to patients given Ringers acetate.

3.2 Rationale for Fluid-TRIPS

This proposed project – the Fluid Translation of Research Into Practice Study (Fluid-TRIPS) – is an international collaboration that will be coordinated by the George Institute for Global Health. Fluid-TRIPS builds on the infrastructure already established by SAFE-TRIPS[3] and aims to provide key evidence to describe and understand international fluid prescribing habits in different regions of the world. This includes determining if patterns of fluid resuscitation within ICUs globally have been influenced by the publication of systematic review and meta-analyses[10-14,21-23] and clinical trials,[4-6,8,9,24] since the SAFE-TRIPS study was conducted in 2007.

4 Aims and Objectives

The aim of this project is to describe international trends in the prescription of intravenous fluid resuscitation and to determine factors influencing choice.

4.1 Primary objectives

1. To describe the amount and type of resuscitation fluid currently administered to adult patients in intensive care units (ICU) in different countries
2. To compare the types of fluids used for resuscitation collected in this survey to data collected in the international survey conducted by our group in the 2007 Saline versus Albumin Fluid Evaluation – Translating Research Into Practice Study.[3]

4.2 Secondary objectives

1. To describe and compare the costs of fluid choice between different geographical regions
2. To develop policy recommendations for practice guidelines

5 Study Design – Cross Sectional Survey

The study is based on the methodological design of SAFE-TRIPS. An international cross-sectional survey will be undertaken which audits fluid resuscitation practice in participating

adult ICUs on a single day, commencing at the beginning of the relevant chart day and including all patients in the ICU and admitted during the 24-hour study period. The cross-sectional survey will address both primary objectives.

5.1 Sampling

Convenience sampling will be used leveraging from the previous collaborators in SAFE-TRIPS (391 centres from 25 countries). Additionally, sampling will be sought through established ICU clinical trials networks.

5.2 Inclusion/exclusion criteria

Adult patients (16 years or older) present in the ICU at the start of the study day or admitted during the 24-hour study period will be included in the study sample. The study period will correspond to the local chart day in individual units.

5.3 Data source

Data will be extracted from patient clinical records and bedside notes during the study day.

5.4 Data collection

Data will be collected over a designated 24-hour study day. Screening will be conducted on all patients present in the ICU at the start of the study day or admitted during the 24-hour study period, with total patient numbers recorded for the study day. Data will be collected only on those patients receiving fluid resuscitation on the study day.

Fluid resuscitation will be defined as administration of any of the following:

- a bolus of crystalloid
- a crystalloid infusion of 5mL/kg/hour or greater for one or more hours
- a colloid bolus
- any colloid by infusion

5.4.1 Site specific data collection

For ICUs participating in this study, a site questionnaire will also be administered to document the total number of patients in the ICU on the study day plus availability and cost of different fluid types.

5.4.2 Individual patient data

Patients who receive fluid resuscitation will have the following data collected:

Baseline data

- Sex
- Age
- ICU admission date
- Admission source and type
- Diagnosis
- Weight

- Diagnostic subcategories and details (trauma/sepsis/ARDS)
- GCS
- Cranial CT scan performed
- Abnormality on cranial CT
- Severity of disease score

Fluid Resuscitation Episode Data

- Time of resuscitation episodes
- Indications
- Prescriber characteristics
- SOFA score – respiratory and cardiovascular only
- Renal replacement therapy
- Mechanical ventilation
- Non-invasive ventilation
- ECMO
- ICP monitor
- ICP value
- Heart rate
- MAP
- Systolic and diastolic ABP
- CVP
- PCWP
- Lab results (creatinine, bilirubin, base excess or deficit, lactate, serum albumin)
- Urine and fluid output previous complete hour
- Crystalloid type and volume
- Colloid type and volume
- Fluid resuscitation infusion totals for the study day
- Total daily fluid balance – input and output volumes

6 Safety Monitoring

As this is a cross-sectional study using data collected as part of routine clinical practice, no safety monitoring will be undertaken.

7 Statistical Analysis Plan

7.1 Sample size and power

Due to the uncertain nature of observational research, no specific sample size has been calculated for this study. Based on the experience of SAFE TRIPS we anticipate recruiting a similar sample size (n>5000 patients; n>350 sites). A sample size of 280 ICUs and 2100 patients will allow us to estimate the overall prevalence of each fluid type very precisely with 95% confidence intervals that will be no wider than 6 percentage points. Furthermore,

we will be able to suitably estimate country specific prevalence rates with a precision of around 20 percentage points. Additionally, by recruiting between 5 and 10 patients from 350 ICUs, we will have 90% power to detect absolute changes in fluid prevalence over time of 6 percentage points.

All calculations assume a baseline prevalence of 50% which leads to the lowest precision (compared to lower prevalence assumptions); it is therefore likely that actual confidence intervals and detectable changes will be even smaller. These estimates also take into account the correlation of patients within ICUs. Based on the SAFE-TRIPS data, we have estimated that the Intraclass Coefficient (ICC) for fluid use is approximately 12%. Sample size calculations were performed using PASS 2008 and procedures appropriate for cluster-randomised studies.[25]

7.2 Data analysis

Data analysis will be guided by a statistical analysis plan, which will be developed before the database is locked. Data analysis will be undertaken at the George Institute for Global Health by statisticians using SAS software. To address the primary objectives descriptive statistics will be used including univariate comparisons. Only sites participating in both SAFE TRIPS and FLUID TRIPS will be included in the comparison of fluid use over time. To address the secondary objective – a multivariate analysis will be completed adjusting for predictors of fluid choice. An example of the proposed analysis can be found in the SAFE TRIPS publication[3].

8 Data Management

The data management and analysis will be undertaken by the George Institute for Global Health. The principal means of data collection and data processing will be via online data entry performed by the research coordinators at each site.

8.1 Site monitoring

No site monitoring will be performed.

8.2 Data recording and document retention

Each participating site will enter de-identified data into an electronic CRF (eCRF) using REDCap, a secure online data capture system developed by Vanderbilt University and hosted at the George Institute. Each site will access the system through an individual password protected account, and will only have access to site-specific data.

All data sent to the George Institute will be de-identified. Master log sheets with identifying details will remain confidential and will be stored securely at participating sites to enable data queries to be addressed if required. Master log sheets or any other identifying information will not be submitted to the study office at the George Institute.

All data collected by the study will be kept for a minimum of 7 years, or as otherwise required by regulatory authorities. The George Institute will be the data custodian and all

electronic data will be stored and backed up on password-protected databases. All paper data will be archived and stored in a secure facility.

8.3 Data quality assurance

Data entered by each site will be password-protected and the ability to access or change data prior to locking of the database will be restricted to that site and staff managing data at the George Institute. Once initial data collection has been completed, missing data and implausible values will be identified using predetermined objective criteria, and queries resolved through direct communication with sites if required. The Fluid-TRIPS management committee will oversee this data cleaning process. Treatment of outliers and missing data will be in accordance with the statistical analysis plan.

9 Funding

The George Institute will fund data management, operations and analysis. No site payments are available at the time of writing but funding is currently being sought. A participating centre Memorandum of Understanding (MOU) will be signed if required between the participating sites and the George Institute for Global Health.

10 Project Timeline

Anticipated timelines:

Date	Project Milestone
September 2013	Invite expressions of interest from international collaborators
October 2013	Identify site and country coordinators and make initial contact
November 2013	Managment committee finalise protocol & CRF
December 2013	Comments from international liaison committee on protocol and CRF
January 2014	Finalise protocol and CRF. Submit low & negligible risk ethics application to lead HREC in NSW
January 2014	Finalise participating countries/sites and distribute study documents
February 2014	Submit low & negligible risk ethics applications to Australian and international HRECs where appropriate
30th April 2014	Data collection day 1
21st May 2014	Data collection day 2
11th June 2014	Data collection day 3
16th July 2014	Data collection day 4
20th August 2014	Data collection day 5
17th September 2014	Data collection day 6
15th October 2014	Data collection day 7
November 2014	Finalise data collection
February 2015	All data entered and queries resolved

March 2015	Data analysis
June 2015	Final manuscript(s) submitted for publication

11 Participating Sites

11.1 Site eligibility

The site must have identified personnel for the collection and entry of data onto the study website. Human research ethics committee approval must be sought and obtained or waived at each site prior to commencement of data collection.

11.2 Hospital PIs

A Principal Investigator (PI) will be nominated for each participating site, and will be responsible for the conduct of the study and ethics approval at that site. Site communications and study documents will be sent to hospital PIs in addition to any nominated research personnel associated with that site.

11.3 Region/Country coordinators

Individuals who are able to represent Regional ICU Networks (where applicable) or individuals who may be able to coordinate the project in specific countries will be approached. Region/Country coordinators will be responsible for identifying hospitals to participate in the study within their jurisdiction. Network/Country coordinators will assist in distributing initial information about the study to sites within their jurisdiction, and may coordinate the project (for example by facilitating applications for ethics approval etc) in their region/country.

12 Operations Structure

12.1 Management committee

The Fluid-TRIPS management committee is responsible for all aspects of study design, management, analysis and publication of results. In addition the management committee is responsible for ensuring the study meets the proposed milestones and deadlines.

12.2 International liaison committee

The Fluid-TRIPS international liaison committee will be responsible for coordinating the project within their networks/country. All members of this group will be copied in on management committee meeting minutes and participate in management committee meetings on an *ad hoc* bases.

13 Regulatory Requirements

This study will be conducted in accordance with the ICH and GCP principles.

This study is low risk and it will be an observational study of various elements of routine intensive care practice. There are no interventions in the study and patient management

will not be influenced in any way. The study meets all the criteria for Quality Assurance as specified by the National Health and Medical Research Council (NHMRC) in Australia.

Given the observational nature of the study and the need to include all patients in order to avoid a biased sample, ethical approval will be sought for a waiver of consent. There are no risks to patient health or safety. Given that data will be collected at participating sites from identified medical records, procedures will be put in place to protect patient privacy. Information identifying individual patients will be kept confidential at each site and will be stored securely. This will allow data queries to be addressed, which is essential to ensure data integrity, but this information will not be sent to the George Institute. De-identified data sent to the George Institute will be stored securely in locked files or password-protected electronic files. Data from individual patients will be combined and will not be presented in a manner that would allow the identification of any individual patient.

Participating ICUs are involved voluntarily, and there is implied consent from participating units, indicated by their agreement to participate and a MOU if necessary will be signed between the participating ICUs and the George Institute for Global Health.

An application for low and negligible risk ethics approval will be lodged with a lead Ethics committee in each Australian state and territory. A nominated PI in each state will be responsible for submitting the protocol to the relevant Human Research Ethics Committee as required by local ethics authorities. Once ethical approval is obtained in each state, PIs at each site will be responsible for obtaining local governance approval for the project at their site where necessary.

Applications for ethics approval at international sites will be submitted by individual PIs, or by a nominated PI or country coordinator in each area where possible. Once ethical approval is obtained, PIs at individual sites will be responsible for obtaining local governance approval for their site where necessary.

14 Publication Policy

Data collected in the study will be presented at the Annual Scientific Meeting of ANZICS, Scientific Meetings of the CTG, and other forums as appropriate. Data will subsequently be used for scientific publications in academic journals. It may also provide support for research applications. All data will be de-identified.

14.1 Authorship

This study will be published under the authorship of the Fluid-TRIPS investigators with the writing committee listed as primary authors. All participating investigators will be listed under such group identifier in an appendix.

15 Trial Registration

This protocol has been registered on the following registries:

- WHO International Clinical Trials Registry Platform, UTN: U1111-1148-7823
- Australian New Zealand Clinical Trials Registry, Number: ACTRN12613001172796
- ClinicalTrials.gov register Number: NCT02002013

16. References

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